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New Evidence in Oncology is a publication that provides oncology specialists with scientific data from research presented at international and Canadian oncology conferences. A special feature of the journal, the Canadian Perspective, gives key opinion leaders a forum to discuss recent developments in oncology and to comment on how these advances may shape Canadian clinical practice. In addition, the Investigator Commentary sections provide information on key clinical studies from interviews with principal investigators. New Evidence also publishes discussion and expert opinion papers on timely topics of interest to oncologists in Canada.

Our January 2018 issue presents coverage from the 2017 European Society for Medical Oncology (ESMO) Congress and the 7th International Symposium on Acute Promyelocytic Leukemia (APL). This issue reports on key clinical trials evaluating treatment for lung cancer, urothelial cancer, melanoma, mesothelioma, gastric cancer, pancreatic cancer, Hodgkin lymphoma, and acute promyelocytic leukemia. The studies presented in this issue highlight new and emerging therapies that can reduce toxicities in patients by minimizing or eliminating the need for systemic chemotherapy while also maintaining or improving patient outcomes.

We would like to thank Dr. Oussama Abla, Dr. Michael Ong, and Dr. Matthew Seftel for their Canadian Perspectives. We would also like to thank Dr. Anand Jillella for his Expert Commentary.

Launched in 2016, the NE Live app is available to provide physicians with a forum to discuss the latest clinical data presented at national and international conferences. NE Live collaborates with Key Opinion Leaders in Oncology to provide up-to-date, unbiased perspectives and commentary on the latest studies. These perspectives are presented in short videos or in written format, highlighting key takeaways and opinions. Physicians who wish to stay up-to-date with the reports are invited to visit www.newevidence.live, as well as Apple’s App Store or the Google Play store to download the NE Live app.

We also invite you to visit our website at www.newevidence.com any time for the online version of New Evidence and more reports on current research.
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Contributors

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Dr. Oussama Abla is a staff oncologist at the Division of Hematology/Oncology in The Hospital for Sick Children in Toronto, where he has been on faculty since the year 2000. He is also an Associate Professor in the Department of Pediatrics at the University of Toronto. He received his medical degree from the University of Genoa, Italy in 1989. His post-graduate training included a pediatric residency at the Gaslini Children’s Hospital in Genoa and a pediatric hematology/oncology fellowship at the Hospital for Sick Children.

Dr. Abla’s clinical and research interests include pediatric leukemias and lymphomas with a special focus on acute promyelocytic leukemia (APL), pediatric primary central nervous system lymphoma and other rare pediatric lymphomas, as well as Langerhans cell histiocytosis (LCH) and rare histiocytic disorders. He is the chair of the Histiocyte Society “Rare Histiocytoses Steering Committee” and the primary investigator for the International Registry for Rare Histiocytic Disorders, as well as the Canadian Coordinator of the LCH-IV trial. He is also the co-editor of an upcoming textbook on Histiocytic Disorders. In addition, Dr. Abla is a member of the Children’s Oncology Group-APL study committee and co-editor of an upcoming textbook on APL. He is also a member of the international-BFM study group committees on non-Hodgkin lymphoma and acute myeloid leukemia. Dr. Abla has more than 80 scientific publications and book chapters in the fields of supportive care, leukemias, lymphomas, and histiocytic disorders.

Matthew Seftel, MD, MPH, MRCP, FRCPC

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Dr. Jillella’s professional training included a fellowship in hematology/oncology at Yale University School of Medicine and intensive training in Bone Marrow Transplantation at Johns Hopkins Oncology Center. In 1996, he was appointed Assistant and then Associate Professor and Director of the BMT Program at Medical College of Georgia (MCG). He then became Associate Professor at Temple University and Associate Director of the Fox Chase-Temple BMT Program in 2002. Dr. Jillella returned to MCG at Georgia Health Sciences University in 2005 as Professor of Medicine and Chief of the Division of Hematology/Oncology and BMT, and Director of the Bone Marrow/Stem Cell Transplant Program, and then became Associate Director for Clinical Affairs of the Georgia Regents University (GRU) Cancer Center Service Line. In 2013, Dr. Jillella left GRU to become Associate Director for Community Affairs and Outreach at the Winship Cancer Institute of Emory University in Atlanta.

Michael Ong, MD

Dr. Ong is a medical oncologist who specializes in genitourinary malignancies, malignant melanoma, and experimental therapeutics. His training has included an undergraduate medicine degree in Ottawa, as well as an internal medicine and medical oncology residency at Western University, and further fellowship training in experimental therapeutics at the Royal Marsden Hospital in London, U.K., before being recruited to The Ottawa Hospital Cancer Centre.

Dr. Ong’s research interests primarily include development of anticancer drug combination strategies including immunotherapy and targeted therapies, dose-optimization and sequencing-optimization of currently developed therapeutics, and development of non-invasive biomarker strategies. Dr. Ong is the lead investigator for a number of clinical trials for bladder and prostate cancers, and the main investigator for novel experimental therapeutics for genitourinary cancers and melanoma, in Ottawa.
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Lung Cancer

Focus on Immune Checkpoint Inhibitors and Third-Generation TKIs in NSCLC

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for over 80% of all cases. At diagnosis, approximately one third of patients with NSCLC present with stage III, locally-advanced disease. The standard of care for these patients with good performance status and unresectable disease is first-line platinum-based doublet chemotherapy concurrent with radiation (this excludes patients with oncogenic driver mutations). Platinum-based chemotherapy is associated with a 5-year survival rate of 15%, highlighting a significant unmet need for novel therapeutics for the treatment of these patients.

As one of the hallmarks of cancer is a tumour’s ability to evade the host immune surveillance system; immunotherapies that target immune checkpoint molecules, such as programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1), have emerged in many cancer types, including NSCLC. These therapies function by blocking the interaction between PD-1 (expressed on T cells) and PD-L1 (expressed on tumour cells and antigen presenting cells), thus relieving the immune inhibitory signals from this interaction. This leads to the enhanced activity of cytotoxic T cells, which can recognize tumour-specific antigens on tumour cells and target them for cell death.

A number of clinical trials investigating PD-(L)1 inhibitors in NSCLC have been completed or are ongoing. Pembrolizumab, an anti–PD-1 humanized monoclonal antibody, has demonstrated an OS benefit in the first-line setting for patients with advanced NSCLC who have ≥50% PD-L1 expression, compared with platinum-based chemotherapy (HR = 0.60, 95% CI: 0.41–0.89; p = 0.005). In the relapsed setting, pembrolizumab monotherapy also demonstrated an OS benefit over docetaxel in patients with advanced NSCLC and ≥1% PD-L1 expression. As chemotherapy has been shown to mediate immunologic effects, a combination of an anti–PD-1 antibody and chemotherapy may have synergistic effects. The ongoing phase II KEYNOTE-021 trial is investigating this theory by evaluating the combination of pembrolizumab with chemotherapy and other agents in patients with unresectable or metastatic NSCLC.

Also being investigated in NSCLC are atezolizumab and durvalumab, two humanized IgG1 antibodies targeted against PD-L1. Atezolizumab has also demonstrated an OS benefit over docetaxel in a phase II trial for previously-treated patients with advanced NSCLC. In an early-phase clinical study, durvalumab showed encouraging antitumour activity in patients with relapsed stage III or IV NSCLC, particularly in patients with high PD-L1 expression. There is preclinical evidence suggesting that PD-L1 expression may be upregulated in tumour cells following chemotherapy and radiotherapy, providing the rationale for an ongoing phase III study investigating durvalumab versus placebo as consolidation therapy after chemoradiation in patients with advanced NSCLC.

For patients with NSCLC whose tumours harbour oncogenic driver mutations, targeted therapies, such as epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs), can be an effective therapeutic option. EGFR mutations are one of the oncogenic alterations commonly present in NSCLC tumours. They occur in approximately 22% of cases and are frequently a result of exon 19 deletions (Del19) or an exon 21 L858R point mutation (L858R) in the EGFR gene. The EGFR TKIs gefitinib, erlotinib, and afatinib have
been approved by Health Canada for the first-line treatment of patients with advanced NSCLC who harbour these EGFR mutations, as they have demonstrated progression-free survival (PFS) benefits compared to standard chemotherapy.16–20 Unfortunately, despite initial response to EGFR TKIs, the majority of patients with NSCLC will progress after treatment. Resistance to EGFR TKIs has been associated with an acquired exon 20 T790M resistance mutation (T790M), which has been reported in about 60% of NSCLC patients with disease progression who initially responded to EGFR TKI therapy.21 Osimertinib, a third-generation, central nervous system-active TKI can selectively inhibit Del19, L858R, and T790M mutations and has demonstrated activity in patients with NSCLC who have disease progression after treatment with earlier-generation EGFR TKIs.22,23 Early clinical data have also suggested a benefit of osimertinib for patients with EGFR mutation positive (EGFR M+) NSCLC in the first-line setting.24

Both immunotherapies and next-generation EGFR TKIs show promise in improving response rates and survival in NSCLC patients with limited treatment options. In this section, we report the results of five studies, presented at the European Society for Medical Oncology 2017 Congress in Madrid, which focused on the use of these novel therapies in NSCLC:

- In the phase III PACIFIC study, consolidation therapy with durvalumab following chemoradiation demonstrated a statistically significant and robust improvement (>11 months) in PFS versus placebo at a planned interim analysis, in patients with stage III, locally advanced, unresectable NSCLC. (Paz-Ares L, et al. ESMO 2017:LBA1_PR)
- First-line therapy with pembrolizumab, pemetrexed, and carboplatin resulted in significant improvements in PFS and overall response rate compared with pemetrexed and carboplatin alone, in a phase II trial for patients with nonsquamous NSCLC. (Borghaei H, et al. ESMO 2017:LBA49)
- In the phase III FLAURA study, osimertinib resulted in significant improvement in PFS over gefitinib or erlotinib, as well as a trend towards favourable OS, in patients with advanced EGFR M+ NSCLC. (Ramalingam SS, et al. ESMO 2017:LBA2_PR)
- In a phase Ib expansion study, the combination of nectumumab and pembrolizumab showed antitumour activity and a manageable safety profile in patients with previously treated NSCLC. (Besse B, et al. ESMO 2017:1309P)
- Ilie et al. presented optimized protocols to determine PD-L1 expression in tumour biopsy and cytology specimens using the 22C3 antibody concentrate and the ASL48 and BenchMark ULTRA autostainers. (Ilie M, et al. ESMO 2017:1178P)

References:

PACIFIC: A double-blind, placebo-controlled phase III study of durvalumab after chemoradiation therapy in patients with stage III, locally advanced, unresectable NSCLC

**Background**
Most patients with locally advanced, unresectable non-small cell lung cancer (NSCLC) progress after concurrent chemoradiation therapy (cCRT), highlighting a need for novel therapeutic approaches in these patients. At the European Society of Medical Oncology (ESMO) 2017 Congress, interim results from a randomized phase III study evaluating durvalumab, an immune checkpoint inhibitor, in patients with stage III, locally advanced, unresectable NSCLC were presented.1

**Study design**
- PACIFIC is a phase III, randomized, double-blind, placebo controlled, multicentre, international study investigating the anti-programmed death-ligand 1 [PD-L1] antibody durvalumab as consolidation therapy in patients with stage III, locally advanced, unresectable NSCLC without progression, following platinum-based cCRT.
- Patients were randomized 2:1 to receive durvalumab or placebo up to 6 weeks post-cCRT.
- The planned sample size was 702 patients.
- Co-primary endpoints were progression-free survival (PFS) by blinded, independent central review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and overall survival (OS).
- PFS was defined as the time from randomization to the first documented event of tumour progression or death in the absence of progression.
- For PFS, this study has a ≥95% power to detect a hazard ratio (HR) of 0.67 with 458 events, using a two-sided 0.025 level log-rank test.
- The interim analysis of PFS was planned after approximately 367 (80%) of events; however, the actual interim analysis was conducted after 371 events.
- For OS, this study has a ≥85% power to detect an HR of 0.73 with 491 deaths, using a two-sided 0.025 level log-rank test.
- This study currently remains blinded to OS until the final analysis, planned after the target number of deaths has been reached.
- Key secondary endpoints included overall response rate (ORR) (per BICR), duration of response (DOR) (per BICR), safety, tolerability, and patient-reported outcomes.

**Key findings**
- Baseline characteristics were well balanced between arms.
- In both arms, approximately 45% of patients were 65 years of age or older, 70% were male, 9% had never smoked, and 53% had stage IIIa disease.
- PD-L1 expression on tumour cells was ≥25% in 24.2% of patients in the durvalumab arm and 18.6% of patients in the placebo arm.
- PD-L1 status was unknown for approximately 37% of patients in each arm.
• The best response to prior cCRT for patients in the durvalumab versus placebo arm, respectively, are as follows:
  - Complete response, 1.9% vs. 3.0%;
  - Partial response, 48.7% vs. 46.8%;
  - Stable disease, 46.6% vs. 48.1%; and
  - Progressive disease, 0.4% vs. 0%.

• The median follow-up was 14.5 months (range: 0.2–29.9).

• Completion of 12 months of treatment was reported in 42.7% of patients in the durvalumab arm and 30.1% in the placebo arm.

• Study treatment was discontinued in 241 patients (51.0%) in the durvalumab arm and 153 patients (64.8%) in the placebo arm. The most common reasons for discontinuation were adverse events (AEs) (durvalumab = 15.4% of patients; placebo = 9.7% of patients) and disease worsening (durvalumab = 31.3% of patients; placebo = 49.2% of patients).

Efficacy

• At data cutoff, 214 patients in the durvalumab arm and 157 patients in the placebo arm progressed by BICR.

• The median PFS from randomization was significantly longer with durvalumab (16.8 months, 95% CI: 13.0–18.1) versus placebo (5.6 months, 95% CI: 4.6–7.8; stratified HR = 0.52, 95% CI: 0.42–0.65; \(p < 0.0001\)). (Figure 1)

• The PFS benefit of durvalumab was seen across all subgroups analyzed (sex, age, smoking status, disease stage, histology, best response to cCRT, PD-L1 status, and epidermal growth factor receptor status).

• For patients with ≥25% tumour cell PD-L1 expression, the HR in favour of durvalumab was 0.41 (95% CI: 0.26–0.65) compared to 0.59 (95% CI: 0.43–0.82) in patients with <25% tumour cell PD-L1 expression.

• ORR was higher in the durvalumab versus placebo arm (28.4%, 95% CI: 24.28–32.89 vs. 16.0%, 95% CI: 11.31–21.59; \(p < 0.0001\)). (Table 1)

• Patients in the durvalumab arm had a 1.78-fold greater probability of responding to treatment than patients in the placebo arm (relative risk = 1.78, 95% CI: 1.27–2.51).

• The median DOR was longer in the durvalumab arm (not reached [NR]) compared to the placebo arm (13.8 months, 95% CI: 6.0–NR; HR = 0.43, 95% CI: 0.22–0.84). (Table 1)

• The incidence of new lesions was more frequent in patients in the placebo arm (32.1%) compared to the durvalumab arm (20.4%).

• The most frequent sites of new lesions in the durvalumab and placebo arms, respectively, were lymph nodes (5.7% vs. 11.4%), brain (5.5% vs. 11.0%), and lung (11.8% vs. 17.3%).

• The time to distant metastases or death by BICR was prolonged in the durvalumab arm (23.2 months, 95% CI: 23.2–NR) compared with the placebo arm (14.6 months, 95% CI: 10.6–18.6; stratified HR = 0.52, 95% CI: 0.39–0.69; \(p < 0.0001\)). (Figure 2)

---

**Table 1. Antitumour activity by BICR (ITT population)**

<table>
<thead>
<tr>
<th></th>
<th>Durvalumab (n = 443)*</th>
<th>Placebo (n = 213)*</th>
<th>Treatment effect (HR [95% CI])**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best overall response, n (%)†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>6 (1.4)</td>
<td>1 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>120 (27.1)</td>
<td>33 (15.5)</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>233 (52.6)</td>
<td>119 (55.9)</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>73 (16.5)</td>
<td>59 (27.7)</td>
<td></td>
</tr>
<tr>
<td>Non-evaluable</td>
<td>10 (2.3)</td>
<td>1 (0.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Duration of response, months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>NR</td>
<td>13.8 (6.0–NR)</td>
<td>0.43 (0.22–0.84)</td>
</tr>
<tr>
<td><strong>Ongoing response at data cutoff, %‡</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 12 months</td>
<td>72.8</td>
<td>56.1</td>
<td></td>
</tr>
<tr>
<td>At 18 months</td>
<td>72.8</td>
<td>46.8</td>
<td></td>
</tr>
</tbody>
</table>

BICR = blinded independent central review; CI = confidence interval; HR = hazard ratio; ITT = intent to treat; NR = not reached; RR = relative risk

* Patients with measurable disease at baseline, as determined by either of the two independent reviewers.

† One patient could not be grouped into any of the best overall response categories due to inconsistency in baseline assessment for measurable disease between the two independent central reviewers.

‡ Percentages calculated by Kaplan-Meier method.

** Placebo was the reference group when RR and HR were calculated; therefore, an RR value >1 is in favour of durvalumab and an HR value <1 is in favour of durvalumab.
Safety

- Grade 3/4 all-causality adverse events (AEs) were reported in 29.9% of patients in the durvalumab arm and 26.1% of patients in the placebo arm.
- AEs led to discontinuation in 15.4% and 9.8% of patients in the durvalumab and placebo arms, respectively.
- In the durvalumab and placebo arms, respectively, any-grade treatment-related AEs occurred in 67.8% and 53.4% of patients and any-grade immune-mediated AEs occurred in 24.2% and 8.1% of patients.
- The most frequent AEs occurring in >11% of patients in either treatment arm are presented in Table 2.

### Table 2. Most frequent adverse events*

<table>
<thead>
<tr>
<th>Event</th>
<th>Durvalumab (N = 475)</th>
<th>Placebo (N = 234)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event, n (%)</td>
<td>460 (96.8)</td>
<td>222 (94.9)</td>
</tr>
<tr>
<td>Cough</td>
<td>168 (35.4)</td>
<td>59 (25.2)</td>
</tr>
<tr>
<td>Pneumonitis/radiation pneumonitis†</td>
<td>161 (33.9)</td>
<td>58 (24.8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>113 (23.8)</td>
<td>48 (20.5)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>106 (22.3)</td>
<td>56 (23.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>87 (18.3)</td>
<td>44 (18.8)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>70 (14.7)</td>
<td>21 (9.0)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>68 (14.3)</td>
<td>30 (12.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>66 (13.9)</td>
<td>31 (13.2)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>62 (13.1)</td>
<td>18 (7.7)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>59 (12.4)</td>
<td>26 (11.1)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>58 (12.2)</td>
<td>11 (4.7)</td>
</tr>
<tr>
<td>Rash</td>
<td>58 (12.2)</td>
<td>17 (7.3)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>58 (12.2)</td>
<td>23 (9.8)</td>
</tr>
<tr>
<td>Constipation</td>
<td>56 (11.8)</td>
<td>20 (8.5)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>55 (11.6)</td>
<td>4 (1.7)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>51 (10.7)</td>
<td>31 (13.2)</td>
</tr>
<tr>
<td>Back pain</td>
<td>50 (10.5)</td>
<td>27 (11.5)</td>
</tr>
</tbody>
</table>

* Safety analysis set (all-causality). Adverse events occurring in >11% of patients in either treatment arm. Two patients randomized to placebo received at least one dose of durvalumab and were considered part of the durvalumab arm for safety reporting.

† Pneumonitis/radiation pneumonitis was assessed by investigators with subsequent review and adjudication by the study sponsor. In addition, pneumonitis, as reported in the table, is a grouped term, which includes acute interstitial pneumonitis, interstitial lung disease, pneumonitis, and pulmonary fibrosis.

‡ Five patients (1.1%) and four patients (1.7%) in the durvalumab and placebo arms, respectively, experienced grade 5 pneumonitis/radiation pneumonitis. Thirty patients (6.3%) and 10 patients (4.3%) experienced pneumonitis/radiation pneumonitis leading to discontinuation in the durvalumab and placebo arms, respectively.

![Figure 2. Time to distant metastasis or death by BiCR (ITT)](image-url)
Durvalumab demonstrated a statistically significant and robust improvement in PFS versus placebo at the planned interim analysis (HR = 0.52; \( p < 0.0001 \); median improvement of >11 months).

PFS improvement with durvalumab was observed across all pre-specified subgroups.

Durvalumab demonstrated a clinically meaningful benefit in ORR (28.4% vs. 16.0%; \( p < 0.001 \)), with durable responses versus placebo (median DOR NR vs. 13.8 months).

Patients receiving durvalumab had a lower incidence of new lesions, including brain metastases, compared with patients receiving placebo.

The safety profile of durvalumab was consistent with that of other immunotherapies and with its known safety profile as monotherapy in patients with more advanced disease.

- No new safety signals were identified.

The study remains blinded for OS.

Durvalumab is a promising new therapeutic option in patients with stage III, locally advanced, unresectable NSCLC who have completed cCRT.

Key conclusions


Borghaei H, et al. ESMO 2017:LBA49

Updated results from KEYNOTE-021 cohort G: A randomized phase II study of pemetrexed and carboplatin with or without pembrolizumab as first-line therapy for advanced, non-squamous non-small cell lung cancer

Background

Previous analyses from cohort G of the phase II KEYNOTE-021 trial have reported significant improvements in overall response rate (ORR) and progression-free survival (PFS) for pembrolizumab plus pemetrexed and carboplatin (PC) versus PC alone in patients with previously untreated, advanced, non-squamous non-small cell lung cancer (NSCLC), as well as a manageable safety profile for this combination therapy.1,2 An updated analysis of these results were presented at the ESMO 2017 Annual Congress.3

Study design

- Cohort G of the KEYNOTE-021 study was a phase II, randomized, open-label trial of PC plus pembrolizumab versus PC alone in patients with previously untreated, advanced, non-squamous NSCLC with no activating epidermal growth factor receptor mutations or anaplastic lymphoma kinase translocations.
- The primary endpoint of the study was ORR (by Response Evaluation Criteria in Solid Tumors version 1.1 per blinded, independent central review).
- The key secondary endpoint was PFS.

- Other secondary endpoints included overall survival (OS), safety, and the relationship between antitumour activity and programmed death-ligand 1 (PD-L1) tumour proportion score.
- There was no alpha allocated for the updated analysis; all \( p \)-values are nominal (one-sided \( p < 0.025 \)).
**Study design**

**KEYNOTE-021 Cohort G**

**Study population**
- Untreated stage IIIb or IV non-squamous NSCLC
- No activating EGFR mutation or ALK translocation
- Provision of a sample for PD-L1 assessment*
- ECOG PS 0 or 1
- No untreated brain metastases
- No ILD or pneumonitis requiring systemic steroids

**Randomize**

(1:1)*

N = 123

**Pembrolizumab**

200 mg q3w for 2 years

**Pemetrexed**

500 mg/m² +

carboplatin AUC 5 mg/mL/min q3w for 4 cycles†

**PD**

Pembrolizumab

200 mg q3w for 2 years

---

* Randomization was stratified by PD-L1 TPS <1% vs. ≥1%.
† Indefinite maintenance therapy with pemetrexed 500 mg/m² q3w permitted.

**Key findings**

- At the time of data cutoff (May 31, 2017), the median follow-up was 18.7 months (range: 0.8–29.0).
- After screening (219 patients), 60 patients were allocated to the pembrolizumab plus PC arm (59 patients treated) and 63 patients were allocated to the PC alone arm (62 patients treated).
- In the pembrolizumab arm, 14 patients remain on trial, 3 patients have completed the trial, and 42 have discontinued therapy.
- Of the patients discontinuing therapy, 48% of patients (29/60) in the intent-to-treat (ITT) population received subsequent therapy (64% [29/45] received subsequent therapy excluding those ongoing in the trial or not treated).
- In the PC alone arm, nine patients remain on trial and 53 have discontinued therapy.
- Twenty-five patients crossed over to the pembrolizumab arm on study and 15 patients received anti–PD-(L)1 therapy outside of the crossover, totalling 63% of patients (40/63) in the ITT population and 75% of patients (40/53), excluding those ongoing or not treated, who have received an anti–PD-(L)1 therapy.
- There were no major imbalances in baseline characteristics between treatment arms.

**Efficacy**

- ORR was 56.7% in the pembrolizumab plus PC arm and 31.7% in the PC alone arm (Δ24.8%, 95% CI: 7.2–40.9; p = 0.0029 [p-value is descriptive, one-sided p <0.025]).
- Compared with the prespecified analysis,¹ there was a similar between-arm difference in ORR and a similar pattern of response across PD-L1 distribution.
- The median duration of response was not reached in either of the treatment arms.
- Fifty percent of responders in the pembrolizumab arm, and 40% of responders in the PC alone arm had an ongoing response, defined as being alive without subsequent disease progression.
- The median PFS was longer in the pembrolizumab plus PC arm (19.0 months, 95% CI: 8.5–NR) versus the PC alone arm (8.9 months, 95% CI: 6.2–11.8). (Figure 1)
- The median OS was not reached (95% CI: 22.8–NR) in the pembrolizumab plus PC arm versus 20.9 months (95% CI: 14.9–NR) in the PC alone arm. (Figure 2)

**Safety**

- The median exposure to treatment was 10.1 months (range: 0–25.0) and 4.9 months (range: 0–25.0) in the pembrolizumab plus PC and PC alone arms, respectively.
- Treatment-related adverse events (AEs) for the pembrolizumab plus PC arm and PC alone arm, respectively, were:
  - Any grade, 93% and 92%;
  - Grade 3–5, 41% and 29%;
  - Leading to discontinuation, 15% and 15%; and
  - Leading to death, 2% and 3%.
- Treatment-related AEs and AEs with possible immune etiology are presented in Figures 3 and 4.
Key conclusions

- Upon longer follow-up, the hazard ratio (HR) for OS continues to improve for pembrolizumab plus PC versus PC alone.
  - In this analysis, the HR for OS was 0.59 after a median follow-up of 18.7 months, compared to the primary analysis where the HR for OS was 0.90 (median follow-up 10.6 months),1 and a previous update where HR for OS was 0.69 (median follow-up 14.5 months).2
  - In the current analysis, pembrolizumab plus PC continued to demonstrate significant improvements in ORR and PFS compared to PC alone.
  - The combination of pembrolizumab with PC continued to show a manageable safety profile.

Osimertinib versus standard of care EGFR TKIs as first-line treatment in patients with EGFR M+ advanced NSCLC: FLAURA

Background
Osimertinib, a central nervous system (CNS)-active epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI), has shown promising preclinical and early clinical trial data for the first-line treatment of EGFR mutation-positive (M+) advanced non-small cell lung cancer (NSCLC). Osimertinib was studied in the first-line setting in a phase III trial compared against standard of care (SoC) in patients with EGFR M+ advanced NSCLC. Efficacy and safety results from this study were presented at the ESMO 2017 Congress.

Study design
• The FLAURA study is a phase III, double-blind, randomized study assessing the efficacy and safety of osimertinib versus an SoC EGFR TKI (gefitinib or erlotinib) in first-line therapy for patients with advanced EGFR M+ NSCLC.
• The primary endpoint of the study was progression-free survival (PFS) according to investigator-assessed Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.
• This study had a 90% power to detect a hazard ratio (HR) of 0.71 (representing an improvement in median PFS from 10 months to 14.1 months) at a two-sided alpha-level of 5%.

Secondary endpoints included:
• Objective response rate (ORR);
• Duration of response (DOR);
• Disease control rate;
• Depth of response;
• Overall survival (OS);
• Patient-reported outcomes; and
• Safety.

Patients in the SoC arm could cross over and receive open-label osimertinib upon central confirmation of progression and exon 20 T790M resistance mutation positivity.

Key findings
• Globally, 556 patients were randomized to treatment (osimertinib, n = 279; SoC, n = 277 [with 66% of patients receiving gefitinib and 34% receiving erlotinib]).
• Baseline characteristics were balanced across treatment arms.
• In the osimertinib and SoC arms, respectively, 64% and 62% of patients were female, and 19% and 23% of patients had CNS metastases at study entry.
In both treatment arms, median age was 64 years, 62% of patients were of Asian race, 63% of patients had an EGFR exon 19 deletion, and 37% of patients had an EGFR exon 21 L858R point mutation.

Efficacy
- At data cutoff (June 12, 2017), 342 events had occurred in 556 patients (62% maturity; osimertinib = 136 events [49%], SoC = 206 events [74%]).
- Osimertinib significantly prolonged PFS compared to SoC with an HR of 0.46 (95% CI: 0.37–0.57; \( p < 0.0001 \)). (Figure 1)
  - The median PFS was 18.9 months in the osimertinib arm and 10.2 months in the SoC arm.
- PFS outcomes favoured the osimertinib arm in all subgroups analyzed (sex, age, race, smoking history, CNS metastases, World Health Organization performance status, and EGFR mutation).
  - In particular, for patients with CNS metastases (\( n = 116 \)) and without CNS metastases (\( n = 440 \)), osimertinib significantly prolonged PFS compared to SoC (HR = 0.47 and 0.46, respectively). (Figure 2)
  - In all patients, CNS progression events occurred in 17 patients (6%) receiving osimertinib versus 42 patients (15%) receiving SoC.
- There was not a significant difference in ORR between treatment arms (osimertinib: 80% vs. SoC: 76%, odds ratio = 1.28, 95% CI: 0.85–1.93; \( p = 0.2335 \)).
- The estimated percentage of patients remaining in response at 12 months was 64% (95% CI: 58–71) and 37% (95% CI: 31–44) for the osimertinib arm versus SoC arm, and at 18 months was 49% (95% CI: 41–56) versus 19% (95% CI: 13–26), respectively.
- The DOR was more than 2-fold higher in the osimertinib arm versus SoC arm, with non-overlapping CIs (17.2 months, 95% CI: 13.8–22.0 vs. 8.5 months, 95% CI: 7.3–9.8, respectively).
- At data cutoff, 141 deaths occurred in 556 patients (25% maturity; osimertinib = 58 deaths [21%]; SoC = 83 deaths [30%]).
- A trend towards an OS benefit for osimertinib over SoC was observed (HR = 0.63, 95% CI: 0.45–0.88; \( p = 0.0068 \)); however, the \( p \)-value did not reach what was required (\( p < 0.0015 \)) for statistical significance at the current maturity. (Figure 3)
Table 1. All-causality adverse events (≥15% of patients)

<table>
<thead>
<tr>
<th>AE by preferred term, n (%)</th>
<th>Any grade</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Any grade</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>161 (58)</td>
<td>120 (43)</td>
<td>35 (13)</td>
<td>6 (2)</td>
<td>0</td>
<td>159 (57)*</td>
<td>116 (42)</td>
<td>35 (13)</td>
<td>6 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Dry skin</td>
<td>88 (32)</td>
<td>76 (27)</td>
<td>11 (4)</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>90 (32)</td>
<td>70 (25)</td>
<td>17 (6)</td>
<td>3 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Paronychia</td>
<td>81 (29)</td>
<td>37 (13)</td>
<td>43 (15)</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>80 (29)</td>
<td>46 (17)</td>
<td>32 (12)</td>
<td>2 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>80 (29)</td>
<td>65 (23)</td>
<td>13 (5)</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>56 (20)</td>
<td>47 (17)</td>
<td>8 (3)</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Dermatitis acneiform</td>
<td>71 (25)</td>
<td>61 (22)</td>
<td>10 (4)</td>
<td>0</td>
<td>0</td>
<td>134 (48)</td>
<td>71 (26)</td>
<td>50 (18)</td>
<td>13 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>56 (20)</td>
<td>27 (10)</td>
<td>22 (8)</td>
<td>7 (3)</td>
<td>0</td>
<td>51 (18)</td>
<td>24 (9)</td>
<td>22 (8)</td>
<td>5 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritis</td>
<td>48 (17)</td>
<td>40 (14)</td>
<td>7 (3)</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>43 (16)</td>
<td>30 (11)</td>
<td>13 (5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>46 (16)</td>
<td>34 (12)</td>
<td>12 (4)</td>
<td>0</td>
<td>0</td>
<td>42 (15)</td>
<td>25 (9)</td>
<td>16 (6)</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>42 (15)</td>
<td>33 (12)</td>
<td>9 (3)</td>
<td>0</td>
<td>0</td>
<td>35 (13)</td>
<td>25 (9)</td>
<td>7 (3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AST increased</td>
<td>26 (9)</td>
<td>18 (6)</td>
<td>6 (2)</td>
<td>2 (1)</td>
<td>0</td>
<td>68 (25)</td>
<td>38 (14)</td>
<td>18 (6)</td>
<td>12 (4)</td>
<td>0</td>
</tr>
<tr>
<td>ALT increased</td>
<td>18 (6)</td>
<td>11 (4)</td>
<td>6 (2)</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>75 (27)</td>
<td>31 (11)</td>
<td>19 (7)</td>
<td>21 (8)</td>
<td>4 (1)</td>
</tr>
</tbody>
</table>

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; SoC = standard of care

* In the SoC arm there was one patient with grade missing and one patient with grade 5 diarrhea.

Key conclusions

- Osimertinib resulted in a significant improvement in PFS over SoC, with a 54% reduction in the risk of progression or death relative to SoC (HR = 0.46 and an early separation of Kaplan-Meier curves).
  - There was a consistent PFS benefit in patients with and without CNS metastases at study entry.
  - The duration of response was doubled in the osimertinib versus SoC arm (median: 17.2 months vs. 8.5 months).
  - The interim OS results showed promising survival favouring osimertinib versus SoC; however, data is not yet significant at 25% maturity (HR = 0.63, 95% CI: 0.45–0.88; p = 0.0068).
  - The safety profile of osimertinib was comparable to SoC, although with lower rates of grade ≥3 AEs and a lower discontinuation rate.
  - Osimertinib may be a new SoC as first-line therapy in patients with EGFR M+ advanced NSCLC.

Besse B, et al. ESMO 2017:1309P

Efficacy and safety of necitumumab and pembrolizumab combination therapy in patients with stage IV NSCLC

Background
Part A (dose-escalating) of an expansion cohort study investigating necitumumab (an epidermal growth factor receptor [EGFR] inhibitor) in combination with a standard dose of pembrolizumab for patients with stage IV non-small cell lung cancer (NSCLC) was completed without dose-limiting toxicities (DLTs) and with no additive adverse events (AEs) observed. At the European Society of Medical Oncology (ESMO) 2017 Congress, the efficacy and safety results from Part B of the study were reported.1

Study design
• This ongoing phase Ib, multicentre, single-arm expansion cohort study is examining the safety, tolerability, and preliminary efficacy of necitumumab combined with pembrolizumab in patients with stage IV NSCLC who have progressed after one line of platinum-based therapy.
• The primary objective was overall response rate (ORR).
  - Tumour response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.
  - Initial tumour imaging was performed within 21 days of the first dose of treatment and every 6 weeks thereafter.
• Secondary objectives included disease control rate (DCR), duration of response (DOR), progression-free survival (PFS) by RECIST version 1.1, safety, overall survival (OS), immunogenicity, and pharmacokinetics (PK) of necitumumab in the presence of pembrolizumab.
• The null hypothesis is based on the assumption that the ORR is 20% and the alternative response rate of the combination treatment on ORR is 35%.
• Statistical power was 83%, with a nominal one-sided alpha level of 0.10, based on a sample size of 54 evaluable patients (27 squamous and 27 non-squamous) in Part B.
• An interim safety analysis was performed after the first 15 evaluable patients in part B (including patients in part A who received the part B dose) completed 2 cycles of study treatment (or otherwise discontinued treatment).
• Programmed death-ligand 1 (PD-L1) was retrospectively assessed at a central location using the immunohistochemistry 22C3 pharmDx assay.
• PD-L1 expression was defined as follows:
  - Negative, <1% stained tumour cells;
  - Weak positive, 1%–49% stained tumour cells; and
  - Strong positive, ≥50% stained tumour cells.

Study design

- Pembrolizumab 200 mg D1 q3w
- Necitumumab 600 mg D1, D8 q3w
- Part A (n = 3–12)
  - ECOG PS score 0/1
  - Patients must have progressed after 1 platinum-based chemotherapy
  - Part B: Histologically or cytologically confirmed stage IV squamous or non-squamous NSCLC
  - ≤1 DLT
  - ≥2 DLTs/6 patients
  - N = 54

- Pembrolizumab 200 mg D1 q3w
- Necitumumab 800 mg D1, D8 q3w
- Part B (n = 6)
  - ECOG PS score 0/1
  - Patients must have progressed after 1 platinum-based chemotherapy
  - Part B: Histologically or cytologically confirmed stage IV squamous or non-squamous NSCLC
  - ≤1 DLT
  - ≥2 DLTs/6 patients
  - N = 54

- Pembrolizumab 200 mg D1 q3w
- Necitumumab dose from part A D1 and D8 q3w

D = day; DLT = dose-limiting toxicity; ECOG PS = Eastern Cooperative Oncology Group performance status; MTD = maximum tolerated dose; NSCLC = non-small cell lung cancer; q3w = every 3 weeks
Key findings

- A total of 64 patients of squamous (n = 30) and non-squamous (n = 34) histology were enrolled (Parts A and B).
- Overall, three patients received necitumumab 600 mg, 61 patients received necitumumab 800 mg, and all patients received pembrolizumab 200 mg.
- The median age of patients was 65 years (range: 43–81), 71.9% of patients were male, and 43.7% had two or more prior lines of therapy.
- In the population studied, 32 patients (50%) had PD-L1 negative status, 12 (18.8%) had weak positive status, and 10 (15.6%) had strong positive status.
- PD-L1 status was unknown in 10 patients (15.6%).
- At the time of data cutoff (January 26, 2017), 15 patients remained on treatment.

Efficacy

- The median DOR was 10.9 months (95% CI: 4.2–NR).
- One squamous (PD-L1 negative) and one non-squamous (PD-L1 weak positive) patient achieved a complete response.
- In all evaluable patients, ORR was 23.4%, DCR was 64.1%, median PFS was 4.1 months, and the 6-month OS rate was 74.7%. (Table 1)

- ORR was comparable in patients with squamous and non-squamous histology (20.0% vs. 26.5%, respectively); however, PFS was better in non-squamous versus squamous histology groups (median PFS 6.9 months vs. 2.79 months, respectively). (Figure 1)

Figure 1. Progression-free survival by histology

Table 1. Efficacy results by PD-L1 status and histology

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (N = 64)</th>
<th>Squamous (n = 30)</th>
<th>Non-squamous (n = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR, n (%) (95% CI)</td>
<td>15 (23.4) (13.8–35.7)</td>
<td>6 (20.0) (7.7–38.6)</td>
<td>9 (26.5) (12.9–44.4)</td>
</tr>
<tr>
<td>mPFS, months (95% CI)</td>
<td>4.1 (2.4–6.9)</td>
<td>2.8 (1.4–5.5)</td>
<td>6.9 (1.5–12.3)</td>
</tr>
<tr>
<td>6-month OS, % (95% CI)</td>
<td>74.7 (61.5–83.9)</td>
<td>63.6 (42.8–78.6)</td>
<td>84.2 (66.0–93.1)</td>
</tr>
<tr>
<td><strong>PD-L1 status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>32 (50.0)</td>
<td>13 (43.3)</td>
<td>19 (55.9)</td>
</tr>
<tr>
<td>ORR, n (%) (95% CI)</td>
<td>4 (12.5) (3.5–29.0)</td>
<td>1 (7.7) (0.2–36.0)</td>
<td>3 (15.8) (3.4–39.6)</td>
</tr>
<tr>
<td>mPFS, months (95% CI)</td>
<td>2.7 (1.4–4.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-month OS, % (95% CI)</td>
<td>68.2 (47.7–82.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weak positive</td>
<td>12 (18.8)</td>
<td>7 (23.3)</td>
<td>5 (14.7)</td>
</tr>
<tr>
<td>ORR, n (%) (95% CI)</td>
<td>3 (25.0) (5.5–57.2)</td>
<td>1 (14.3) (0.4–57.9)</td>
<td>2 (40.0) (5.3–85.3)</td>
</tr>
<tr>
<td>mPFS, months (95% CI)</td>
<td>5.4 (0.8–NR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-month OS, % (95% CI)</td>
<td>83.3 (48.2–95.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strong positive</td>
<td>10 (15.6)</td>
<td>5 (16.7)</td>
<td>5 (14.7)</td>
</tr>
<tr>
<td>ORR, n (%) (95% CI)</td>
<td>4 (40.0) (12.2–73.8)</td>
<td>2 (40.0) (5.3–85.3)</td>
<td>2 (40.0) (5.3–85.3)</td>
</tr>
<tr>
<td>mPFS, months (95% CI)</td>
<td>7.6 (1.0–12.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-month OS, % (95% CI)</td>
<td>80.0 (40.9–94.6)</td>
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</tr>
<tr>
<td>Unknown</td>
<td>10 (15.6)</td>
<td>5 (16.7)</td>
<td>5 (14.7)</td>
</tr>
<tr>
<td>ORR, n (%) (95% CI)</td>
<td>4 (40.0) (12.2–73.8)</td>
<td>2 (40.0) (5.3–85.3)</td>
<td>2 (40.0) (5.3–85.3)</td>
</tr>
<tr>
<td>mPFS, months (95% CI)</td>
<td>NR (0.8–NR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-month OS, % (95% CI)</td>
<td>78.8 (38.1–94.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; mPFS = median progression-free survival; NR = not reached; ORR = overall response rate; OS = overall survival; PD-L1 = programmed death-ligand 1
Efficacy appeared to be associated with PD-L1 status.
- In patients with a strong positive, weak positive, and negative status, ORR was 40.0%, 25.0%, and 12.5%, respectively; and median PFS was 7.6 months, 5.4 months, and 2.7 months, respectively. (Table 1)

Safety
- Part A was completed without DLTs (9 patients; 2 squamous, 7 non-squamous).
- Treatment-related AEs (TRAEs) of any grade were observed in 60 patients (94%), 20 patients (31%) experienced grade ≥3 TRAEs, 11 patients (17%) experienced serious TRAEs, and 2 patients (3%) experienced AEs leading to death (both grade 5 respiratory tract infections).
- Treatment-emergent AEs occurring in 10% or more patients are presented in Table 2.

Key conclusions
- The results suggest that the combination of necitumumab and pembrolizumab has activity in a pretreated NSCLC population with a relatively high proportion of PD-L1 negative patients.
- The safety profile observed corresponded to the individual profiles for necitumumab and pembrolizumab, with no additive toxicities.
- The strategy to target both the programmed cell death-1 and EGFR pathways may be beneficial in extending treatment response and delay resistance in the biomarker-selected population.
- Additional exploratory biomarker analyses are ongoing.


Ilie M, et al. ESMO 2017:1178P

Optimized protocols to determine PD-L1 expression on tumour tissue and cytology samples from NSCLC patients using the 22C3 antibody with various immunohistochemistry autostainers

Background
The U.S. Food and Drug Administration (FDA) has approved pembrolizumab in non-small cell lung cancer (NSCLC) for treatment-naive patients with a programmed death-ligand 1 (PD-L1) tumour proportion score (TPS) ≥50% and previously treated patients with a PD-L1 TPS ≥1%. As a result, reliable evaluation of PD-L1 TPS on widely available equipment and sample types is essential to identify patient eligibility for pembrolizumab treatment across global institutions. At the European Society of Medical Oncology (ESMO) 2017 Congress, Ilie et al. described optimized protocols for laboratory-developed tests (LDTs) that use the 22C3 antibody concentrate (Agilent Technologies, Carpinteria, CA) on more widely available immunohistochemistry (IHC) autostainers for tumour tissue, as well as LDT protocols for cytology specimens.1

ALT = alanine aminotransferase
* Denominator adjusted for female patients only.

Table 2. Treatment-emergent adverse events in ≥10% of patients

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Total (N = 64)</th>
<th>Any grade</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatitis acneiform</td>
<td>43 (67)</td>
<td>3 (5)</td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>24 (38)</td>
<td>3 (5)</td>
<td></td>
</tr>
<tr>
<td>Dry skin</td>
<td>23 (36)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>21 (33)</td>
<td>4 (6)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>20 (31)</td>
<td>4 (6)</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>17 (27)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17 (27)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>14 (22)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>14 (22)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Stomatitis</td>
<td>14 (22)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>12 (19)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>11 (17)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>11 (17)</td>
<td>6 (9)</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>10 (16)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Skin fissures</td>
<td>10 (16)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Paronychia</td>
<td>8 (13)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hirsutism*</td>
<td>2 (11)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>ALT increased</td>
<td>7 (11)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>7 (11)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>7 (11)</td>
<td>3 (5)</td>
<td></td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>7 (11)</td>
<td>2 (3)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (11)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Skin infection</td>
<td>7 (11)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>7 (11)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Xerosis</td>
<td>7 (11)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase
* Denominator adjusted for female patients only.
**Methods**

- The objectives of this study were to:
  - Optimize the protocols for LDTs that assess PD-L1 expression in tumour biopsy samples using the 22C3 antibody concentrate on commonly available IHC platforms;
  - Examine the concordance of the optimized LDTs with the PD-L1 IHC 22C3 pharmDx assay on the Autostainer Link 48 (ASL48) platform (Agilent Technologies, Carpinteria, CA; FDA approved assay); and
  - Assess the concordance in PD-L1 expression TPS in matched biopsy and cytology samples using these LDTs.

**Assay Development**

- PD-L1 expression was evaluated using the 22C3 antibody concentrate on the following commercially available IHC auto-stainers: ASL48, BenchMark ULTRA (Ventana, Tucson, AZ, USA), and BOND-III (Leica Microsystems, Buffalo Grove, IL, USA).
- Several protocols were tested on each IHC platform, with the best protocol being selected for further study.
- Multiple technical conditions were tested for optimization including slide thickness, pretreatment delays, primary antibody dilution, incubation time, and amplification systems.
- The PD-L1 expression in NSCLC biopsy samples stained according to the optimized LDT protocols on the ASL48 and BenchMark ULTRA platforms was compared to the stained results with the PD-L1 IHC 22C3 pharmDx kit on the ASL48 platform (according to manufacturer’s recommendations).

**Clinical Samples**

- Technical conditions for LDTs were investigated in tonsil specimens and in a training set of 3 NSCLC specimens.
- Validation of optimized protocols was completed using 120 archival formalin-fixed, paraffin-embedded NSCLC biopsy samples from patients who underwent surgical resection at Hôpital Pasteur between March 2007 and March 2016.
- For cytology samples, PD-L1 TPS was assessed in 70 paired tissue biopsy samples (collected at Hôpital Pasteur between July 2014 and November 2016) and cell blocks that were prepared from bronchial washes/pleural effusions with >100 tumour cells.
- The sample slides were freshly cut and stained within 24 hours.
- Informed written consent was provided from patients for tumour sample collection, storage, and use.

**Statistical Analyses**

- TPS was assessed separately as a continuous and categorical variable in statistical models.
- Concordance of TPS classification (negative percentage agreement [NPA] and positive percentage agreement [PPA]) was evaluated between each of the LDTs and the PD-L1 IHC pharmDx 22C3 assay, as well as between sample types.

**Key findings**

- The optimized protocols for 22C3 antibody-based LDTs were successfully developed on the ASL48 and BenchMark ULTRA platforms using serial sections from a tonsil specimen. (Figure 1)
- The LDT developed on the BOND-III autostainer had a prohibitively high concentration of the antibody.
- PPA and NPA for PD-L1 TPS in NSCLC biopsy samples stained with the 22C3 antibody-based LDTs was high (~100%) both on the ASL48 and BenchMark ULTRA platforms compared with the PD-L1 IHC 22C3 pharmDx kit on the ASL48 at both TPS cut points analyzed (≥1% and ≥50%; TPS in each assay was independently evaluated by three pathologists).

**Figure 1. Optimized protocols for PD-L1 IHC assays using 22C3 antibody concentrate**

<table>
<thead>
<tr>
<th>ASL48</th>
<th>BenchMark ULTRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue preparation</td>
<td>Tissue preparation</td>
</tr>
<tr>
<td>Sectioned at a thickness of 3 µm</td>
<td>Sectioned at a thickness of 3 µm</td>
</tr>
<tr>
<td>Deparaffinization/rehydration/antigen retrieval</td>
<td>Deparaffinization/rehydration/antigen retrieval</td>
</tr>
<tr>
<td>Performed on PT Link using EnVision™ FLEX Target Retrieval Solution, low pH 6.0 for 53 minutes</td>
<td>C1 (prediluted, pH 8.0) antigen retrieval solution (Ventana) performed on the BenchMark ULTRA automated slide stainer for 64 minutes at 100°C</td>
</tr>
<tr>
<td>Blocking</td>
<td>FLEX peroxidase for 5 minutes</td>
</tr>
<tr>
<td>Primary antibody incubation</td>
<td>Primary antibody incubation</td>
</tr>
<tr>
<td>Mouse anti-PD-L1 monoclonal antibody (Ref. M365329, Agilent) using a concentration of 1:50 (60 minutes at room temperature)</td>
<td>Mouse anti-PD-L1 monoclonal antibody (Ref. M365329, Agilent) using a concentration of 1:50 (32 minutes at 37°C)</td>
</tr>
<tr>
<td>Visualization</td>
<td>Visualization</td>
</tr>
<tr>
<td>EnVision FLEX + Mouse LINKER (30 minutes at room temperature)</td>
<td>OptiView DAB IHC Detection Kit + OptiView Amplification Kit (12 minutes)</td>
</tr>
<tr>
<td>EnVision FLEX HRP visualization reagent (30 minutes at room temperature)</td>
<td>DAB chromogen</td>
</tr>
<tr>
<td>DAB enhancer</td>
<td></td>
</tr>
<tr>
<td>Counterstaining</td>
<td>Counterstaining</td>
</tr>
<tr>
<td>Hematoxylin</td>
<td>Hematoxylin II Bluing Reagent</td>
</tr>
</tbody>
</table>

DAB = diaminobenzidine; HRP = horseradish peroxidase; IHC = immunohistochemistry; PD-L1 = programmed death-ligand 1
• ICCs of TPS on biopsy samples from 120 patients with NSCLC were between 0.987 and 0.999 when stained with 22C3 antibody-based LDTs on both platforms tested relative to the PD-L1 IHC 22C3 pharmDx kit on ASL48.

• Total percent agreement between biopsy and cytology samples from 70 patients with NSCLC using LDTs were as follows: 97.1% and 95.7% for the ≥1% and ≥50% TPS cut points, respectively, for both the ASL48 and BenchMark ULTRA platforms (TPS in each assay was independently evaluated by two pathologists).

• ICCs for TPS assessment in tumour biopsy and cytology samples using LDTs on the ASL48 and BenchMark ULTRA platforms are presented in Table 1.

• ICCs for TPS assessment in matched tumour biopsy and bronchial wash cytology samples using LDTs on the ASL48 and BenchMark ULTRA platforms and the PD-L1 IHC pharmDx 22C3 assay are presented in Table 2.

### Table 1. Intraclass correlation coefficients for evaluation of TPS in tumour biopsy and cytology samples using LDTs on the ASL48 and BenchMark ULTRA platforms*

<table>
<thead>
<tr>
<th></th>
<th>ASL48 LDT ICC</th>
<th>BenchMark ULTRA LDT ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pathologist A</td>
<td>Pathologist B</td>
</tr>
<tr>
<td>Biopsy vs. cytology samples (n = 70)</td>
<td>0.897</td>
<td>0.884</td>
</tr>
<tr>
<td>Cytology sample type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchial wash (n = 40)</td>
<td>0.963</td>
<td>0.951</td>
</tr>
<tr>
<td>Pleural effusion (n = 30)</td>
<td>0.830</td>
<td>0.815</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma (n = 48)</td>
<td>0.879</td>
<td>0.864</td>
</tr>
<tr>
<td>Squamous (n = 22)</td>
<td>0.966</td>
<td>0.962</td>
</tr>
</tbody>
</table>

* ICC = intraclass correlation coefficient; LDT = laboratory-developed test; TPS = tumour proportion score

### Table 2. Intraclass correlation coefficients for evaluation of TPS in matched tumour biopsy and bronchial wash cytology samples from 37 patients with NSCLC using LDTs on the ASL48 and BenchMark ULTRA platforms and the PD-L1 IHC pharmDx 22C3 assay on the ASL48 platform*

<table>
<thead>
<tr>
<th></th>
<th>ASL48 LDT ICC</th>
<th>BenchMark ULTRA LDT ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pathologist A</td>
<td>Pathologist B</td>
</tr>
<tr>
<td>Cytology LDT vs. PD-L1 IHC 22C3 pharmDx assay</td>
<td>0.944</td>
<td>0.936</td>
</tr>
<tr>
<td>Biopsy LDT vs. PD-L1 IHC 22C3 pharmDx assay</td>
<td>0.999</td>
<td>0.999</td>
</tr>
</tbody>
</table>

* ICC = intraclass correlation coefficient; IHC = immunohistochemistry; LDT = laboratory-developed test; NSCLC = non-small cell lung cancer; PD-L1 = programmed death-ligand 1; TPS = tumour proportion score

### Key conclusions

• Optimized protocols to determine PD-L1 expression in tumour biopsy and cytology specimens using the 22C3 antibody concentrate were developed on the ASL48 and BenchMark ULTRA IHC platforms.

• PD-L1 expression in tumour tissue samples determined using the 22C3 antibody concentrate on both ASL48 and BenchMark ULTRA autostainers showed high agreement (~100%) with the PD-L1 IHC 22C3 pharmDx assay at both TPS cut points evaluated.

• The optimized LDTs established on both the ASL48 and BenchMark ULTRA platforms exhibited approximately 90% agreement in TPS between biopsy and cytology samples at both cut points evaluated.

• The presented 22C3 antibody-based LDTs, optimized across multiple IHC platforms, may be used to evaluate PD-L1 expression in both biopsy and cytology samples.

  – This will increase the number of laboratories able to offer reliable, high quality PD-L1 testing to identify patients with NSCLC who are eligible for pembrolizumab monotherapy.

Bladder cancer is the fifth most common cancer in Canada, with urothelial carcinoma (UC) accounting for an estimated 90% of cases.1,2 Currently, the standard treatment for advanced or metastatic UC is platinum-based chemotherapy, including cisplatin- and carboplatin-based combinations.3 Though cisplatin-based combination chemotherapy is preferred, related toxicities and patient ineligibility pose a concern and there is no internationally-accepted standard of care following platinum-based chemotherapy.3,4 Among alternative treatment strategies, immune checkpoint inhibitors have recently emerged and have shown promising outcomes in various tumour types.5

Immune checkpoint proteins, such as programmed death-1 (PD-1), are receptors expressed on the surface of cytotoxic T cells that trigger the inhibition of T-cell-mediated death when bound to their respective ligands, in this case programmed death-ligand 1 (PD-L1).1,5 In patients with cancer, this signalling pathway may become dysfunctional and lead to immune surveillance evasion.5 Immune checkpoint inhibitors have been designed to block this interaction, thereby disrupting this signal and restoring anti-cancer T-cell activity.5 Among various immune checkpoint inhibitors currently being assessed in clinical trials, atezolizumab and pembrolizumab have been approved in Canada for the treatment of patients with locally advanced or metastatic UC, who have disease progression during or following platinum-based chemotherapy, or within 12 months of neoadjuvant or adjuvant treatment with platinum-based chemotherapy.6,7

Atezolizumab is a humanized, immunoglobulin G1 monoclonal anti-PD-L1 antibody that showed encouraging durable response rates, overall survival (OS) rates, and tolerability in cisplatin-ineligible patients in the IMvigor210 study.8 Despite these promising results, preliminary findings from the current phase III IMvigor 211 study failed to meet the primary endpoint (OS) in the atezolizumab arm, compared to chemotherapy.9 The other checkpoint inhibitor, pembrolizumab, is a highly selective, humanized monoclonal anti–PD-1 antibody that has previously demonstrated anti-tumour activity in the phase Ib KEYNOTE-12 study, and clinically meaningful and durable responses in cisplatin-ineligible patients in the phase II KEYNOTE-052 study.10,11

In this section, New Evidence reports the results of three studies presented at the European Society for Medical Oncology 2017 Congress, which focus on the efficacy and safety of pembrolizumab treatment for UC:

- In patients with recurrent UC following platinum-based chemotherapy, pembrolizumab treatment resulted in a significantly longer OS, higher overall response rate (ORR), and longer duration of response (DOR) compared with chemotherapy in the phase III KEYNOTE-045 study. (De Wit R, et al. ESMO 2017:LBA37)
- A post hoc analysis of the phase III KEYNOTE-045 study similarly demonstrated a significant benefit in OS, higher ORR, and longer DOR with pembrolizumab when compared individually to paclitaxel, docetaxel, and vinflunine chemotherapies. (Petrilak DP, et al. ESMO 2017:851PD)
- First-line therapy with pembrolizumab in a subgroup of senior cisplatin-ineligible patients with advanced UC and poor Eastern Cooperative Oncology Group performance status demonstrated ORR, OS, and progression-free survival rates comparable to those of the total patient population in the phase II KEYNOTE-052 trial. (Grivas P, et al. ESMO 2017:857P)
Background
In Canada, pembrolizumab is approved for the treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) who have disease progression during or following platinum-containing chemotherapy, or within 12 months of completing neoadjuvant or adjuvant platinum-containing chemotherapy.1 The KEYNOTE-045 trial was stopped prematurely after pembrolizumab was shown to significantly improve overall survival (OS) when compared with chemotherapy in this patient population.2 Mature results from the trial and subgroup analyses of pembrolizumab compared to each investigator’s choice of chemotherapy were presented at the ESMO 2017 Annual Congress.3,4

Study design
• KEYNOTE-045 was an international, open-label, phase III trial of pembrolizumab versus investigator’s choice of chemotherapy (paclitaxel, docetaxel, or vinflunine) in patients with advanced UC that had failed platinum-based chemotherapy.
• Key inclusion criteria were:
  ◦ Histologically or cytologically confirmed UC of the renal pelvis, ureter, bladder, or urethra;
  ◦ Disease progression after platinum-based chemotherapy or recurrence <12 months after periphereat platinum-based therapy;
  ◦ No more than two prior lines of systemic chemotherapy;
  ◦ Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2; and
  ◦ Provision of tumour sample for biomarker assessment.
• Patients were randomized 1:1 to receive pembrolizumab (200 mg intravenously every 3 weeks [q3w]) or investigator’s choice of paclitaxel (175 mg/m² q3w), docetaxel (75 mg/m² q3w), or vinflunine (320 mg/m² q3w).
• Patients were stratified based on ECOG PS, presence/absence of liver metastases, hemoglobin level, and time from last chemotherapy dose.
• Response was assessed at Week 9, then every six weeks for the first year, and every 12 weeks thereafter.
• The primary endpoints were overall survival (OS) and progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (blinded, independent central review).
• Secondary endpoints included objective response rate (ORR) per RECIST version 1.1 (blinded, independent central review), duration of response (DOR), and safety.
• Efficacy outcomes with pembrolizumab compared to chemotherapy were assessed in the total intention-to-treat population and in the subgroup of patients whose tumours expressed programmed death-ligand 1 (PD-L1).
• Safety with pembrolizumab compared to chemotherapy was assessed in all patients who received at least one dose of study treatment (as-treated population).
• The median duration of follow-up was 22.5 months for both pembrolizumab (range: 18.5–30.5) and chemotherapy (range: 18.2–29.3).
• Detailed inclusion and exclusion criteria can be found at https://clinicaltrials.gov/ct2/show/NCT02256436.

Key findings

Baseline characteristics and disposition
• A total of 270 patients were assigned to the pembrolizumab arm and 272 patients to the chemotherapy arm (paclitaxel, n = 84; docetaxel, n = 84; vinflunine, n = 87). (Figure 1)
• Baseline demographics were generally balanced between the treatment arms.
  - The median age was 67 years in the pembrolizumab arm and 65 years in the chemotherapy arm.
  - The majority of patients had an ECOG PS ≤1 (97.0% in the pembrolizumab arm and 97.1% in the chemotherapy arm).
  - First-line therapy was the most recent prior therapy in the majority of the patients in both arms (68.1% in pembrolizumab arm versus 58.1% in the chemotherapy arm).
  - The majority of patients in both arms had received cisplatin as prior platinum therapy (73.7% vs. 78.7%).
  - A PD-L1 combined positive score (CPS) of ≥10 was found in 27.4% of patients on pembrolizumab versus 33.1% of patients on chemotherapy.
• At the time of data analysis, all patients in the chemotherapy arm had discontinued treatment, whereas 9% of patients in the pembrolizumab arm continued to receive treatment.

Efficacy
• Median OS was significantly longer with pembrolizumab when compared with chemotherapy in all patients (10.3 months vs. 7.4 months) and in patients with CPS ≥10 (8.0 months vs. 5.2 months). (Figure 2)
  - A significant benefit in OS was also demonstrated in the pembrolizumab arm when compared to paclitaxel (7.0 months), docetaxel (7.4 months), and vinflunine (7.4 months) arms.
  - An OS benefit for the pembrolizumab arm was observed across all subgroups analyzed including age, hemoglobin levels, presence of visceral disease, and presence of liver metastases. An OS benefit was observed with pembrolizumab regardless of age, presence of liver metastases, hemoglobin levels, and presence of visceral disease.
• PFS was not significantly different between the pembrolizumab and chemotherapy groups or between the pembrolizumab group and each type of chemotherapy. (Figure 3)
  - In the pembrolizumab arm, a plateau can be seen in the tail of the Kaplan-Meier curve, representing a subset of patients with long-term benefit.
• The ORR was higher in patients receiving pembrolizumab when compared with those receiving chemotherapy in all patients (21.1% vs. 11.0%) and in patients with CPS ≥10 (20.3% vs. 6.7%).
• A similar trend was observed when the pembrolizumab arm was compared to each chemotherapy group (11.9% for paclitaxel, 6.0% for docetaxel, and 17.2% for vinflunine).

Figure 1. Patient disposition
Figure 2. Overall survival

- The median time to response was 2.1 months in both arms for all patients and 2.0 months in the pembrolizumab arm versus 2.1 months in the chemotherapy arm for patients with CPS ≥10.
- Responses were more durable with pembrolizumab than with chemotherapy in all patients and in patients with CPS ≥10 (median DOR not reached vs. 4.4 months [range: 1.4–24.0] for both).
  - The median duration of response in the paclitaxel, docetaxel, and vinflunine chemotherapy groups were 5.6 months (range: 2.8–20.9), 4.4 months (range: 1.4–20.8), and 4.3 months (range: 1.5–24.0), respectively.
  - Sixty-seven percent of the responses in the pembrolizumab arm lasted ≥12 months, compared to 38%, 38%, and 30% in the paclitaxel, docetaxel, and vinflunine arms, respectively.
- Responses were ongoing at data cutoff.
- In all patients, 57.9% were still responding in the pembrolizumab arm versus 20.0% in the chemotherapy arm.
- In patients with CPS ≥10, 73.3% were still responding in the pembrolizumab arm versus 33.3% in the chemotherapy arm.

Safety
- Fewer treatment-related adverse events (TRAEs) of any grade were observed in the pembrolizumab arm (62.0%) than the chemotherapy arm (90.6%). (Figure 4)
- This trend was also observed in subgroup analyses of the pembrolizumab arm versus each of the chemotherapy groups.
- TRAEs of grade ≥3 were observed in 16.5% of patients in the pembrolizumab arm versus 50.2% in the chemotherapy arm (44.0% for paclitaxel, 54.8% for docetaxel, and 51.7% for vinflunine).
• Some TRAEs demonstrated a primary drug association.
• Immune-mediated adverse events (AEs) were observed in 19.5% of patients in the pembrolizumab arm versus 7.5% in the chemotherapy arm (6.0% for paclitaxel, 8.3% for docetaxel, and 8.0% for vinflunine). (Figure 4)
• The discontinuation rate due to TRAEs was 7.1% in the pembrolizumab arm versus 12.5% in the chemotherapy arm (10.7% for paclitaxel, 11.9% for docetaxel, and 14.9% for vinflunine).
• There were eight deaths due to TRAEs: four patients in the pembrolizumab arm, one patient in the paclitaxel arm, and three patients in the vinflunine arm.

![Figure 3. Progression-free survival](image-url)
Figure 4. Treatment-related (A; ≥10% of patients) and immune-mediated adverse events (B; ≥2% of patients) in either treatment arm

Key conclusions

- Pembrolizumab is the first immunotherapy to demonstrate a superior, clinically meaningful OS benefit when compared with paclitaxel, docetaxel, and vinflunine chemotherapies.

- However, no statistically significant PFS difference was observed.

- ORR continues to be higher and responses are more durable with pembrolizumab when compared with any of the chemotherapies assessed.

- The median DOR was not reached in the pembrolizumab group, whereas the response ranged between 4.3 and 5.6 months in the chemotherapy groups.

- The results in patients with PD-L1 CPS ≥10 were consistent with the primary analysis.

- No new safety signals were identified in KEYNOTE-045 and pembrolizumab continues to demonstrate a better safety profile than chemotherapy.

- Overall, pembrolizumab should be considered a standard of care in patients with advanced UC after failure on platinum-based therapy.

Background

Previous results from the phase II KEYNOTE-052 study exhibited clinically meaningful anti-tumour activity following pembrolizumab treatment in cisplatin-ineligible patients with advanced urothelial cancer (UC), with an objective response rate (ORR) of 29% and an unmet median duration of response (DOR) after a median follow-up of 8 months. Subsequent analyses of the anti-tumour activity and safety of pembrolizumab treatment in senior patients (aged ≥65 years and ≥75 years) with poor Eastern Cooperative Oncology Group performance status (ECOG PS) were presented at the ESMO 2017 Annual Congress.

Study design

- KEYNOTE-052 was a phase II, open-label trial.
- Eligibility criteria included:
  - Histologically or cytologically confirmed advanced, unresectable, or metastatic UC of the renal pelvis, ureter, bladder, or urethra (with transitional and mixed transitional/non-transitional cell histologies);
  - Cisplatin ineligibility;
  - Lack of prior systemic chemotherapy for advanced or metastatic UC;
  - ECOG PS of 0–2;
  - Measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; and
  - Obtainable tumour sample for biomarker analysis.
- Detailed inclusion and exclusion criteria can be found at https://clinicaltrials.gov/ct2/show/NCT02335424.
- Patients received intravenous infusions of 200 mg pembrolizumab every 3 weeks for 24 months or until confirmed disease progression, intolerable toxicity, or withdrawal as per physician/patient choice.
- Response assessment was conducted at Week 9, then every six weeks for the first year and every 12 weeks thereafter.
- The primary endpoint was ORR assessed by central imaging vendor review according to RECIST version 1.1.
- Secondary endpoints were DOR, overall survival (OS), progression-free survival (PFS), and safety.
- Secondary efficacy endpoints were assessed by central imaging vendor review according to RECIST version 1.1.
- Tumour programmed death-ligand 1 (PD-L1) expression was defined as having a combined positive score (CPS) of ≥10.
- This cutoff was established based on the first 100 patients enrolled, and validated by determining ORR in all subsequent patients.
- Efficacy and safety analyses were conducted on the following four patient groups:
  - Aged ≥65 years;
  - Aged ≥75 years;
  - Aged ≥65 years with an ECOG PS of 2; and
  - Aged ≥75 years with an ECOG PS of 2.

Key findings

Baseline characteristics and disposition

- Of the 370 patients that were treated, 82% were aged ≥65 years, 48% were aged ≥75 years, 32% were aged ≥65 years with an ECOG PS of 2, and 21% were aged ≥75 years with an ECOG PS of 2.
- The percentage of patients receiving ongoing treatment as of the data cut-off date (March 9, 2017) was comparable among the patient groups, with 24%, 17%, 21%, and 19% of patients aged ≥65 years, ≥75 years, ≥65 years with an ECOG PS of 2, and ≥75 years with an ECOG PS of 2, respectively, continuing treatment.
- Baseline characteristics were comparable among the patient groups, with the exception of reasons for cisplatin ineligibility.
- Renal dysfunction and ECOG PS of 2 were the majority of reasons for cisplatin ineligibility for patients aged ≥65 years (80%) and ≥75 years (80%), whereas ECOG PS of 2 and the combination of ECOG PS of 2 and renal dysfunction were the majority of reasons for patients aged ≥65 years with an ECOG PS of 2 (91%) and ≥75 years with an ECOG PS of 2 (89%).
- The median follow-up for all patients was 10 months.
Efficacy

- ORRs were comparable among all patient groups and with that of the total patient population, indicating that increased age or poor PS does not impact the ORR to pembrolizumab. (Figure 1)
  - Median ORRs were 29%, 27%, 29%, and 32% in patients aged ≥65 years, ≥75 years, ≥65 years with an ECOG PS of 2, and ≥75 years with an ECOG PS of 2, respectively.
  - An informal analysis of ORR in a small group of patients aged ≥85 years demonstrated a similar rate of 28%.
  - Higher ORRs were demonstrated by patients with a CPS ≥10, similar to results from the total patient population. (Figure 2)
    - Median ORRs were 52%, 50%, 52%, and 55% in patients with a CPS ≥10 and aged ≥65 years, ≥75 years, ≥65 years with an ECOG PS of 2, and ≥75 years with an ECOG PS of 2, respectively.

- Across all patient subsets, a similar proportion of patients exhibited a reduction in tumour size.
- The median time to response and DOR were comparable among all patient groups.
  - All groups exhibited a median time to response of 2.1 months.
  - The response duration was not reached for patients aged ≥65 years, ≥75 years, and ≥65 years with an ECOG PS of 2, though patients aged ≥75 years with an ECOG PS of 2 had a median DOR of 9.7 months (range: 2.8–19.6).
  - The proportion of patients with responses lasting ≥6 months was 83%, 77%, 76%, and 72% for patients aged ≥65 years, ≥75 years, ≥65 years with an ECOG PS of 2, and ≥75 years with an ECOG PS of 2, respectively.
OS and PFS of all patient groups were similar to those of the total study population, indicating that poor PS or advanced age did not impact these factors.

- OS rates of 67%, 64%, 56%, and 55% were demonstrated at Month 6 by patients aged ≥65 years, ≥75 years, ≥65 years with an ECOG PS of 2, and ≥75 years with an ECOG PS of 2, respectively.
- PFS rates of 34%, 32%, 33%, and 32% were exhibited at Month 6 by patients aged ≥65 years, ≥75 years, ≥65 years with an ECOG PS of 2, and ≥75 years with an ECOG PS of 2, respectively.

### Safety

- The safety profile of pembrolizumab in patients with poor ECOG PS and advanced age was comparable to that of the total patient population. (Table 1)

- Similar incidences of Grade 3–5 treatment-related adverse events (TRAEs) were exhibited by patients aged ≥65 years (20%), ≥75 years (18%), ≥65 years with an ECOG PS of 2 (20%), and ≥75 years with an ECOG PS of 2 (19%) as the total study population (19%).

- Though the most common TRAEs were shared between the patient subgroups, the incidence of some AEs differed with ECOG PS. (Table 2)

---

**Table 1. Summary of adverse events**

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Age subgroups</th>
<th>Age/ECOG PS 2 subgroups</th>
<th>Total population N = 370</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age ≥65 years n = 302</td>
<td>Age ≥75 years n = 179</td>
<td>Age ≥65 years with ECOG PS 2 n = 119</td>
</tr>
<tr>
<td>TRAE, any grade</td>
<td>204 (68)</td>
<td>122 (68)</td>
<td>70 (59)</td>
</tr>
<tr>
<td>TRAE, grades 3–5</td>
<td>59 (20)</td>
<td>33 (18)</td>
<td>24 (20)</td>
</tr>
<tr>
<td>Serious TRAE</td>
<td>31 (10)</td>
<td>21 (12)</td>
<td>15 (13)</td>
</tr>
<tr>
<td>Immune-mediated AE*</td>
<td>67 (22)</td>
<td>33 (18)</td>
<td>19 (16)</td>
</tr>
<tr>
<td>Discontinued due to a TRAE</td>
<td>22 (7)</td>
<td>15 (8)</td>
<td>10 (8)</td>
</tr>
<tr>
<td>Died due to a TRAE</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
</tbody>
</table>

AE = adverse event; ECOG PS = Eastern Cooperative Oncology Group performance status; TRAE = treatment-related adverse event

AEs graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

* AEs of potentially drug-related immunologic causes reported regardless of attribution by the investigator.

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**Table 2. Treatment-related AEs occurring in ≥5% of patients**

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Age subgroups</th>
<th>Age/ECOG PS 2 subgroups</th>
<th>Total population N = 370</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age ≥65 years n = 302</td>
<td>Age ≥75 years n = 179</td>
<td>Age ≥65 years with ECOG PS 2 n = 119</td>
</tr>
<tr>
<td>Fatigue</td>
<td>57 (19)</td>
<td>32 (18)</td>
<td>12 (10)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>54 (18)</td>
<td>32 (18)</td>
<td>15 (13)</td>
</tr>
<tr>
<td>Rash</td>
<td>37 (12)</td>
<td>16 (9)</td>
<td>8 (7)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>33 (11)</td>
<td>21 (12)</td>
<td>9 (8)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>28 (9)</td>
<td>11 (6)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25 (8)</td>
<td>12 (7)</td>
<td>10 (8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>24 (8)</td>
<td>12 (7)</td>
<td>7 (6)</td>
</tr>
</tbody>
</table>

AE = adverse event; ECOG PS = Eastern Cooperative Oncology Group performance status
A Canadian Perspective by Dr. Michael Ong on the KEYNOTE-045 and KEYNOTE-052 trials that assessed the efficacy and safety of pembrolizumab in patients with urothelial carcinoma

The therapeutic landscape of metastatic urothelial carcinoma (mUC) is rapidly changing with the introduction of immune checkpoint inhibitors (ICIs). Nevertheless, mUC remains a challenging cancer to treat, and the selection of a suitable therapy is dependent on factors including comorbidities and specific goals of care, which may focus on the survival advantage of treatment, quality of life, and patient preferences. Options for mUC treatment include chemotherapy with cisplatin, carboplatin, taxanes, or vinflunine; anti-programmed death-1 (PD-1) receptor and anti-programmed death-ligand 1 (PD-L1) ICIs; radiotherapy; and clinical trials. In Canada, cisplatin-based chemotherapy is the standard of care for fit patients with advanced mUC in the first-line setting. For patients who are cisplatin-ineligible due to renal dysfunction, neuropathy, hearing deficit, or poor performance status, carboplatin chemotherapy is an alternative. Before the introduction of ICIs, second-line treatment options for mUC were chemotherapy with taxanes (in Ottawa, we use paclitaxel) or vinflunine (not typically used in Canadian practice). However, recent data regarding ICIs suggest that both anti–PD-1 and anti–PD-L1 treatments likely have similar or improved antitumour activity over chemotherapy, with improved tolerability.

The international phase III KEYNOTE-045 trial examined the efficacy and safety of pembrolizumab (200 mg every three weeks [q3w]) in comparison with investigator’s choice of paclitaxel (175 mg/m² q3w), docetaxel (75 mg/m² q3w), or vinflunine (320 mg/m² q3w) in patients with advanced mUC that recurred or progressed following platinum-based chemotherapy.1 The primary endpoints were overall survival (OS) and progression-free survival (PFS). Secondary endpoints included objective response rate (ORR), duration of response (DOR), and safety.

The main result of this study was the significant improvement in median OS with pembrolizumab compared to investigator’s choice of chemotherapy (10.3 months vs. 7.4 months, respectively; hazard ratio [HR] = 0.70; p = 0.0003). This result is particularly important as this is the first study to demonstrate improved survival in the second-line setting of UC therapy. There was no significant difference in PFS between the two arms, but patients in the pembrolizumab group exhibited a longer DOR (not reached vs. 4.4 months) and higher ORR (21.1% vs. 11.0%) compared to chemotherapy. Finally, the treatment-related adverse event profile was improved in the pembrolizumab treatment group (62.0%) compared to the chemotherapy group (90.6%).

In a post hoc analysis of the KEYNOTE-045 trial, the efficacy and safety of pembrolizumab was compared to each chemotherapy (paclitaxel, docetaxel, and vinflunine).2 The benefit in median OS obtained with pembrolizumab compared to each chemotherapy was consistent with original findings, as paclitaxel (7.0 months), docetaxel (7.4 months), and vinflunine (7.4 months) exhibited similar results.

Though there was no significant difference in median PFS between pembrolizumab and each chemotherapy arm, it is important to consider the different mechanisms of action of chemotherapy and anti–PD-1 antibody therapy. Though chemotherapy initially shrinks the tumour by eliminating sensitive cancer cells, it is later followed by an expansion of chemotherapy-resistant tumour cells, resulting in a PFS curve with an initial plateau followed by a gradual drop. In contrast, anti–PD-1 antibody therapy augments the pre-existing inflammatory response to the tumour, specifically benefiting a small group of patients with this response. As many patients have very little to no benefit in PFS, the PFS curve shows an initial sharp drop, followed by a plateau, representing the group experiencing therapeutic benefit. Thus, the absence of a significant difference does not indicate the lack of a therapeutic effect; rather, these results suggest that median PFS is not an effective parameter to assess patient benefit following this type of therapy.

Data from the KEYNOTE-045 study demonstrate evidence of patient benefit in all subgroups, with an impressive OS benefit and manageable safety profile exhibited with pembrolizumab.
treatment, compared to chemotherapy. In the similarly-designed phase III IMvigor211 trial, which evaluated atezolizumab (a PD-L1 inhibitor) compared to single-agent chemotherapy in a similar patient population as KEYNOTE-045, the results favoured atezolizumab in the intention-to-treat population (OS: 8.6 vs. 8.0 months; HR: 0.85; p = 0.038). While the IMvigor211 study did not meet its primary endpoint of improved median OS in a patient cohort with high PD-L1 expression, there was still evidence of benefit for patients including good tolerability of treatment, antitumour activity, long DOR, and a benefit of atezolizumab over taxane chemotherapy. These results demonstrate that anti–PD-1/PD-L1 ICIs are a new standard treatment strategy in the second-line setting for mUC.

Pembrolizumab has also been evaluated in the first-line setting for patients with advanced mUC who are ineligible for cisplatin therapy. The phase II KEYNOTE-052 study investigated the efficacy and safety of first-line pembrolizumab in a cisplatin-ineligible patient population with advanced mUC, poor Eastern Cooperative Oncology Group performance status (ECOG PS), a creatinine clearance (CrCl) rate of ≥30 to <60 mL/min, and grade ≥2 neuropathy or hearing loss. The patient inclusion criteria address an important patient demographic seen in my clinic, including geriatric patients with comorbidities, patients with chronic vasculopathy due to diabetes or hypertension leading to renal dysfunction, and patients with upper tract UC post nephroureterectomy and disease recurrence.

Patients included in the KEYNOTE-052 study received 200 mg pembrolizumab every 3 weeks for 24 months or until confirmed disease progression, intolerable toxicity, or withdrawal. The primary endpoint was ORR, and the secondary endpoints were DOR, OS, PFS, and safety. The median ORRs were 29% in patients aged ≥65 years, 27% in patients aged ≥75 years, 29% in patients aged ≥65 years with an ECOG PS of 2, and 32% in patients aged ≥75 years with an ECOG PS of 2. Interestingly, higher ORRs were exhibited by patients with PD-L1 combined positive scores ≥10 in all subgroups (50%–55%). In terms of safety, the rates of grade 3–5 treatment-related adverse events were 20%, 18%, 20%, and 19% in patients aged ≥65 years, ≥75 years, ≥65 years with an ECOG PS of 2, and ≥75 years with an ECOG PS of 2, respectively. These results indicated that pembrolizumab was highly active and well tolerated in the first-line setting in cisplatin-ineligible patients.

Considering data from both KEYNOTE trials, the safety profile of pembrolizumab is an improvement over standard chemotherapy in the majority of patients. Though unexpected and more serious toxicities requiring management are possible, grade 5 events were extremely rare in these studies and there were no concerning safety signals presented. However, it is important to consider the conservative language of clinical trial inclusion criteria, as it may not reflect the scope of patients seen in the “real world”. Thus, vigilance is necessary when applying data from clinical trials in broader practice.

While the clinical trial data for pembrolizumab as a new standard of care for post-platinum and platinum-ineligible patients are compelling, the cost associated with this therapy remains an obstacle, as public reimbursement is not available at this time (at least in Ontario). Furthermore, there are several unmet needs in this disease setting. Though there is a significant improvement in survival outcomes with anti–PD-1 therapy, the number of patients benefiting with disease response remains relatively low (approximately 20%); thus, clinical trials with new or combination therapies are required for further improvement. Additional clinical trials are also necessary to determine the ideal duration of therapy and tolerability in patients with modest autoimmune comorbidities (i.e., psoriasis/psoriatic arthritis).

The higher ORRs demonstrated in the KEYNOTE-052 study, compared to KEYNOTE-045, should also prompt the examination of clinical characteristics that may assist in the selection of patients most likely to benefit from anti–PD-1/PD-L1 antibody therapy. For example, in patients with Lynch syndrome, presence of upper tract disease and mismatch repair deficiencies are strongly correlated with an enhanced benefit from ICI therapy. In some analyses, a high burden of cigarette smoking was also associated with treatment benefit.

Naturally there is significant interest in biomarker development, such as PD-L1 status and tumour mutational burden, to improve patient selection and enhance patient benefit. PD-L1 expression is likely both prognostic and predictive, but current clinical trial data are conflicting in terms of the utility of PD-L1 as a biomarker. Data from the KEYNOTE-045 study suggested that tumour PD-L1 expression was not associated with enhanced benefit from therapy, whereas data from the KEYNOTE-052 trial suggested a connection between a higher ORR and PD-L1 combined positive score of ≥10. Though a similar positive association has also been demonstrated in other studies, results may have been influenced by study inclusion criteria and additional research is required prior to routine use.

Overall, results from the KEYNOTE-045 study support the use of pembrolizumab as a new standard of care in advanced mUC in the second-line setting. For cisplatin-ineligible patients with advanced mUC, the KEYNOTE-052 study also demonstrated compelling results for the use of pembrolizumab in the first-line setting. However, access to pembrolizumab may be heterogeneous without standard public funding for these new therapy indications, and a number of suitable alternatives (i.e., atezolizumab, clinical trials, and systemic chemotherapy) are available. Hopefully the treatment paradigm of today will soon be another page in history as clinical trials evaluate ICIs and ICI combinations in the first-line and (neo)adjuvant settings.

New Evidence in Oncology

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Other Malignancies

New Therapies Improve Outcomes in Multiple Cancers

In recent years, new strategies for treating cancer have improved patient outcomes in a wide variety of tumour types. Examples of recent innovations include the use of immunotherapy and the development of encapsulated chemotherapeutic drugs.

The role of the immune system in controlling cancer has been well defined over the past decade. Dysfunctional tumour-immune interactions lead to immunity evasion and subsequent tumourigenesis/metastasis.1 One such example is the programmed death-1 (PD-1) pathway, which is frequently co-opted by tumour cells and leads to inhibition of active T-cell-mediated immune surveillance.2 High expression of the PD-1 ligand programmed death-ligand 1 (PD-L1) on tumour cells correlates with poor prognosis and survival in various cancer types.3 Pembrolizumab is a highly selective, humanized monoclonal anti–PD-1 antibody designed to block the interaction between PD-1 and its ligands. The KEYNOTE group of trials has demonstrated the antitumour activity and safety of pembrolizumab across a wide range of cancers.4

Systemic chemotherapy is an established cancer treatment that is known to have wide-ranging side effects. Recently, liposomal constructs have been engineered to encapsulate chemotherapy drugs, which improves drug distribution and minimizes toxicity. Nanoliposomal irinotecan (nal-IRI), in combination with 5-fluorouracil and leucovorin (5-FU/LV), was shown to significantly improve overall survival in patients with previously treated metastatic pancreatic ductal adenocarcinoma (mPDAC) compared to 5-FU/LV alone in the phase III NAPOLI-1 trial.5

New Evidence reported on the results of six studies, presented at the 2017 European Society for Medical Oncology (ESMO) Congress, which focused on the use of pembrolizumab and nal-IRI across multiple cancers, as well as outcome biomarkers for these therapies:

- An exploratory post hoc analysis of the randomized phase II KEYNOTE-002 trial found that best responses to pembrolizumab were durable and evolved over time in patients with ipilimumab-refractory melanoma. (Daud A, et al. ESMO 2017:1224PD)
- Results from a Swiss retrospective registry study of pembrolizumab in patients with relapsed malignant pleural mesothelioma were promising, with survival outcomes that were comparable to currently available treatment options. (Mauri LA, et al. ESMO 2017:1615O)
- Updated results from the phase II KEYNOTE-059 study demonstrated promising antitumour activity with pembrolizumab in patients with advanced gastric or gastroesophageal junction adenocarcinoma, both as monotherapy and in combination with chemotherapy. (Wainberg ZA, et al. ESMO 2017:LBA28_PR)
- A post hoc analysis of the NAPOLI-1 trial found that survival outcomes were significantly increased in patients with mPDAC who had a low (vs. high) baseline neutrophil-to-lymphocyte ratio and who were treated with the combination of nal-IRI and 5-FU/LV. (Hubner R, et al. ESMO 2017:741P)
- An analysis of health-related quality of life showed clinically meaningful improvements in patients with classic Hodgkin lymphoma who responded to pembrolizumab treatment in the KEYNOTE-087 study. (Wu E, et al. ESMO 2017:1119P)
- The phase Ib KEYNOTE-028 study demonstrated that T-cell inflamed gene expression profile score, PD-L1 expression, and mutational load were predictive of response to pembrolizumab in patients with one of 20 different types of PD-L1–positive advanced solid tumours. (Ott PA, et al. ESMO 2017:84PD)

Background
Checkpoint inhibitor treatment results in durable responses and deepening of responses over time.1–3 In the randomized phase II KEYNOTE-002 study, pembrolizumab significantly improved progression-free survival (PFS) compared with chemotherapy in patients with ipilimumab-refractory melanoma.3 Pembrolizumab also demonstrated durable responses and a manageable safety profile.3 An exploratory post hoc analysis of these results was presented at the ESMO 2017 Congress, which assessed the evolution of response and survival by best overall response in the patients from KEYNOTE-002 treated with pembrolizumab.4

Study design
• Patients with ipilimumab-refractory melanoma were randomized to receive pembrolizumab 2 mg/kg or 10 mg/kg (n = 361) or investigator’s choice of one of five chemotherapy regimens (n = 179).
• Patients were treated until disease progression or unacceptable toxicity.
  ◦ Patients with disease progression in the chemotherapy arm were allowed to cross over to the pembrolizumab arm.
• In the post hoc analysis, response was assessed at Week 12, every six weeks until Week 48, and then every 12 weeks thereafter.
  ◦ Response was assessed by investigator review using Response in Evaluation Criteria in Solid Tumors version 1.1.
  ◦ Responses were confirmed by subsequent scan and were based on best overall response with confirmation.
• Survival was assessed every 12 weeks during follow-up.
• Given that there was no difference in efficacy between the doses, pembrolizumab arms were combined for analyses.
• Outcomes included PFS, overall survival (OS), and duration of response (DOR).

Key findings
Baseline characteristics and disposition
• As of February 3, 2017, the median follow-up was 42.7 months (range: 38.7–49.9) for all pembrolizumab-treated patients.
• Among all pembrolizumab-treated patients (all-treated population), median age was 61 years (range: 15–89).
  ◦ The majority of patients were male (59%), had stage M1c disease (82%), had normal lactate dehydrogenase levels (51%), and had more than one prior line of therapy (73%).
  ◦ Median tumour size was 94.5 mm (range: 10–560).
• Baseline characteristics in the subsets of patients who achieved a complete response (CR), partial response (PR), or stable disease (SD) were similar to the all-treated population.
• At the time of data cutoff, 22 patients (6%) in the all-treated population were still receiving pembrolizumab and nine patients were on treatment hold for observation.
  ◦ Patients discontinued treatment for the following reasons: progressive disease (57%), adverse events (19%), patient withdrawal (11%), physician decision (6%), and other (1%).

Efficacy
• Of the patients treated with pembrolizumab, 187 had a best overall response of CR, PR, or SD.
  • Median DOR was not reached in the all-treated population.
    ◦ Median time to response was 2.9 months (range: 1.9–27.9).
  • Nine patients with CR (31%), 28 patients with PR (40%), and 63 patients with SD (72%) had subsequent progression.
    ◦ In these patients, median DOR was:
      – For CR: 17.1 months (range: 5.5–36.1);
      – For PR: 7.7 months (range: 2.0–31.8); and
      – For SD: 5.8 months (range: 2.7–25.3).
• Time and duration of response to pembrolizumab in the CR, PR, and SD populations are summarized in Table 1.
• PFS and OS of the all-treated, CR, PR, and SD populations are summarized in Figures 1 and 2.

Safety
• No new safety signals were observed with long-term follow-up.
Table 1. Time to and duration of responses to pembrolizumab

<table>
<thead>
<tr>
<th>Patients with CR, n = 29*</th>
<th>Median, months (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to CR</td>
<td>2.9 (2.4–24.9)</td>
</tr>
<tr>
<td>Time from SD to CR (n = 5)</td>
<td>6.9 (3.9–21.9)</td>
</tr>
<tr>
<td>Time from PR to CR (n = 21)</td>
<td>8.0 (1.4–25.2)</td>
</tr>
<tr>
<td>Duration of CR</td>
<td>Not reached (5.5–41.6+)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients with PR, n = 70†</th>
<th>Median, months (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to PR</td>
<td>2.9 (1.9–27.9)</td>
</tr>
<tr>
<td>Time from SD to PR (n = 28)</td>
<td>2.7 (0.9–25.2)</td>
</tr>
<tr>
<td>Duration of PR</td>
<td>Not reached (1.9+ to 43.5+)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients with SD, n = 88‡</th>
<th>Median, months (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of SD</td>
<td>6.9 (0.8+ to 38.8+)</td>
</tr>
</tbody>
</table>

AE = adverse event; CR = complete response; PR = partial response; SD = stable disease

* Of 20 patients without progression, 14 discontinued because of an AE (n = 3) or patient/physician decision (n = 11).
† Of 42 patients without progression, 29 discontinued because of an AE (n = 15) or patient/physician decision (n = 14).
‡ Of 25 patients without progression, 24 discontinued because of an AE (n = 11) or patient/physician decision (n = 14).

Figure 1. PFS in all pembrolizumab-treated patients and in those with a best response of CR, PR, or SD

Figure 2. OS in all pembrolizumab-treated patients and in those with a best response of CR, PR, or SD

Key conclusions

• Responses to pembrolizumab were durable and associated with prolonged OS in patients with ipilimumab-refractory melanoma.

• Even in these heavily pretreated patients, best response evolved over time with late conversions from SD to PR/CR and from PR to CR observed.

Pembrolizumab as second- or further-line treatment in relapsed malignant pleural mesothelioma: A Swiss registry

Background
Programmed death (ligand)-1 (PD-L1) checkpoint inhibitors have demonstrated promising activity for patients with malignant pleural mesothelioma (MPM) in early clinical trials, leading to the off-label use of pembrolizumab in Switzerland as second- or further-line treatment in patients with MPM. Data from a retrospective registry study on pembrolizumab use in patients with MPM in Switzerland were presented at the ESMO 2017 Annual Congress.

Study design
• This registry study was a retrospective analysis of data on patients with relapsed MPM who received pembrolizumab in 13 cancer centres in Switzerland.
• Response outcomes for pembrolizumab were assessed by the local investigators using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.
• PD-L1 expression was quantified in a central laboratory using antibody SP263 (Ventana).

Key findings
Baseline characteristics and disposition
• Data were collected on 48 patients who received pembrolizumab for relapsed MPM between September 2015 and April 2017.
• The median age at diagnosis was 68.5 years (range: 25–86), 96% of patients were male, and 18 patients (39%) had an Eastern Cooperative Oncology Group performance status (ECOG PS) ≥2 at the start of pembrolizumab treatment.
• Pembrolizumab was the second-line treatment in 31 patients (65%).
• Platinum chemotherapy and pemetrexed was given to 46 patients (96%) in a prior line of therapy.
• The median time since diagnosis was 8.7 months (interquartile range: 6.9–18.1).
• Doses of pembrolizumab included:
  • 10 mg/kg every two weeks (q2w) (5 patients, 10%);
  • 200 mg q2w (1 patient, 2%);
  • 2 mg/kg q2w (4 patients, 8%);
  • 200 mg every three weeks (q3w) (28 patients, 58%); and
  • 2 mg/kg q3w (9 patients, 19%).
• The median duration of treatment was 3.0 months (95% CI: 2.7–4.1) and treatment is ongoing in eight patients.

Efficacy
• At a median follow-up of 8.8 months, the overall response rate (ORR) in the total population was 25% (1 complete response and 11 partial responses).
• The disease control rate (DCR) was 52%, including 13 patients with stable disease.
• The median progression-free survival (PFS) and median overall survival (OS) in the total population were 3.6 months (95% CI: 2.6–5.5) and 7.2 months (95% CI: 4.9–10.2), respectively. (Figure 1)
  • The 3-month and 6-month PFS rates were 57% (95% CI: 44–73) and 30% (95% CI: 19–47), respectively.
  • The 6-month and 12-month OS rates were 63% (95% CI: 50–79) and 21% (95% CI: 10–47), respectively.
• Response and survival outcomes by subgroup are listed in Table 1.
• Of the 28 patients with epithelioid histology, 24 patients (86%) had less than 5% membraneous PD-L1 staining of their tumour cells. (Figure 2)
Table 1. Outcomes by subgroup

<table>
<thead>
<tr>
<th>Performance status and line of treatment</th>
<th>ORR (%)</th>
<th>DCR (%)</th>
<th>Median PFS, months (95% CI)</th>
<th>HR PFS (95% CI)</th>
<th>Median OS, months (95% CI)</th>
<th>HR OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG PS 0/1 and ≤1 prior therapy n = 19 (40%)</td>
<td>42</td>
<td>74</td>
<td>5.3 (3.6–NA)</td>
<td>0.40 (0.20–0.81)</td>
<td>p = 0.01</td>
<td>10.2 (8.2–NA)</td>
</tr>
<tr>
<td>ECOG PS &gt;1 and &gt;1 prior therapy n = 27 (60%)</td>
<td>11</td>
<td>33</td>
<td>2.6 (1.9–4.8)</td>
<td>0.22 (0.07–0.76)</td>
<td>p = 0.016</td>
<td>4.9 (3.7–8.4)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epithelioid n = 35 (73%)</td>
<td>23</td>
<td>43</td>
<td>2.8 (2.1–4.2)</td>
<td>NA</td>
<td>7.2 (4.1–NA)</td>
<td>NA</td>
</tr>
<tr>
<td>Mixed n = 8 (17%)</td>
<td>13</td>
<td>63</td>
<td>4.4 (2.9–NA)</td>
<td>0.73 (0.30–1.78)</td>
<td>p = 0.489</td>
<td>6.8 (3.7–NA)</td>
</tr>
<tr>
<td>Sarcomatoid n = 5 (10%)</td>
<td>60</td>
<td>100</td>
<td>7.3 (7.2–NA)</td>
<td>0.22 (0.07–0.76)</td>
<td>p = 0.016</td>
<td>8.6 (6.8–NA)</td>
</tr>
<tr>
<td>PD-L1 quantification*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD-L1 &lt;5% n = 25 (67%)</td>
<td>16</td>
<td>32</td>
<td>2.6 (2.0–3.8)</td>
<td>NA</td>
<td>6.2 (3.7–NA)</td>
<td>NA</td>
</tr>
<tr>
<td>PD-L1 5%–49% n = 8 (22%)</td>
<td>63</td>
<td>88</td>
<td>4.9 (3.7–NR)</td>
<td>0.55 (0.23–1.31)</td>
<td>p = 0.177</td>
<td>7.9 (6.8–NR)</td>
</tr>
<tr>
<td>PD-L1 ≥50% n = 4 (11%)</td>
<td>50</td>
<td>100</td>
<td>6.7 (4.8–NR)</td>
<td>0.27 (0.08–0.93)</td>
<td>p = 0.039</td>
<td>9.3 (9.3–NR)</td>
</tr>
</tbody>
</table>

CI = confidence interval; DCR = disease control rate; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; NA = not available; NR = not reached; ORR = overall response rate; OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = progression-free survival

* PD-L1 expression was quantified as the percentage of tumour cells with membranous PD-L1 staining.

Safety

- Fifteen treatment-related adverse events (TRAEs) were observed in 14 patients (29%).
- The most common grade 1/2 TRAEs included fatigue (3 patients, 6%), dyspnea (2 patients, 4%), and diarrhea/colitis (2 patients, 4%).
- Five grade 3/4 TRAEs were observed (one event of each non-cardiac chest pain, heart failure, and nephrotic syndrome; two events of hepatitis), four of which were resolved.
- Seven patients (15%) discontinued pembrolizumab due to TRAEs.

Figure 2. PD-L1 quantification and association with histology

Key conclusions

- The response rate (ORR 25%) and survival outcomes (in selected patients) with pembrolizumab in this Swiss registry trial were comparable to early clinical trial data with PD-(L)1 inhibitors.1,2,4
- Survival outcomes in the unselected population (“real-life” setting) were promising compared to available second-line and beyond treatment options (median PFS = 3.6 months, median OS = 7.2 months).
- Patients with an ECOG PS of 0/1 receiving pembrolizumab in the second line benefitted substantially from treatment (median PFS = 5.3 months, median OS = 10.2 months).
- Sarcomatoid histology might be predictive of better outcomes with pembrolizumab and higher PD-L1 expression correlated with better outcomes.
- PD-L1 expression was significantly associated with histology.
- Ongoing prospective randomized control trials will help to elucidate the role of checkpoint inhibitors in MPM.

Background

Previous results from the phase II KEYNOTE-059 study demonstrated manageable safety and promising antitumour activity for pembrolizumab alone and pembrolizumab plus chemotherapy in patients with recurrent or metastatic gastric or gastroesophageal junction adenocarcinoma (G/GEJ). An updated analysis of these results was presented at the ESMO 2017 Annual Congress.

Study design

- KEYNOTE-059 is a global, multicohort, phase II study evaluating pembrolizumab alone and in combination with chemotherapy in patients with recurrent or metastatic G/GEJ.
- In cohort 1 and 2, patients were enrolled regardless of tumour programmed death-ligand 1 (PD-L1) expression.
- In cohort 3, only patients with PD-L1–positive tumours were enrolled.
- PD-L1–positive expression was defined as having a combined positive score (CPS) of ≥1% using the PD-L1 immunohistochemistry 22C3 pharmDx assay (Agilent Technologies).
  - CPS was calculated as the number of PD-L1–positive cells (tumour cells, lymphocytes, and macrophages) divided by the total number of tumour cells, multiplied by 100.
- Primary endpoints were safety (all three cohorts) and overall response rate (ORR) by central review per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (cohorts 1 and 3).
- For response assessment per RECIST version 1.1, the first scan was performed nine weeks after Cycle 1, followed by every six weeks for the first year, and every nine weeks thereafter.
- Key secondary endpoints included:
  - ORR (cohort 2);
  - Duration of response (DOR) by RECIST version 1.1;
  - Progression-free survival (PFS); and
  - Overall survival (OS).
- Inclusion and exclusion criteria can be found at https://clinicaltrials.gov/ct2/show/NCT02335411.

Key findings

- At data cutoff (April 21, 2017), the median follow-up for cohorts 1 (259 patients), 2 (25 patients), and 3 (31 patients) was 5.6 months (range: 0.5–24.7), 13.8 months (range: 1.8–24.1), and 17.5 months (range: 1.7–20.7), respectively.

Cohort 1 (N = 259)

- The median age of patients was 62 years (range: 24–89).
In terms of prior therapies, 134 (52%), 75 (29%), and 50 (19%) patients had 2, 3, and 4 or greater prior therapies, respectively.

In terms of PD-L1 expression, 148 patients (57%) were positive and 109 patients (42%) were negative for PD-L1 expression.

Response rates in all patients and by PD-L1 expression are reported in Table 1.

- Of the 134 patients who received pembrolizumab as third-line therapy, ORR was 16% and the disease control rate (DCR) was 31%.
- Of the 125 patients who received pembrolizumab as fourth-line or greater therapy, ORR was 7% and DCR was 23%.
- Of the 223 patients with measurable disease per RECIST version 1.1 at baseline who had one or more post-baseline assessment, 95 patients (42%) experienced a reduction in target lesion size.
- Of the 31 patients with confirmed response, the DOR was 14.2 months (range: 2.4–19.4+).

The median PFS in all patients was 2.0 months (95% CI: 2.0–2.1) and the 6-month PFS rate was 14.6%.

The median OS in all patients was 5.5 months (95% CI: 4.2–6.5) and the 6-month OS rate was 45.7%.

PFS and OS results by PD-L1 expression are presented in Figure 1.

Treatment-related adverse events (TRAEs) were reported in 159 patients (61%), with 46 patients (18%) experiencing grade 3–5 TRAEs, and 29 patients (11%) experiencing serious TRAEs.

- Seven patients (3%) experienced grade 3 anemia, 6 patients (2%) experienced grade 3 fatigue, and 3 patients (1%) experienced grade 3 dehydration.
- Treatment led to discontinuation in 7 patients (3%) and death in 2 patients (1 patient acute kidney injury, 1 patient pleural effusion).
- Immune-mediated adverse events and infusion-related reactions occurred in 19% of patients. (Table 2)

### Table 1. Response by cohort

<table>
<thead>
<tr>
<th>Response*, % (95% CI)</th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>N = 259</td>
<td>N = 25</td>
<td>N = 31</td>
</tr>
<tr>
<td>Response†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD-L1 positive‡</td>
<td>N = 148</td>
<td>N = 16</td>
<td>N = 8</td>
</tr>
<tr>
<td>PD-L1 negative</td>
<td>n = 109</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>12 (8–17)</td>
<td>60 (39–79)</td>
<td>26 (12–45)</td>
</tr>
<tr>
<td>DCR†</td>
<td>27 (22–23)</td>
<td>80 (59–93)</td>
<td>36 (19–55)</td>
</tr>
<tr>
<td>BOR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>3 (1–6)</td>
<td>3 (1–8)</td>
<td>13 (0–53)</td>
</tr>
<tr>
<td>PR</td>
<td>9 (6–13)</td>
<td>13 (8–19)</td>
<td>25 (3–65)</td>
</tr>
<tr>
<td>SD</td>
<td>16 (12–21)</td>
<td>15 (9–23)</td>
<td>19 (8–38)</td>
</tr>
<tr>
<td>PD</td>
<td>56 (49–62)</td>
<td>60 (50–69)</td>
<td>39 (22–58)</td>
</tr>
</tbody>
</table>

BOR = best overall response; CI = confidence interval; CPS = combined positive score; CR = complete response; DCR = disease control rate; ORR = overall response rate; PD = progressive disease; PD-L1 = programmed death-ligand 1; PR = partial response; SD = stable disease

* Only confirmed responses were included.
† CR + PR + SD ≥ 2 months in cohort 1, CR + PR + SD ≥ 6 months in cohorts 2 and 3.
‡ PD-L1 positive was defined as CPS ≥ 1, where CPS = ratio of PD-L1–positive cells (tumour cells, lymphocytes, and macrophages) to the total number of tumour cells × 100.

**Figure 1. PFS and OS by PD-L1 expression**
Cohort 2 (N = 25)

- The median age of patients was 64 years (range: 21–82).
- In terms of PD-L1 expression, 16 patients (64%) were positive and 8 patients (32%) were negative for PD-L1 expression.
- Response rates in all patients and by PD-L1 expression are reported in Table 1.
- Of the 25 patients with measurable disease per RECIST version 1.1 at baseline who had one or more post-baseline assessment, 24 patients (96%) experienced a reduction in target lesion size.
- The median DOR was 4.6 months (range: 2.6–20.3+).
- The median PFS in all patients was 6.6 months (95% CI: 5.9–10.6) and the 6-month PFS rate was 68.0%.
- The median OS in all patients was 13.8 months (95% CI: 8.6–not reached) and the 6-month OS rate was 76.0%.
- TRAEs were reported in all patients, with 19 patients (76%) experiencing grade 3/4 TRAEs.

- Grade 3/4 TRAEs included neutropenia (24%), stomatitis (20%), anemia (8%), decreased platelet count (8%), decreased appetite (8%), and fatigue (8%).
- Three patients (12%) discontinued treatment due to chemotherapy-related adverse events; however, no patients discontinued treatment because of pembrolizumab-related adverse events.
- Immune-mediated adverse events occurred in 48% of patients. (Table 2)

Cohort 3 (N = 31)

- The median age of patients was 62 years (range: 32–75).
- ORR was 26% (95% CI: 12–45) and DCR (complete response, partial response, and stable disease ≥ 6 months) was 36% (95% CI: 19–55). (Table 1)
- Of the 31 patients with measurable disease per RECIST version 1.1 at baseline who had one or more post-baseline assessment, 24 patients (77%) experienced a reduction in target lesion size (assessments were not available for 3 patients).

### Table 2. Immune-mediated adverse events* and infusion-related reactions by cohort

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>All grades in &gt;2 patients</th>
<th>Grade 3†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>50 (19)</td>
<td>13 (5)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>24 (9)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>9 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Colitis</td>
<td>4 (2)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Infusion-related reactions</td>
<td>4 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>4 (2)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>3 (1)</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>All grades in &gt;2 patients</th>
<th>Grade 3 in all patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>12 (48)</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>4 (16)</td>
<td>0</td>
</tr>
<tr>
<td>Palmar-planter erythodysesthesia</td>
<td>2 (8)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Rash</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Maculopapular rash</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>All grades in &gt;2 patients</th>
<th>Grade 3</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>10 (32)</td>
<td>2 (7)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>4 (13)</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Colitis</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>0</td>
</tr>
</tbody>
</table>

* Based on a list of terms specified by the sponsor and included regardless of attribution to study treatment or immune relatedness by the investigator.
† Two patients (1%) experienced grade 3 rash; one patient (<1%) experienced grade 3 adverse events: uveitis, hepatitis, jaundice, encephalitis, and maculopapular rash.
‡ There were no grade 4/5 immune-mediated or infusion reactions.
• The median DOR was 9.6 months (range: 2.1–17.8+).
• The median PFS in all patients was 3.3 months (95% CI: 2.0–6.0) and the 6-month PFS rate was 34.9%.
• The median OS in all patients was 20.7 months (95% CI: 9.2–20.7) and the 6-month OS rate was 72.9%.
• TRAEs were reported in 24 patients (77%), with 7 patients (23%) experiencing grade 3–5 TRAEs.

Grade 3 adverse events included neutropenia, diffuse uveal melanocytic proliferation, colitis, bile duct obstruction, decreased neutrophils, dehydration, hyponatremia, and rash (each experienced in 1 patient).

• One patient died of a TRAE event during safety follow-up (pneumonitis).
• Immune-mediated adverse events occurred in 32% of patients. (Table 2)

Key conclusions

• In patients with advanced G/GEJ adenocarcinoma:
  – Pembrolizumab monotherapy showed promising antitumour activity in patients whose disease had progressed after ≥2 prior lines of therapy and in previously untreated patients with PD-L1–positive tumours; and
  – Pembrolizumab in combination with chemotherapy demonstrated promising antitumour activity in previously untreated patients.
• Patients responded regardless of PD-L1 expression, but responses were higher in patients with PD-L1–positive tumours (cohorts 1 and 2).
• Safety was manageable and consistent with previous reports.
• Two randomized phase III trials studying pembrolizumab in G/GEJ are ongoing:
  – KEYNOTE-061: pembrolizumab versus paclitaxel in patients with advanced G/GEJ whose disease progressed after first-line therapy with platinum and fluoropyrimidine; and


Hubner R, et al. ESMO 2017:741P

Prognostic value of baseline neutrophil-to-lymphocyte ratio for predicting clinical outcome in metastatic pancreatic ductal adenocarcinoma patients treated with liposomal irinotecan plus 5-fluorouracil and leucovorin (5-FU/LV) vs. 5-FU/LV alone

Background

Neutrophils have been shown to inhibit the activity of T cells, which is associated with a poor prognosis, while tumour-infiltrating lymphocytes are associated with better outcomes in a variety of cancers. High peripheral blood neutrophil-to-lymphocyte ratio (NLR) is associated with a poor outcome in patients with pancreatic cancer. An exploratory post hoc analysis of the NAPOLI-1 trial assessed the relationship between NLR and overall survival (OS) in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) treated with nanoliposomal irinotecan (nal-IRI) and/or 5-fluorouracil and leucovorin (5-FU/LV). Results were presented at the ESMO 2017 Congress.
Study design

- NAPOLI-1 was a large phase III trial that evaluated nal-IRI alone and in combination with 5-FU/LV compared with 5-FU/LV alone for patients with mPDAC previously treated with gemcitabine-based therapy.7
- Patients were initially randomized to receive nal-IRI (120 mg/m² every three weeks) or 5-FU/LV (2,000/200 mg/m² weekly for four weeks of each six-week cycle).
- After 63 patients were enrolled, a third arm, nal-IRI (80 mg/m² every two weeks) plus 5-FU/LV (2,400/400 mg/m² every two weeks) was added.
- Treatment was continued until disease progression or unacceptable toxicity.
- Primary endpoint was OS.
- Key secondary endpoints included progression-free survival (PFS), objective response rate, and safety.
- The exploratory post hoc analysis was performed on patients from NAPOLI-1 who were enrolled in the study after the addition of the third arm, who received nal-IRI plus 5-FU/LV or 5-FU/LV alone, and who had baseline NLR data available.
- Data cutoff was November 16, 2015.
- Hazard ratios for OS comparisons based on high (>5) or low (≤5) baseline NLR in individual and pooled treatment arms were estimated by Cox regression analysis, and Fisher’s exact test was used for comparisons; p-values were descriptive.

Key findings

Baseline characteristics and disposition

- A total of 222 patients met the criteria of enrolling in the study after the third arm was added and received study drug; 221 (99%) of these had baseline NLR available.
- Median age was 62.2 years in the pooled population (NLR ≤5 and NLR >5 groups pooled by treatment arm).
- The majority of patients were male (56.1% in the pooled NLR ≤5 group and 59.1% in the pooled NLR >5 group), Caucasian (62.6% in the pooled NLR ≤5 group and 68.2% in the pooled NLR >5 group), and had received one prior line of metastatic therapy (56.1% in the pooled NLR ≤5 group and 54.5% in the pooled NLR >5 group).

Efficacy

- After pooling treatment arms, the NLR ≤5 group had significantly increased OS compared with the NLR >5 group (p = 0.02). (Figure 1)
- In the nal-IRI plus 5-FU/LV arm, the NLR ≤5 group had significantly increased OS compared with the NLR >5 group (p = 0.001). (Figure 2)
- The difference in the 5-FU/LV arm was not significant (p = 0.6). (Figure 3)
- PFS was significantly increased in patients with NLR ≤5 vs. NLR >5 in the pooled (2.7 vs. 1.4 months; HR = 0.7; p = 0.05) and nal-IRI plus 5-FU/LV (4.2 vs. 1.4 months; HR = 0.5; p = 0.002) treatment arms, but not the 5-FU/LV arm (1.5 vs. 1.4 months; HR = 1.1; p = 0.6).

Safety

- Grade 3/4 adverse events in the post hoc analysis population were consistent with the overall population.

Figure 1. OS by high vs. low NLR: pooled treatment arms

Figure 2. OS by high vs. low NLR: nal-IRI + 5-FU/LV arm

Figure 3. OS by high vs. low NLR: 5-FU/LV arm
• nal-IRI plus 5-FU/LV significantly improved OS and PFS compared with 5-FU/LV alone in the NAPOLI-1 trial of patients with mPDAC following gemcitabine-based therapy.

• Based on these post hoc analyses, median OS and PFS were significantly increased in patients with low (vs. high) baseline NLR in the nal-IRI plus 5-FU/LV arm, but not in the 5-FU/LV arm.

• These data are consistent with previous reports suggesting the prognostic value of baseline NLR in mPDAC and extend it to the post-gemcitabine setting.

• Adverse events in this population were consistent with the overall population.

• These analyses may be limited by the small sample size of post hoc analysis subgroups.

• HRQoL data was presented by response and disease progression status.
  ◦ Response was defined by International Working Group criteria and was investigator-assessed.
• HRQoL scores obtained at all visits before progression were used to estimate utility for progression-free state.
• HRQoL scores at on- versus off-treatment period for progression-free state were estimated.
• Health disability outcomes were stratified by the patients who experienced grade $\geq 3$ adverse events (AEs) and by Eastern Cooperative Oncology Group performance status (ECOG PS).
  ◦ Time points associated with grade 3–5 AEs were identified for each patient.
  ◦ HRQoL scores collected at these time points were used to estimate health utility by comparing patients with and without AEs.
  ◦ Utility of progression-free state without AEs was estimated using the HRQoL scores of patients without AEs at any time points.
• This analysis measured statistically significant differences, with a difference of 0.08 (U.K.-based scores) and 0.06 (U.S.-based scores) being the threshold for clinically meaningful differences.3

Key findings
• The majority of patients in the trial were male (53.8%), younger than 65 years of age (91.4%), had an ECOG PS of 0 or 1 (99.5%), and were previously treated with BV (83.3%).
• Of the 210 patients on trial, HRQoL data were collected for 207 patients.
• The mean HRQoL score at baseline for the total population was 0.759, and there was no significant difference in HRQoL scores between cohorts.
• A clinically meaningful difference in HRQoL scores (0.082) at baseline between patients with an ECOG of 0 ($n = 102$; mean score: 0.804) and $\geq 1$ ($n = 107$; mean score: 0.722) was observed.
• In the total population, the difference in mean HRQoL scores between responders (0.829) and nonresponders (0.764) was considered clinically meaningful ($>0.06$). (Figure 1)
• In patients with an ECOG PS $\geq 1$, the difference in mean HRQoL scores between responders and nonresponders was considered clinically meaningful. (Figure 2)
• The mean utility value for time spent prior to progression (0.821, 95% CI: 0.809–0.833) decreased post disease progression (0.808, 95% CI: 0.784–0.833).
• There was no statistical difference in HRQoL scores by disease progression status, except in cohort 3.
  ◦ In cohort 3, mean HRQoL for patients who were progression-free was 0.840 (95% CI: 0.821–0.858) and for patients with progressive disease was 0.795 (95% CI: 0.745–0.845).
• The mean health utility scores for progression-free patients who experienced grade $\geq 3$ AEs ($n = 17$) versus those who did not were 0.827 (95% CI: 0.814–0.839) and 0.847, respectively.
• Experiencing a grade $\geq 3$ AE reduced the HRQoL score to 0.737 (95% CI: 0.677–0.796), irrespective of disease state.
• The following study limitations exist:
  ◦ The response duration and progression-free duration were not taken into account (a repeated measure mixed model will be considered for further investigation); and
  ◦ Due to having only a single follow-up 30 days after treatment discontinuation, HRQoL scores for progressive disease state may be overestimated.

Figure 1. Mean HRQoL scores and 95% CI by response status

CI = confidence interval; HRQoL = health-related quality of life
* Number of patients with non-missing HRQoL score. HRQoL score at baseline is not included.
**Key conclusions**

- Response to pembrolizumab was associated with clinically meaningful improvement in HRQoL.
- HRQoL was not sensitive to disease progression, potentially due to the short post-treatment follow-up.
- Utility estimates from this study will be useful for economic evaluations of treatments in patients with R/R cHL.


Ott PA, et al. ESMO 2017:84PD

**Relationship of PD-L1 and a T-cell inflamed gene expression profile to clinical response in a multicohort trial of solid tumours (KEYNOTE-028)**

**Background**

Pembrolizumab has demonstrated durable antitumour activity with manageable safety profiles in multiple human cancers.1 Biomarkers are needed to increase the accuracy of programmed death-1 (PD-1) response and resistance prediction across different tumour types. Emerging biomarkers that may be predictive of response to anti–PD-1 immunotherapy include a T-cell inflamed gene expression profile (GEP) and mutational load (ML).2,3 A study of the relationships between programmed death-ligand 1 (PD-L1) expression, GEP score, and ML with pembrolizumab efficacy was reported at the 2017 EMSO Congress.4

**Study design**

- The KEYNOTE-028 study was a multicentre phase Ib trial of pembrolizumab in patients with one of 20 different types of PD-L1–positive advanced solid cancers.
- Types of tumours studied included anal, biliary, breast [estrogen receptor-positive and human epidermal growth factor receptor 2-negative], carcinoid, cervical, colorectal, endometrial, esophageal, glioblastoma, leiomyosarcoma, mesothelioma, nasopharyngeal, neuroendocrine, ovarian epithelial, pancreatic, prostate, salivary gland, small cell lung, thyroid, and vulvar.
• Eligible patients were ≥18 years of age and had unresectable and/or metastatic advanced tumours, measurable disease by Response in Evaluation Criteria in Solid Tumors (RECIST) version 1.1, an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, and PD-L1 positivity (≥1% by modified proportion score or interface pattern, QualTek IHC).5

• Pembrolizumab 10 mg/kg was given to patients every two weeks for up to two years or until confirmed progression, unacceptable toxicity, death, or withdrawal of consent.

• Response was assessed every eight weeks for six months, then every 12 weeks thereafter.

• Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

• Data cut-off date was February 20, 2017.

• The primary endpoint was best overall response rate (ORR) assessed per RECIST version 1.1 by investigator review (INV).

• Secondary endpoints included safety, progression-free survival (PFS), and overall survival (OS) by INV.

• Exploratory endpoints included ORR assessed per RECIST version 1.1 by central radiology (independent review committee [IRC]) and relationships of PD-L1 expression, GEP score, and ML with ORR and PFS.

• Assessment of PD-L1 expression was performed in pre-treatment samples by immunohistochemistry (IHC) staining using the PD-L1 IHC 22C3 pharmDx kit (Agilent Technologies).

• PD-L1 expression was reported as the combined positive score (CPS) (PD-L1–positive cells divided by the total number of tumour cells and multiplied by 100).

• A total of 198 patients had PD-L1 IHC data in 13 of the 20 cohorts assessed (anal, biliary, carcinoid, cervical, esophageal, endometrial, mesothelioma, ovarian, prostate, salivary, small cell lung, thyroid, and vulvar).

• The GEP was comprised of 18 inflammatory genes related to chemokine expression, antigen presentation, cytolytic activity, and adaptive immune resistance.2

• Tumour RNA was extracted from pre-treatment formalin-fixed, paraffin-embedded (FFPE) slides and analyzed on the NanoString nCounter system.

• GEP scores were calculated as a weighted sum of normalized expression values for all the genes.

• GEP data were presented for 19 of the 20 cohorts (n = 313).
  – Patients with pancreatic cancer had no responders in the trial and were excluded from all biomarker analyses.

• To measure ML, DNA isolated from FFPE slides of normal and tumour samples (n = 79) were subjected to whole-exome sequencing methods.

Key findings

Baseline characteristics and disposition

• Patient disposition is summarized in Figure 1.

• The median age was 59 years (range: 18–87).

• The majority of patients were female (59.2%) and white (60.2%), with an ECOG PS of 1 (63.8%) and a metastatic stage of M1 (68.2%).

• A total of 147 patients (30.9%) received prior adjuvant or neoadjuvant systemic therapy, and the majority of patients had received at least one prior line of therapy for advanced disease (85.7%).

Figure 1. Patient disposition

Efficacy

• In 19 of 20 tumour types, ORR ranged from 4.2% (95% CI: 0.1–21.1) to 33.3% (95% CI: 15.6–55.3) and was 14.0% (95% CI: 11.0–17.5) overall. (Figure 2)

• Across the 20 tumour types, median PFS ranged from 1.7 months (95% CI: 1.5–2.9) to 6.8 months (95% CI: 1.9–14.1) and was 2.2 months (95% CI: 1.9–3.4) overall. (Figure 2)

• Among the 20 tumour types, median OS ranged from 1.7 months (95% CI: 0.1–21.1) to 33.3% (95% CI: 15.6–55.3) and was 14.0% (95% CI: 11.0–17.5) overall. (Figure 2)

• Median OS was not reached in patients with thyroid cancer.

• ORR, median PFS, and median OS results were comparable in both IRC and INV assessments.
A higher distribution of GEP scores was observed in patients who achieved an objective response compared to patients who did not. (Figure 3)

Patients with higher GEP scores had generally longer PFS than those with lower GEP scores. (Figure 3)

The range of responses across GEP scores suggests that a T-cell inflamed phenotype is necessary for a clinical response, but not always sufficient.

Validation testing confirmed these observations, with statistically significant associations observed for ORR \( (p = 0.012) \) and PFS \( (p = 0.017) \) across 14 tumour types \( (n = 203) \).

PD-L1 showed coordinated expression, although derived from different cell types.

PD-L1 CPS was associated with ORR \( (p = 0.034, n = 198) \) and PFS \( (p = 0.012, n = 198) \).

A higher distribution of ML was observed in patients who achieved ORR and PFS. (Figure 4)
• ML was associated with ORR ($p = 0.016$) and PFS ($p = 0.028$).

• A low but significant correlation ($r = 0.19; p = 0.053$) was observed for ML and GEP.

**Safety**

• Treatment-related AEs (TRAEs) occurred in 65.5% of patients.
  - Of these TRAEs, 14.1% were grades 3–5, 9.1% were serious, 3.6% led to discontinuations, and 0.6% resulted in deaths.

• Grade 1–3 AEs that occurred in $\geq 10\%$ of patients included fatigue, nausea, decreased appetite, diarrhea, constipation, and anemia.

**Figure 4. Association of ML with ORR and PFS in overall study cohort (n = 79)**

* ML = mutational load, ORR = overall response rate, PFS = progression-free survival
* Nonresponder = not partial or complete response.
† Responder = partial or complete response.
‡ Censoring information not shown.

**ML (Log10 scale)**

<table>
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<tr>
<th>10000</th>
<th>5000</th>
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<th>500</th>
<th>100</th>
<th>20</th>
<th>5</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Nonresponder*</td>
<td>Responder†</td>
<td></td>
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<table>
<thead>
<tr>
<th>ORR</th>
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<tbody>
<tr>
<td>10</td>
<td>2000</td>
</tr>
<tr>
<td>5000</td>
<td>1,000</td>
</tr>
</tbody>
</table>

**Figure 5. Association of GEP and ML with ORR**

* GEP = gene expression profile, ML = mutational load, ORR = overall response rate

- T-cell inflamed GEP score, PD-L1 expression, and ML were predictive of response to pembrolizumab across multiple tumour types.
  - The GEP and PD-L1 coexpressed in the GEP gene set are indicative of a T-cell inflamed microenvironment while ML is reflective of tumour antigenicity, representing distinct but complementary functions of tumour biology.
  - Together or separately, these biomarkers may be useful in identifying patients with a higher likelihood of response to anti–PD-1 therapies.

- Pembrolizumab-mediated objective tumour responses occurred in the majority of tumour types in the KEYNOTE-028 trial.

- Safety profiles in this study were consistent with those previously reported with pembrolizumab in patients with advanced cancers.

- Patients who have both high ML and GEP scores may represent a population that is most likely to respond to pembrolizumab.

**Key conclusions**

Acute promyelocytic leukemia (APL) is a disease that can be highly curable.\(^1\) For example, the LPA-2005 study by the Spanish PETHEMA (Programa para el Estudio de la Terapéutica en Hemopatía Maligna) group demonstrated high complete remission rates (94%) and high overall survival (OS) rates with the AIDA regimen (the combination of all-trans retinoic acid [ATRA] and idarubicin) in patients with newly diagnosed APL.\(^2\)

The combination of arsenic trioxide (ATO) and ATRA is a chemotherapy-free treatment option with highly effective outcomes and low incidences of hematological toxicity in clinical trials.\(^3\) A multicentre phase III trial found significantly higher event-free survival (EFS) and OS with an improved toxicity profile in patients with non–high-risk APL who received ATRA plus ATO compared to those who received AIDA.\(^3\) The APML4 study by the ALLG (Australasian Leukaemia and Lymphoma Group) demonstrated that the addition of ATO to induction and consolidation reduced the risk of relapse in standard-risk and high-risk patients with newly diagnosed APL compared to regimens that excluded ATO.\(^4\) This year, final results from the Italian-German APL0406 trial found significantly improved EFS, cumulative incidence of relapse, and OS with ATRA plus ATO compared to ATRA plus chemotherapy in patients with newly diagnosed, standard-risk APL.\(^5\) Clinicians are moving towards this chemotherapy-free approach due to the reported toxicities associated with chemotherapy.

Some treatment protocols take patient age into account when determining treatment options, such as the PETHEMA protocols after 1999.\(^6\) In these protocols, doses are reduced for elderly patients. However, pediatric patients and some elderly patients are treated with the same regimens as standard-risk young adult patients, which may not be appropriate.\(^7,8\) Current studies are investigating the use of chemotherapy-free regimens and/or dose reductions in these special patient populations.

Unfortunately, patient outcomes from real-world data are inferior to those in clinical trials. The U.S. SEER (Surveillance, Epidemiology, and End Results) data from 2000 to 2008 showed survival rates of 71% after one year and 64% after five years for patients with APL in the U.S. population.\(^9\) Early death rates due to APL are as high as 30% in population studies.\(^10\) Decreasing early deaths is believed to be the most impactful way to increase survival in real-world situations.

The 7th International Symposium on APL occurred in September 2017 in Rome. This meeting, which is held once every four years, provides a rare opportunity for scientists, researchers, and clinicians to learn about the most recent advances in APL research, diagnostics, and management. The following is a report on several presentations made at the conference:

- Key opinion leaders emphasized the importance of observational and real-world studies in APL research, particularly with regards to early death in APL. (APL 2017:Session VII)
- The combination of ATRA, ATO, and gemtuzumab ozogamicin was reported to be safe with excellent response rates and few relapses in patients with high-risk APL and in low-risk patients with risk of leukocytosis. (Ravandi F, et al. APL 2017:CO028)
- A registry study from Germany provided further evidence for the safety and efficacy of ATRA plus ATO in patients with low/intermediate risk APL in a real-world setting. (Platzbecker U, et al. APL 2017:P0027bis)
- Results from a prospective study demonstrated that a simplified treatment algorithm and easily accessible support from APL experts might decrease real-world induction mortality and improve overall survival in patients with APL. (Jillella A, et al. APL 2017:P0020)
• Updates of recent front-line trials demonstrated the effectiveness of ATO in patients with newly diagnosed APL. (APL 2017:Session IX)

• Updates from clinical trials highlighted a shift towards the use of chemotherapy-free protocols for the treatment of front-line and relapsed APL. (APL 2017:Session X)

• A presentation about study designs in APL examined the difficulties of performing clinical trials on patients with this rare disease. (Estey E, et al. APL 2017:Session X)

• Results from the APL 2006 trial showed that in elderly patients with standard-risk APL, ATRA plus ATO was associated with high complete remission rates and a similar relapse rate to ATRA plus chemotherapy. (Adès L, et al. APL 2017:CO024)

• A study of elderly patients with APL found that ATRA-based treatments were safe and effective in patients over 70 years of age. (De Luca ML, et al. APL 2017:PO0038)

• A retrospective analysis of patients with relapsed APL who received prolonged ATRA plus ATO in consolidation provided preliminary data showing that this regimen may be effective. (Cicconi L, et al. APL 2017:CO032)

• The use of ATO in consolidation for pediatric patients with newly diagnosed APL allowed for dose reductions of anthracyclines while maintaining excellent outcomes in a European study. (Kutny MA, et al. APL 2017:CO023)

• A study of the ATRA plus ATO regimen in pediatric patients with low-risk APL found that the therapy was well tolerated, but recommended that it only be used in experienced clinics with expert consultation. (Cruetzig U, et al. APL 2017:PO0037)

• Another study of ATRA plus ATO in patients with standard-risk APL indicated that the regimen was safe and highly effective. (Giummari C, et al. APL 2017:PO0041)

• ATO, when combined with ATRA or the combination of ATRA and chemotherapy, was found to be a feasible treatment with better outcomes than ATRA plus chemotherapy alone in patients with therapy-related APL. (Kayser S, et al. APL 2017:CO033)

• A single-centre analysis demonstrated a reduction in hospitalization and transfusion support with the use of ATRA plus ATO compared to ATRA plus chemotherapy in patients with APL. (Autore F, et al. APL 2017:PO0029)

• Long-term follow-up of patients with APL who were treated with ATRA plus ATO found that the regimen reduced the need for transfusion support and reduced the risk of myelodysplastic syndrome compared to patients who received ATRA plus chemotherapy. (Autore F, et al. APL 2017:PO0050)

• The APL-2005 study compared two ATRA/chemotherapy protocols for patients with newly diagnosed APL and found that the more intensive regimen resulted in lower relapse rates at the cost of increased toxicity. (Lengfelder E, et al. APL 2017:CO027)

• A report from the PETHEMA group showed an increased risk of relapse among patients with APL who had a very complex karyotype. (Labrador J, et al. APL 2017:CO0017)

• A case study illustrated the challenges of treating obese patients with APL, specifically regarding the development of differentiation syndrome in these patients. (Jitani AK, et al. APL 2017:PO031)


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Observational studies in APL

Observational studies are an important part of medical research, especially in rare diseases like APL. The objectives of Dr. Matthew Seftel’s presentation were to (a) summarize the merits and limitations of observational data, (b) review the role of observational data in APL, and (c) discuss future opportunities for observational data in APL.\(^1\)

**Merits and limitations of observational data**

Observational studies can be divided into two categories: hospital-based and population-based registries. Both types of studies lead to the generation of research hypotheses, but hospital-based registries aim for quality improvement and professional education, while population-based registries focus on rates and trends and patterns of care/outcomes. While both types of registries have their pros and cons, as well as their own biases, population-based registries have the advantage of having a larger patient number. This can be especially important for rare diseases like APL, although sometimes the quality and annotation of the data may not be as good as in hospital-based registries.

**Impact of observational data in APL**

Observational data remain important in APL when looking at incidence and distribution of disease, rates of early deaths, long-term outcomes, and analyses of patient subgroups. While the theme of early death remains significant, observational studies of subgroups are vital in APL, given that they are virtually impossible to look at in clinical trials. Such subgroups include molecular APL variants, age extremes, geo-social determinants, and pregnancy.

Furthermore, the incidence and distribution of APL are topics that have come up frequently in recent times. One American registry found that there was a steady increase in newly diagnosed cases of APL from 1975 to 2008 (\(p<0.05\)), while a Canadian registry that reported data between 1993 and 2006 found no such trend.\(^2,3\) (Table 1) A similar American registry over a shorter time period (1992–2007) showed that there was a nonsignificant trend toward an increase in incidence of APL over time.\(^4\) One must consider the possibility that these findings could be skewed by the notion that as diagnosis became more advanced, APL became more readily identifiable. Alternatively, a European study showed a relatively low incidence of APL with no indication of increase over time. Considering the above, Dr. Seftel believes that there is a steady incidence of APL and that there were likely classification issues, which may have led to the findings of lower incidence of APL in the past and an apparent increase with time.

The question of whether APL is more common in certain ethnic or geographic subgroups remains significant. There are strong data concluding that APL is more common in people of Latino origin, residing in Central and South America as well as in the U.S.\(^5\) A recent study found also that the incidence of APL is very high among Brazilian patients with acute myeloid leukemias.\(^6\)

An epidemiologic study, published in 2011, used data from the Surveillance, Epidemiology, and End Results (SEER) program to estimate the true rate of early death.\(^4\) It found that overall survival (OS) was improved in patients diagnosed from 2002 to 2007 when compared with those diagnosed from 1996 to 2001 and from 1992 to 1995 (\(p=0.0002\)). (Figure 1) Furthermore, there was an improvement in OS with younger patients when compared to older patients. (Figure 2) The 3-year OS was significantly lower in patients aged \(\geq 55\) years (46.4%; \(p<0.0001\)).

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**Table 1. APL incidence: population-based registries**

<table>
<thead>
<tr>
<th>Registry</th>
<th>Years</th>
<th>Age-standardized incidence (per 100,000)</th>
<th>Increasing incidence?</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>1992–2007</td>
<td>0.23</td>
<td>Yes ((p=0.068))</td>
</tr>
<tr>
<td>United States</td>
<td>1975–2008</td>
<td>0.18</td>
<td>Yes ((p&lt;0.05))</td>
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<tr>
<td>Canada</td>
<td>1993–2006</td>
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<td>No</td>
</tr>
<tr>
<td>European Union</td>
<td>2000–2007</td>
<td>0.12 (crude)</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

\(^{APL}\) = acute promyelocytic leukemia

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A pan-Canadian study, coauthored by Dr. Seftel, found that there was no improvement in OS for patients with APL unless they were treated at large leukemia referral centres across the country. Together, these data highlight a need to educate healthcare providers across a wide range of medical fields who may be the first to evaluate a patient with APL. This could lead to a positive effect on early death and the cure rate of patients with APL.

To highlight the significance of analyzing long-term outcomes in APL, Dr. Platzbecker and colleagues presented the findings of the APL0406 trial on real-life experience with all-trans retinoic acid (ATRA) and arsenic trioxide (ATO)-based regiments in patients with APL. The results further supported ATO and ATRA as the new standard of care in low- to intermediate-risk APL.

**Future opportunities for observational data in APL**

APL researchers should be regarded as leaders in the design and development of registries for rare diseases. An editorial piece called “All tumours are rare, but some are rarer than others”, published in *Lancet Oncology*, discussed the importance of cancer registries in general. As oncologists continue to further subdivide malignancies based on their molecular phenotype, registries begin to play a more prominent role, since there may not be enough patients for clinical trials in some cases. As a result, solid tumour oncologists will have to learn a new skill set, something that many hematologists have already had to do with rare diseases such as APL.

There are several opportunities for observational data in APL. These include incidence rates, patterns of care, long-term outcomes, cost of therapy, disparities, and genomic and clinical subgroups. Economic burden is of special importance to APL, considering the use of expensive therapeutics, the cost of inpatient care, and the cost of infusion support. Furthermore, hematologists would expect all patients with APL to be cured and continue their normal lives. Unfortunately, this is not always the case, as disparities exist even in a developed country like Canada. This is particularly true in rural areas.

In Canada, there currently exists an open Canadian APL registry. It is expected that within four years, data will become available once the sufficient number of patients has been gathered. Canada is an interesting country to study a rare disease like APL, given its relatively small number of major hospitals within the large area of the country. This tends to lead to a range of disparities, which are something that observational registries can help address.

**Reproducing clinical trial results in the “real world”**

At the 2017 International Symposium on APL, Dr. Anand Jillella gave a presentation on reproducing clinical trial results in real-world populations of patients with acute APL. APL is a very rare disease, with approximately 3,000 new cases a year in the United States. On the other hand, there are about 15,000 oncologists who can treat APL in the country, which can lead to some oncologists only receiving a few patients every couple of months or even years.

**Early death in APL**

Based on several large clinical trials in APL, the median age of patients is between 40–45 years. Early death (ED) occurs in approximately 2.5%–7.7% of patients, and about 30% of patients die within the first month of diagnosis. Many hematologists believe that these deaths can be prevented. ED remains an urgent concern for the treatment of patients with APL and must be addressed. While the consensus appears to be that ED is more likely in patients being treated at small ‘inexperienced’ centres, it has consistently been shown to be a problem in larger centres as well.
There are several potential reasons why ED occurs at such high rates in patients with APL:

- A delay in diagnosis and treatment;
- Unavailable or suboptimal supportive care;
- Oncologists being unaware of the potential of ED;
- Inadequate supervision by APL experts;
- Inexperience by other healthcare staff;
- Lack of continuity of care when patients are transferred; and
- Physician ego and unwillingness to seek advice.

Irrespective of ED, when considering all leukemias, APL has a relatively high OS rate in patients receiving ATRA and ATO (98.7%), as well as in patients receiving ATRA and chemotherapy (91.1%).10 (Figure 3) However, the OS rate was not always that high in the past. Between 1975 and 1990, when idarubicin was the only available treatment for APL, the cumulative relative survival rate was about 15%.2 ATRA led to an improved survival rate of about 50% between 1991 and 1999. More recently (2000–2008), the introduction of several modern medicines had led to another improvement in relative survival to about 65%.

Figure 3. Overall survival in APL

While the current survival rate of >90% in multicentre clinical trials appears to be impressive, it is not an accurate reflection of a real-world population. The death rate of 5%–10% seen in clinical trials is likely an underestimate.2 U.S. SEER data from 2000 to 2008 demonstrated 1-year and 5-year survival rates of 71% and 64%, respectively.2 In addition, at the Augusta University centre, of the 18 patients with APL seen between 2005 and 2009, seven patients (39%) died in the first month during induction.12 The remaining 11 are currently in molecular remission and are presumed cured, meaning that patients who survived the first month had a >90% chance of being cured. All these data show that few patients relapse or die after the first year or even first month, highlighting the importance of reducing the occurrence of ED in patients with APL.

**Tackling early death in APL**

The 39% mortality rate observed at the Augusta University centre was alarming. As a result, the physicians decided to investigate further by hiring an external consultant to review the death charts. Three main causes of death within the first month were identified: bleeding, differentiation syndrome, and infection. Consequently, Dr. Jillella and colleagues developed a proactive algorithm to prevent complications that may lead to ED. In addition, strategies were implemented at affiliate sites, wherein Dr. Jillella’s team would be contacted when new patients with APL were diagnosed and they would in turn share their treatment algorithm. Each patient’s treatment plan would be discussed between Dr. Jillella’s team and the treating physicians and a follow-up would be done several times in the first few weeks in order to reduce the risk of ED.

Since the implementation of the treatment algorithm, Dr. Jillella’s team and affiliate sites have treated 163 patients (85 female and 75 male) in four large and 32 community centres. There were no exclusion criteria and the median age was 54 years (range: 21–83). There were 11 deaths during induction (6.7%) and five patients relapsed. Of the 11 patients who died, only three were <60 years old. Seven patients died late, two from relapse and five from causes unrelated to APL. This translated to an OS of 89%.

**Dose reduction in APL**

While in clinical trials the ED rate in patients >60 years of age is 5%–20%, in real-world populations, it is higher (around 30%–50% depending on the country). Dr. Jillella and colleagues set out to assess the effect of dose reduction of ATRA and ATO on ED rates in older patients. Of the 138 patients who had their dose reduced, 53 were >60 years old. Eight deaths occurred during induction (15%). In addition, there were three relapses (one patient who refused consolidation and two who did not receive dose reduction). As an example, a 73-year-old patient with several severe comorbidities had his dose of ATRA reduced and was able to achieve hematologic remission.

When considering treatment for older patients with APL, it is clear that care must be individualized. Older patients may benefit from dose-reduced ATRA and ATO. The doses could be increased again after the patients reach consolidation. Younger patients with multiple comorbidities could also benefit from a similar approach.

Dr. Jillella’s team is currently starting a clinical trial for patients with APL called ECOG/ACRIN 9131. Its aim is to fully implement their treatment algorithm in order to improve survival rates to >90% across the general population. The trial will be
open across the U.S. and will have no exclusion criteria. Every physician involved will be required to call an APL expert as soon as an APL diagnosis is suspected and will also have to do a follow-up call within three days of starting therapy.

In conclusion, ED in APL can and should be prevented. The model for lowering the incidence of ED is to use a robust algorithm for treatment and communicate with an APL expert in all scenarios. With the right treatment and communication plan, it may not be necessary to transfer patients to a specialized academic centre, in turn reducing waiting times. Results from recent trials have demonstrated that survival can indeed be improved in this patient population.

**Early deaths: The most significant threat to APL patients in real life**

Population-based registries are useful in rare diseases such as APL, as they provide useful results for patient populations that are not covered by clinical studies. Importantly, these registries can also complement clinical trials to guide the treatment of patients. In order to provide valid data, a registry must have good coverage of the defined population, report relevant parameters with good quality, and have close to a complete follow-up. At the 2017 International Symposium on APL, Dr. Soren Lehmann gave a presentation on the threat of ED in patients with APL.13

**Early death in Swedish APL patients**

The Swedish Cancer registry was established in 1958 and requires by law that all cancers be reported by pathologists and treating clinics. Since 1997, the registry has maintained detailed information on patients with acute myeloid leukemia (AML). APL data from the Swedish Acute Leukemia registry, encompassing 1997 to 2006, was first evaluated about 10 years ago. The analysis found a surprisingly high ED rate of approximately 30%. A Brazilian study also reported similar ED rates of about 32%.14 Several other population- or hospital-based reports have found ED rates in the range of 10%–30%. These numbers are in contrast with clinical trials, where ED rates are usually much lower, almost always below 10%.

Around 2009, the Swedish hematology community started to become more vocal about the risk of ED. Guidelines for the early handling of patients with APL remained the same, but were more forcefully communicated. These included starting all patients with AML on ATRA after the slightest suspicion of APL, transfusion of platelets, and the administration of plasma or fibrinogen concentrates when presenting with signs of coagulopathy.

Dr. Lehmann led a study comparing ED rates in the Swedish registry from after 2009 to those prior, thus evaluating the effect of the increased awareness of the risk of ED.15 The results suggested that despite increased awareness and initiation of early treatment with ATRA, ED rates remained high in this population-based setting. (Table 2) This was especially true for high-risk patients with APL. Notably, the population in the registry was relatively old, with about 30% of patients being older than 65 years.

**Table 2. Characteristics of APL patients in the Swedish study**

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<td>Age &gt;75 years (%)</td>
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<td>Performance status</td>
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<td>Early death rate, all (%)</td>
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<tr>
<td>Low/intermediate risk (%)</td>
<td>19</td>
<td>15</td>
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</table>

**Causes and risk factors of ED**

The causes of death seen in the Swedish study were similar to those seen in literature. They included hemorrhages, infections, differentiation syndrome, and thrombosis. Hemorrhages were mainly of the intracranial type with a median time to death of 4–7 days from diagnosis. Infections were prevalent in older patients with a median time to death of 21 days after start of treatment. Differentiation syndrome led to a median time to death of 17 days after start of treatment and is likely an underestimated cause of death in patients with APL. In addition, thrombosis may be an underestimated cause of death.

The Swedish study also identified three main risk factors for ED: age, World Health Organization (WHO) performance status score, and white blood cell count. (Figure 4) While ED rates increased with age, the increase was clearer with poor WHO performance status.

Between 1997 and 2006, Dr. Lehmann’s group attempted to identify reasons why ED occurred in patients who started treatment early.16 No evidence of delays was found between first contact with healthcare provider, first contact with hematologists, bone marrow examination, diagnosis of APL, and start of ATRA treatment. Additionally, no differences in supportive care were found between patients who had ED and those who did not.

**Ongoing Swedish study on ED**

It is clear that patients with APL are experiencing high rates of ED despite the increase in awareness. More education on ED is required and physicians need to identify what can be considered “preventable deaths”. In order to address some of these issues, a study was conducted in Sweden between 2007
and 2016. Patients were identified through a registry and data were obtained from medical records, which were reviewed for details on pre-hematologic and hematologic care. The analysis is currently ongoing.

So far, the study has found that most patients receive ATRA within two days of APL suspicion, while about 29% do not receive ATRA at all. (Figure 5) Furthermore, about 33% of patients who had ED experienced pre-hematological delays of more than three days (pre-hematological delays are delays that occur between the time a patient first sees a healthcare provider and the time when the patient sees a specialized hematologist). Notably, 29% of patients with ED had intracranial hemorrhages before admission to the hospital, highlighting the lethality of this condition.

Much work remains to be done in order to better understand and reduce the risk of ED in patients with APL. First, earlier suspicion is crucial to this goal. This is especially true when looking to reduce the occurrence of pre-hematological delays. Secondly, there is still a need to better adhere to guidelines on the management of patients with APL, which raises the question of whether guidelines to prevent lethal bleeding could be more rigorous. This may include intensive care of all high-risk patients with more frequent monitoring and more aggressive transfusion policies. Finally, hematologists need more education on the mechanisms of coagulopathy in APL and the effects of different treatments on coagulation.

**ATO and ED**

In the past year, ATO in combination with ATRA was introduced in Sweden as first-line therapy for patients with low- and intermediate-risk APL. Randomized trials showed no statistically significant differences in ED rates between patients taking ATRA and ATO and those taking ATRA and chemotherapy. Notably, ED rates were generally low in these trials. It is likely that ED rates due to infections and due to chemotherapy side effects will decrease. However, the relative proportion of ED to total number of deaths may eventually increase, as deaths from relapse and therapy resistance are likely to decrease with the introduction of ATO.

Therefore, physicians must consider whether the use of arsenic can lead to less bleeding and whether oral arsenic should be administered earlier in the treatment cycle, together with ATRA. A potential favourable effect on ED by ATO warrants further investigation, especially in a population-based setting.

Long-term outcomes of patients with APL treated with ATRA, ATO, and gemtuzumab ozogamicin

Background

The combination of all-trans retinoic acid (ATRA) plus arsenic trioxide (ATO) has demonstrated superiority to ATRA plus chemotherapy in the treatment of standard-risk, newly diagnosed acute promyelocytic leukemia (APL).1 A recent study demonstrated the efficacy of ATRA plus ATO with the addition of gemtuzumab ozogamicin (GO) in high-risk patients.2 Long-term outcomes of newly diagnosed patients with APL treated with the ATRA, ATO, and GO combination from three clinical trials were presented at the 7th International Symposium on APL.3

Study design

• All patients received induction treatment with ATRA and ATO.

• A dose of GO was added to high-risk patients as well as low-risk patients who experienced leukocytosis during induction.

• Once in complete remission (CR), patients received four cycles of ATO and seven cycles of ATRA for consolidation.

Key findings

Baseline characteristics and disposition

• A total of 239 patients were assessed for eligibility and 187 were enrolled into clinical trials.

• Patient disposition is presented in Figure 1.

• The median age of the patients was 50 years (range: 14–84), with 28% being at least 60 years old.

• About half of patients were male (52%).

• There were 54 patients (29%) with high-risk APL and 133 patients (71%) with low-risk APL.

• The majority of patients harboured translocation of chromosomes 15 and 17 (t[15;17]) (65%), and had the M3 morphology (87%).

• All patients analyzed (187) had the promyelocytic leukemia gene (PML)-retinoic acid receptor alpha (RARA) translocation.

• Of the total patient population, 42% had the short PML-RARA isoform, 56% had the long PML-RARA isoform, and 2% had both isoforms.

• In the high-risk patients, 66% had the FMS-like tyrosine kinase 3-internal tandem duplication mutation.
**Study design**

**INDUCTION**

- ATRA 45 mg/m²/day
- ATO 0.15 mg/kg/day
- GO* 9 mg/m²/day

**CONSOLIDATION**

- ATRA 45 mg/m²/day for 2 weeks
- ATO 0.15 mg/kg/day 5 days per week

Weeks after achieving CR

- D1 CRm CR 2 4 6 8 10 12 14 16 18 20 22 24 26 28
- 10 D1 CRm 4

**Figure 1. Patient disposition**

- Assessed for eligibility (n = 239)
- Excluded (n = 52)
  - Insurance/socioeconomic reasons (n = 39)
  - Death within 48 hours (n = 13)
- Enrolled into clinical trial (n = 187)
- High-risk patients (n = 54)
  - Complete remission (n = 52)
    - Relapses (n = 5)
    - Died in CR (n = 3)
    - Died in relapse (n = 2)
  - Early deaths (n = 2)
- Low-risk patients (n = 133)
  - Complete remission (n = 127)
    - Relapses (n = 2)
    - Died in CR (n = 14)
  - Not evaluable for response (n = 11*)
  - Early deaths (n = 3)

*CR = complete remission

**Leucocytosis and cytoreductive therapy**

- CR after induction was achieved in 179 (96%) patients, while 176 patients achieved complete molecular remission.
- A total of 53 high-risk patients received cytoreductive therapy:
  - Forty-five (83%) received GO;
  - Seven (13%) received idarubicin;
  - One (2%) received both; and
  - One did not receive any.
- A total of 96 (72%) low-risk patients developed leukocytosis.
  - The median white blood cell count (WBC) was 19.8 x 10⁹/L (range: 10.3–195 x 10⁹/L).
  - Leukocytosis was reached at a median of 10 days (range: 2–26).
  - Among these patients, 60 received cytoreductive therapy (51 received GO, 9 received idarubicin).
- No patients received GO for molecular persistence or relapse.

*One dose of GO (9 mg/m²) was given on Day 1 for high-risk patients (defined by WBC count >10 x 10⁹/L on presentation) and low-risk patients in whom the WBC count increased to more than 10 x 10⁹/L during the first four weeks of therapy.
Efficacy

- The median follow-up was 47.6 months (range: 2.7–159.7).
- The median event-free survival (EFS), median disease-free survival (DFS), and median overall survival (OS) were not reached, while the 5-year EFS, DFS, and OS, were 85%, 96%, and 88%, respectively, for the whole population. (Table 1)
- There were no significant differences in median EFS and OS between the high-risk and low-risk subsets, whereas the median DFS was significantly higher in low-risk patients when compared with high-risk patients \( (p = 0.011) \).
  - Median EFS, DFS, and OS were not reached in either subset.
  - Median EFS was significantly improved in patients <60 years old when compared with patients ≥60 years old (89% vs. 74%; \( p < 0.001 \)). (Figure 2)
  - Median DFS was not different between the two age groups (<60 years vs. ≥60 years) \( (p = 0.484) \).
  - Median OS was significantly higher in patients <60 years old when compared to those ≥60 years old (93% vs. 74%; \( p < 0.001 \)). (Figure 3)
  - Of the high-risk patients who received GO, seven died (5-year OS = 84%) when compared with zero patients who received idarubicin (5-year OS = 100%).
  - Of patients with t(15;17) and additional cytogenetic abnormalities, four died (5-year OS = 90%) when compared with 19 patients with t(15;17) alone (5-year OS = 87%).
  - A total of seven patients relapsed, including three with central nervous system relapse.
  - A total of 26 (14%) patients died:
    - Seven during induction;
    - Two due to refractory relapse; and
    - Seventeen in CR.

Safety

- The most common grade 3/4 adverse event was infection (23.5%), followed by hepatotoxicity (14%), QT prolongation (7.5%), and hemorrhage (5%).
- Differentiation syndrome occurred in 21 patients (11%), but was managed successfully in all.

<table>
<thead>
<tr>
<th>Total patients</th>
<th>Events/relapsed/deaths</th>
<th>Median</th>
<th>5-year rate</th>
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<td>NR</td>
</tr>
<tr>
<td>OS</td>
<td>187</td>
<td>Deaths: 26</td>
<td>NR</td>
</tr>
</tbody>
</table>

DFS = disease-free survival; EFS = event-free survival; NR = not reached; OS = overall survival

Figure 2. Event-free survival by age

Figure 3. Overall survival by age

NR = not reached
• ATRA plus ATO is an effective front-line therapy for standard-risk APL.
  – The study confirms the durability of responses with this regimen.
• The addition of GO in high-risk patients and in low-risk patients whose WBC rises is safe.
• There were excellent outcomes in high-risk patients.
• There was no incidence of veno-occlusive disease in the liver and no significant cardiac arrhythmias with careful monitoring and replacement of electrolytes.
• Most failures after the initial period related to death from other causes.
• There were few relapses after the first year.

Key conclusions


Platzbecker U, et al. APL 2017:PO027bis

Real-life experience with ATRA and ATO-based regimens in APL

Background
In the APL0406 trial, the combination of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) was shown to be superior to standard ATRA and chemotherapy in front-line therapy for patients with low- to intermediate-risk acute promyelocytic leukemia (APL). At the 7th International Symposium on APL, an intergroup APL registry study (NAPOLEAN) on the use of ATRA and ATO in Germany was presented.2

Study design
• The objective of this prospective study was to provide a picture of the clinical reality of APL patient care in Germany.
• This study was initiated by four acute myeloid leukemia study groups.
• Eligible patients were ≥18 years of age with newly diagnosed or with relapsed APL within the first year of diagnosis.
• The study was conducted in accordance with the Declaration of Helsinki and received institutional review board approval by all participating centres.
• This study is registered at ClinicalTrials.gov (NCT02192619).

Key findings
• As of August 1, 2017, 150 patients with newly diagnosed APL have been enrolled in the study.
• Among all patients, 100 (67%) were low- to intermediate-risk according to the Sanz score.
• Of the low- to intermediate-risk patients, 77% received an ATO and ATRA-based induction regimen followed by a median of four courses of ATO and ATRA consolidation (according to the APL0406 study).2
• Of these patients, the median age was 52 years (range: 20–87), median white blood cell count was 2.2 x 10^9/L (range: 0.3–10), and six of 48 patients with mutation data had confirmed FMS-like tyrosine kinase 3 internal tandem duplication.
• For the group of evaluable patients with low- to intermediate-risk, newly diagnosed APL treated with ATO and ATRA-based regimens (n = 76):
  ◊ Complete remission was achieved in 75 patients (99%); and
  ◊ Rate of early death (within 30 days of therapy) was 1%.
• After a median follow-up of 14 months, 12-month event-free survival, cumulative incidence of relapse, and overall survival were 97%, 2%, and 97%, respectively. (Figures 1–3)
• Therapy was well tolerated and no new safety signals were obtained.
Background
Acute promyelocytic leukemia (APL) is considered a curable disease, with results from many large cooperative group studies demonstrating survival rates >90%.

However, recent data from population-wide and institutional studies revealed poorer outcomes, identifying high early death rates as one of the causes. Results from a prospective APL study examining the effects of a simplified treatment algorithm and easily-accessible support from APL experts on induction mortality and overall survival were presented at the 7th International Symposium on APL.


Jillella A, et al. APL 2017:PO020

A prospective study on using a simplified treatment algorithm and expert support to decrease induction mortality in APL: Results from Georgia, South Carolina, and neighbouring states

Key conclusions
- These real-life data from a prospective German registry provide further evidence for the safety and sustained anti-leukemia efficacy of ATO and ATRA in low- to intermediate-risk APL.
- These results further support ATO and ATRA as the new standard of care in this clinical setting.
Study design

• This study was a prospective, multicentre trial that examined the effects of using a simplified treatment algorithm and support from APL experts to improve early death rates and overall survival among patients with APL.

• Prior to patient enrolment, leukemia treatment centres were identified in Georgia, South Carolina, and neighbouring states, and investigators were briefed on the trial and early death rates among patients with APL.

• A two-page algorithm, developed to emphasize early initiation of therapy and complication prevention, and support from APL experts were used to treat newly diagnosed patients.

• Four leukemia treatment centres served as the leading sites, where investigators (experts) offered 24-hour support to other centres regarding APL management.

• Standard treatment guidelines were followed, with dose modifications made depending on comorbid conditions.

• Patient consent was obtained as per the protocol approved by the institutional review boards.

• There were no patient exclusion criteria.

Key findings

Baseline characteristics and disposition

• A total of 120 patients were enrolled between July 2013 and May 2016.

• The median age was 54 years (range: 21–84) and 56% of patients were male.

• The median white blood cell (WBC) count was 4.3 (range: 0.3–170,000/mm³) and 84% of patients were considered low risk (WBC <10,000/mm³).

• All-trans retinoic acid (ATRA) was initiated upon suspicion of APL diagnosis in all patients.

• Regarding treatment:

  ◦ ATRA was given in combination with arsenic in 81.5% of patients and in combination with chemotherapy in 17% of patients.

  ◦ ATRA was the sole treatment provided to the remaining 1.5% of patients.

  ◦ The median follow-up was 641 days.

  ◦ Two patients were excluded from data analysis, of which one was from the Jehovah Witness community.

Efficacy and Safety

• Overall survival is shown in Figure 1.

• Complications included bleeding at presentation (13%), infection (28%), and differentiation syndrome (DS) (34%).

• There were 12 early deaths: one due to refusal of therapy, four due to disseminated intravascular coagulation, two due to severe DS, and five due to multi-organ failure.

Key conclusion

• A simplified treatment algorithm and easily-accessible support from APL experts may decrease induction mortality and improve overall survival in real-world situations.

**New Evidence**: What is the true definition of early death (ED)?

**Dr. Jillella**: Literature defines ED as occurring in the first 30 days after diagnosis; however, this definition is debated in the field. I disagree with this definition and believe that a more accurate definition of ED would be death occurring during the induction period, also known as induction mortality. I believe the entire length of induction should be included in this definition as induction therapy can last up to six weeks, and there are instances where complications that develop within the first 30 days could result in death after the 30-day mark.

**New Evidence**: Why is ED an important topic in the treatment of acute promyelocytic leukemia (APL)?

**Dr. Jillella**: ED is an important topic because it is currently the most common cause of treatment failure in APL; however, these deaths may all be preventable with appropriate and timely care decisions. In our experience with an all-comers population, the cure rate for patients who survive the induction phase of therapy is high (>90%), which highlights the importance of getting patients through this stage of treatment.

**New Evidence**: What was the rationale for the APL trial in Georgia and South Carolina?

**Dr. Jillella**: Almost 10 years ago, we began to notice the high percentage of patients with APL in our institution who died during induction therapy, with the main causes of death being bleeding, infection, and differentiation syndrome. We learned that we were not managing these patients appropriately and wanted to create a treatment algorithm to better care for these patients. At the time, the current treatment algorithm for APL consisted of a 15-page guideline, which was not sufficient for a rarely seen disease that requires quick reaction times. This was the rationale for developing a program using a two-page treatment algorithm for APL that could be implemented quickly. The program allowed us to do a quality control at our own institution and allowed us to gain experience and knowledge that could be shared with surrounding hospitals. After treating 10 patients with no deaths, we sought after and received funding to start a trial in Georgia and South Carolina that involved dissemination of the algorithm to several hospitals in the area and acting as an experienced resource for them to contact with patient management inquiries. The aim of the study was to reduce induction mortality from an estimated 30% to less than 15% in these two states with a population of approximately 15 million people.

**New Evidence**: How different are the ED rates in clinical trials versus population-based/real-world studies? Why is this difference important?

**Dr. Jillella**: In clinical trials the induction mortality rate is about 3%–8%, whereas in population-based studies, such as the Swedish registry trial, induction mortality is approximately 30%. This discrepancy is due to several factors, such as trial exclusion criteria, which lead to the exclusion of older patients with multiple comorbidities. For example, the average median age in trials is approximately 40–45 years, which does not reflect the median age of approximately 55 years reported in real-world studies. Another reason for this discrepancy is that compared to population-based studies, patients in clinical trials are treated on a specific protocol with strict guidelines for supportive care, and generally in experienced centres. This difference tells us that clinical trial results are not translating into the real world, and as not every patient will have the opportunity to enroll in a clinical trial, improving ED rate in the general population is very important.

**New Evidence**: Could you please briefly describe the simplified treatment algorithm used in your study?

**Dr. Jillella**: This treatment algorithm was developed by faculty members with diverse specialties, including bleeding and clotting. Together we reviewed the APL literature to form a best practice guideline that includes treatment and supportive care. As we wanted the algorithm to be simple and used to implement therapy quickly, it began as a 1.5-page, checklist-style document that outlined how to treat a patient with APL and what measures could be taken to prevent fatal complications such as bleeding, differentiation syndrome, and infection. To further simplify the algorithm, referring physicians would call our centre to share their patient details, and we would send them an email outlining 12–15 recommendations specific to their patient. The algorithm has since undergone multiple amendments to accommodate the evolving literature and impracticalities observed during implementation. The most current iteration of the algorithm is now being used in the EA9131 Eastern Cooperative Oncology Group (ECOG) study which started on September 1, 2017.

**New Evidence**: What were some of the difficulties encountered when the algorithm was implemented in the centres in Georgia and South Carolina?

**Dr. Jillella**: Although there were generally few difficulties implementing the algorithm in centres in Georgia and South Carolina due to the strong relationships we have built with physicians over the years, there were some centres who did not feel the need to seek advice in managing their patients with APL. In most cases, the availability of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) at the different centres was not a problem; however, there were three centres who...
New Evidence: Could you please describe the patient population in your study?

Dr. Jillella: As this study had no exclusion criteria, it represents a real-world population. All patients diagnosed with APL were included, even patients who were older, had multiple comorbidities, or who came to a treatment center in critical condition with significant bleeding. The median age of patients in this trial was 54 years, which is what you would expect in the general population.

New Evidence: The overall survival was 89% and there were 11 EDs. In your opinion, had this study met its objectives?

Dr. Jillella: The objective of this study was to reduce ED rate from an estimated 30% to less than 15%. As the ED rate of this study was 6.7%, we can conclude that the study objective was met. However, I believe all EDs are preventable and that we could still do better.

New Evidence: For elderly patients with APL, how was the algorithm modified and what was the rationale for the modification?

Dr. Jillella: It appears that most of the problems with ED occur in older patients, mainly due to differentiation syndrome. After analyzing the data in the first half of the study, we found that five of six patients who died early in induction were older than 60 years. Since the algorithm was created based on studies where dosing and schedules were developed for a patient population with a median age of approximately 40 years, this dosing and schedule would not be appropriate for a patient who is aged 70 years or older. For this reason, treatment doses were reduced to 50% for older patients in the second half of the study, which helped to reduce the number of EDs in these patients.

New Evidence: What are the key takeaways of the study? In your opinion, how will your algorithm impact future practice in APL?

Dr. Jillella: The key takeaway of this study is that by following this simplified algorithm and discussing patient cases with experts in APL, the rate of EDs can be reduced in the general population. It is important to note that although the algorithm is a tool that will improve outcomes, it is equally important to discuss patient management with an expert who treats patients with APL on a more regular basis. There are small details, such as remembering to give steroids on the first day of treatment, that can be forgotten by physicians who treat APL infrequently, and this can have fatal consequences.

By decreasing the frequency of EDs, this study was able to make an impact on the lives of patients and their families. The success of this program is the result of a whole team of people including physicians, pharmacists, nurses, and trainees who are very dedicated to the APL patients. In particular, I would like to acknowledge the significant contributions made by Dr. Vamsi Kota at the Emory Winship Cancer Institute in Georgia, as he played an integral role in the development and implementation of this program. The hope is that in time, this program will become the global paradigm for treatment of patients with APL.

New Evidence: In your opinion, how can your algorithm be adapted for use in other countries such as Canada?

Dr. Jillella: For this program to be implemented in other countries, it will be important to have a champion who has genuine interest in pushing the program forward. This person would be dedicated to visiting many practices to educate them on the program and fielding calls from multiple centers. This physician may not have the needed experience level at the beginning of implementation, but this could be acquired over time. One of the biggest challenges for implementing this program in any country will be getting the physicians in rural areas who may see a patient with APL infrequently to call an expert and discuss patient management.

New Evidence: With the experience in Georgia and South Carolina, what are the next steps in the implementation of your algorithm?

Dr. Jillella: The next step is to implement this algorithm at a national level, which is currently underway through the EA9131 ECOG trial, with the same objective of reducing the induction mortality rate to less than 15%. This trial has currently enrolled seven patients with the plan to recruit 200 patients over the next four years. If we meet our objective, the next goal would be to have the algorithm included in the National Comprehensive Cancer Network guidelines for acute myeloid leukemia, with a recommended list of ten physicians to contact for patient management advice.

Update of the Italian-German study APL0406

The APL0406 trial was a randomized phase III study initiated by the GIMEMA and German APL groups. This trial compared the combination of all-trans retinoic acid (ATRA) and chemotherapy (CHT arm) to the combination of ATRA and arsenic trioxide (ATO) (ATO arm) in patients with non–high-risk APL. The first results from this study indicated that ATO and ATRA was statistically superior to ATRA and chemotherapy with regards to overall survival (OS), event-free survival (EFS), and disease-free survival.\(^1\) Hematological toxicity was also statistically reduced in the ATO arm.\(^1\) Final results confirmed the previous results with respect to OS, cumulative incidence of relapse (CIR), and hematological toxicity.\(^2\) However, non-hematological toxicities occurred more frequently in the ATO arm.\(^2\)

Dr. Avvisati presented updated results of the APL0406 trial with a median follow-up of 66.2 months (range: 0.9–116.7 months; data cutoff September 20, 2017).\(^3\) In this analysis, 6-year OS and EFS rates were significantly higher in the ATO arm than in the CHT arm (OS: 98.3% vs. 88.9%; \(p = 0.0023\); EFS: 96.6% vs. 77.4%; \(p < 0.0001\)). CIR was also significantly lower in the ATO arm (6-year CIR: 1.7% vs. 15.5%; Gray test = 0.0001). In the ATO arm OS, EFS, and CIR were stable from 24 months onward, while in the CHT arm OS and EFS decreased over time and CIR increased over time. (Table 1)

In the CHT arm, 17 patients relapsed and two patients had molecular resistance, while in the ATO arm only two patients relapsed and no molecular resistance was observed. Secondary acute myeloid leukemia was reported in only one patient in the CHT arm. There were 14 deaths in the CHT arm and two deaths in the ATO arm. (Table 2) Notably, there were no deaths in induction or in relapse in the ATO arm.

Results from this updated analysis confirmed that ATO and ATRA should be considered the standard treatment for patients with newly diagnosed, non–high-risk APL. As a next step, the phase III European APOLLO trial will evaluate induction with ATO and ATRA and two low doses of idarubicin compared to ATRA and chemotherapy for newly diagnosed patients with high-risk APL.

**APL0406 study design**

![Diagram of APL0406 study design](image)

6MP = mercaptopurine; ATO = arsenic trioxide; ATRA = all-transretinoic acid; CHT = chemotherapy; CR = complete response; IDA = idarubicin; MTX = methotrexate; MTZ = mitoxantrone; R = randomized

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**Update in Front-Line Trials in APL**

**Presentations from Session IX of the 2017 International Symposium on APL**

At the 2017 International Symposium on APL, Dr. Avvisati, Dr. Adès, and Dr. Sanz presented updates to their front-line trials for patients with acute promyelocytic leukemia (APL). The following provides a summary of these presentations.
The APL 2006 trial was conducted over a 10-year period in France, Switzerland, and Belgium. The objective of this study was to test the role of ATO during consolidation in patients with standard-risk or high-risk acute APL. Inclusion criteria were newly diagnosed patients with APL subsequently confirmed by conventional cytogenetics and/or presence of promyelocytic leukemia-retinoic acid receptor alpha transcript, age <70 years, and no contraindication to intensive chemotherapy or ATO. Patients with therapy-related APL could be enrolled in the trial, and 12% of patients enrolled had therapy-related APL.

The trial was split into two protocols: one for standard-risk APL and one for high-risk APL. In the standard-risk APL protocol, patients received a standardized induction regimen and were then randomized to receive one of three consolidation regimens: idarubicin and cytarabine (AraC), idarubicin and ATO, or idarubicin and ATRA. In the high-risk APL protocol, patients received a standardized induction regimen and were then randomized to receive one of two consolidation regimens: idarubicin and AraC, or idarubicin, AraC, and ATO. After the first interim analysis in September 2010, AraC was deleted from the consolidation cycles in the AraC and ATO arm because of more pronounced hemato logical toxicities compared to the AraC arm. At the 2017 International Symposium on APL, Dr. Adès presented the final results of this trial.4

Findings in standard-risk APL
A total of 584 patients with standard-risk APL received induction therapy. There were no differences in pretreatment characteristics between the groups. Median white blood cell (WBC) count was 1.3 g/L, 1.4 g/L, and 1.51 g/L in the AraC, ATO, and ATRA groups, respectively. Eleven early deaths occurred, and the complete remission (CR) rate was 96%.

After a median follow-up of 58 months, OS was similar between the groups and EFS was significantly better in patients who received ATO for consolidation. (Table 3) Five-year CIR rates were 5.54%, 0%, and 8.2% in the AraC, ATO, and ATRA groups, respectively (p = 0.001). Hematological toxicities were significantly lower in the ATRA arm compared to the other two arms. (Table 4) However, this occurred at the cost of a higher relapse rate.

Findings in high-risk APL
A total of 219 patients with high-risk APL received induction therapy. Pretreatment characteristics were well balanced between the groups. Median WBC count was 23.7 g/L and 19.7 g/L in the AraC and AraC plus ATO groups, respectively. Seven early deaths occurred, due to bleeding (n = 1), thrombosis (n = 3), sepsis (n = 1), or other (n = 2).
Nine patients died in CR, of which seven (7.8%) were in the AraC arm, two (5.1%) were in the AraC plus ATO arm prior to omission of AraC from the protocol, and 0 were in the AraC plus ATO arm after omission of AraC from the protocol (\( p = 0.04 \)).

Overall the CR rate after induction therapy for high-risk patients was 96%. Two-year OS was high in both treatment arms (95.0% and 96.0% in the AraC and AraC plus ATO groups, respectively; \( p = 0.77 \)) and 2-year EFS rates were similar between treatment arms (93.0% vs. 94.5%; \( p = 0.63 \)). Two-year and five-year CIR rates were also similar between groups. (Table 5) This held true even after AraC was removed from the AraC plus ATO protocol, suggesting that AraC could be replaced by ATO during consolidation in patients with high-risk APL.

During consolidation, the times to neutrophil recovery and platelet recovery were significantly longer in the AraC plus ATO arm prior to omission of AraC from the protocol. (Table 6) After removal of AraC from the AraC plus ATO protocol, these times were significantly reduced (\( p <0.001 \)).

### Conclusion

The results of this trial showed that classical ATRA and anthracycline-based chemotherapy combinations resulted in very high CR rates for patients with standard-risk APL, with few relapses. These results strongly suggested that relapse rates observed with regimens without ATO can be significantly reduced by the addition of ATO in patients with standard-risk APL. For patients with high-risk APL, the addition of ATO to an ATRA/chemotherapy regimen did not reduce relapses and added some myelosuppression. However, the addition of ATO to therapy in high-risk APL appeared to be useful when AraC was not included in consolidation therapy.

### Improvements with risk-adapted PETHEMA protocols in newly diagnosed APL

At the 2017 International Symposium on APL, Dr. Sanz presented a review of the protocols that have been used by the PETHEMA group to treat newly diagnosed APL from 1996 to the present. Updated analyses demonstrated how the protocol has been improved over time.

### The first PETHEMA protocols: LPA96 and LPA99

The original PETHEMA protocol for APL was published in 1997. The backbone of the LPA96 protocol was designed by the Italian GIMEMA group and was comprised of the combination of ATRA and idarubicin (AIDA) for induction. This was followed by three sequential consolidation courses and maintenance therapy.

The LPA96 protocol was designed for all patients with APL; however, results from a joint study by the GIMEMA and
PETHEMA groups demonstrated different outcomes for patients according to their WBC and platelet counts at presentation. Based on these results, the LPA96 protocol was modified to create the LPA99 protocol. In the LPA99 protocol doses were reduced for elderly patients and all patients were categorized as being at high, intermediate, or low risk of relapse based on their baseline WBC and platelet counts. The consolidation treatment was then adapted based on the patient’s risk group. This risk-adapted strategy has been used in all subsequent PETHEMA protocols.

**PETHEMA (LPA96) study design**

**Induction therapy**

| AIDA |

**Consolidation therapy**

| #1 Idarubicin | #2 Mitoxantrone | #3 Idarubicin |

**Maintenance therapy**

| Mercaptopurine + Methotrexate + ATRA |

**AIDA = all-trans retinoic acid, idarubicin; ATRA = all-trans retinoic acid**

Adapted from Mandelli et al., Blood 1997.

**Induction therapy with AIDA in the PETHEMA protocols**

The LPA96, LPA99, LPA2005, and LPA2012 protocols all used AIDA for induction. Overall CR rates have improved slightly over time, with CR rates of 89% in the LPA96 protocol and 92% in the LPA2012 protocol ($p = 0.07$). (Figure 1) This is likely due to physicians becoming more experienced with the induction treatment over time.

**Comparison of LPA99 and LPA2005 protocols**

In the LPA2005 protocol, mitoxantrone doses were reduced in the second consolidation course for low- and intermediate-risk patients, as well as for all patients who were ≥60 years of age. The goal of this change was to reduce toxicity. For high-risk patients, cytarabine (AraC) was added in the consolidation courses to increase antileukemic effect and idarubicin was reduced to lower toxicity.

A study comparing the LPA99 and LPA2005 protocols was published in 2010 with 795 patients and a median follow-up of 40 months. An update of this study was completed on September 15, 2017 with 1,397 patients and a median follow-up of 75 months. In this updated analysis, the LPA2005 protocol resulted in lower relapse rates for high-risk patients compared to the LPA99 protocol ($p = 0.02$). (Figure 2) This translated to an increase in overall survival (OS) for all patients in the LPA2005 protocol ($p = 0.02$). (Figure 2)

**Figure 1. Induction therapy with AIDA: the PETHEMA experience**

**Figure 2. Outcome improvements between PETHEMA/HOVON LPA99 and LPA2005**

* CIR = cumulative incidence of relapse; CR = complete remission; OS = overall survival

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**Table 1.**

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<th>Trial</th>
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</tr>
<tr>
<td>LPA2012</td>
<td>234</td>
<td>92</td>
</tr>
</tbody>
</table>

$* Seven patients were assessed very early (Days +18 to +36) and erroneously interpreted as resistant leukemia.
**Comparison of LPA2005 and LPA2012 protocols**

Changes in the LPA2012 protocol included extending the use of AraC in consolidation to the intermediate-risk group, reducing the dose of idarubicin in consolidation for elderly and intermediate-risk patients, and upgrading the risk group for patients who were positive for cluster of differentiation 56 (CD56). This was included after the publication of a 2011 paper that showed higher relapse rates in patients who were CD56-positive compared to those who were CD56-negative. Low-risk patients with CD56 expression ≥20% were upgraded to receive the intermediate-risk treatment, and intermediate-risk patients with CD56 expression ≥20% were upgraded to receive the high-risk treatment.

The LPA2005 and LPA2012 protocols are currently being compared. An interim analysis was completed on September 15, 2017 with 830 patients and a median follow-up of 54 months in the LPA2005 protocol, and 222 patients and a median follow-up of 24 months in the LPA2012 protocol. This interim analysis showed that in the third course of consolidation, the incidences of neutropenia and thrombocytopenia were significantly reduced in the LPA2012 protocol compared to the LPA2005 protocol in the overall and high-risk populations. (Figure 3) This reduction in hematological toxicity occurred without any effect on OS or CIR in the overall population.

A higher CIR was seen in CD56-positive patients compared to CD56-negative patients in the LPA2005 protocol \((p < 0.0001)\). However, in the LPA2012 protocol there was no difference in CIR when patients were stratified by CD56 expression. (Figure 4) It should be noted that this is an interim analysis with a small number of patients from the LPA2012 protocol. A full analysis of the entire patient population will be released in the future.

**Figure 3. Hematological toxicity during consolidation: improvements between PETHEMA/HOVON LPA2005 and LPA2012**
Future PETHEMA protocol: LPA2017

As of July 2017, the PETHEMA protocol has changed to use strategies without or with minimal use of chemotherapy. (Figure 5) The combination of ATRA and ATO is now being used for induction and consolidation in the low- and intermediate-risk groups, as described in the 2013 paper by Lo-Coco et al. For high-risk patients, the PETHEMA group is going to participate in the APOLLO trial which will compare the LPA2012 protocol to ATO, ATRA, and low-dose idarubicin in induction and ATRA plus ATO in consolidation (NCT02688140).

Figure 4. Outcome improvements by CD56 expression between PETHEMA/HOVON LPA2005 and LPA2012

Figure 5. Risk-adapted strategy in APL without or with minimal use of chemotherapy: the PETHEMA LPA2017 protocol

An update on APML4 and APML5

Dr. Harry Iland presented updated results from the APML4 and APML5 trials initiated by the Australasian Leukaemia & Lymphoma Group (ALLG).1 The APML4 study was a phase II, non-randomized trial examining the addition of ATO therapy in induction and consolidation stages for the first-line treatment of APL. The goal of this approach was to improve efficacy of APL treatment while reducing the reliance on chemotherapy. The APML4 treatment protocol included all-trans retinoic acid (ATRA) and idarubicin (age-adjusted), followed by ATO at Day 9 and onwards in the induction phase. (Figure 1) The consolidation phase eliminated anthracyclines and cytarabine, and instead included a combination of ATO and ATRA cycles. A maintenance phase including low-intensity chemotherapy and ATRA was included in the protocol, based on experience from the APML3 study where an amended maintenance protocol rescued the trial by decreasing the rate of relapse.2 This maintenance cohort from the APML3 trial was used as a historical control. Molecular monitoring of bone marrow by quantitative reverse transcription polymerase chain reaction (RT-qPCR) occurred every three months for three years following consolidation.

Updated results from the 124 evaluable patients in this trial were published in The Lancet (median follow-up of 4.2 years).3 The median age of patients was 44 years (range: 3–78) and 23 patients (19%) were high risk. There were four early deaths (3.2%), which was found to be significantly associated with age >70 years based on an exploratory subgroup analysis. Disease-free survival (DFS) was significantly superior in APML4 compared to APML3 (HR = 0.21; p = 0.001). The 5-year DFS rate was 95% vs. 79% for APML4 and APML3, respectively. White blood cell (WBC) count did not impact DFS or cumulative incidence of relapse (CIR) (approximately 5% regardless of WBC count). Despite the availability of ATO as salvage therapy in the APML3 trial, the APML4 trial demonstrated improved results in event-free survival (EFS; HR = 0.34; p = 0.002) and overall survival (OS; HR = 0.35; p = 0.02), with superior 5-year survival rates (EFS: 90% vs. 72%; OS: 94% vs. 83%). In a multifactor analysis, increased age (>70 years) and increasing Sanz risk were significantly correlated with decreased EFS and OS, and complex karyotype (≥2 additional cytogenetic abnormalities) was associated with worse DFS. In a post hoc analysis comparing outcomes stratified by disease risk category, EFS, OS, and DFS in the APML4 trial were superior to APML3 in standard-risk patients. In addition, DFS was superior in the APML4 trial for high-risk patients (n = 23).

Although the chemotherapy-free protocol from the APL406 trial is likely to displace the APML4 protocol due to the outstanding outcomes in standard-risk patients,4 the results from this study highlight the place for the APML4 protocol in the treatment armamentarium for patients with high-risk APL. For many years, ATRA and risk-adapted chemotherapy has been the gold-standard for high-risk APL based on evidence from the PETHEMA LPA2005, European APL2000, and GIMEMA AIDA2000 trials.5-8 Although the population in the APML4 study is smaller than these large European trials, DFS, CIR, and OS in the APML4 trial are comparable or superior to these trials, with significantly lower idarubicin equivalent content, absence of cytarabine, and no deaths in remission. Consequently, this protocol is one of four recommended protocols by the National Comprehensive Cancer Network for patients with high-risk APL and is also recommended by a panel of Canadian experts led by Dr. Seftel.9,10
Some existing complications with the use of ATO in APL therapy are the significant time commitment for patients and the drain on hospital resources associated with the frequent two-hour intravenous (iv) administration of the drug. Although an oral form of ATO would increase convenience, some considerations for this route of administration are possible food restrictions and reduced compliance. Nevertheless, an oral formulation of ATO (Realgar-Indigo naturalis formula [RIF]) was shown to be highly effective and non-inferior to iv ATO in the APL07 trial by the Chinese APL Cooperative Group. As this oral ATO compound is not available outside of China, the ALLG has partnered with Eupharma/Phebra to develop an arsenocarbonate complex derived from ATO that can be encapsulated. This oral form of ATO rapidly dissolves in simulated gastric juice, liberating trivalent inorganic arsenic (the most active form for absorption).

Evaluation of this new compound in clinical trials must be conservative, so as to not compromise the safety of patients with APL for which high cure rates can already be achieved by iv ATO. This forms the rationale for initiating APML5, a phase I pharmacokinetic evaluation of this new oral formulation of ATO in previously untreated patients with APL. Registration for the APML5 study occurs in the consolidation phase, once molecular complete remission (CRm) is achieved. Eligible patients have a diagnosis of APL and have received either induction following the protocol by Lo-Coco et al. for standard-risk patients or the APML4 protocol for high-risk patients. The consolidation phase follows the Lo-Coco et al. protocol consisting of 4 cycles of ATO and 7 cycles of ATRA for all-risk groups. Maintenance is not included in this protocol. Part 1 of the study will enroll eight patients who will receive iv ATO throughout treatment except for the first week of the second cycle and the first week of the fourth cycle, where patients will receive oral ATO starting at a dose of 0.15 mg/kg/day (dose will be adjusted in Cycle 4 based on pharmacokinetic [PK] data from Cycle 2). The aggregate PK data from part 1 will be used to derive an oral dose for part 2 of the study. Part 2 has a similar treatment design; however, there is a randomization in the order for which PK sampling is performed to further eliminate bias. This study is in progress and has currently enrolled its first patient. Beginning with this study, the aim of the ALLG is to develop an oral ATO regimen that is as effective and at least as safe as iv ATO, that improves the overall treatment experience, and is acceptable to regulatory agencies worldwide.

A bortezomib and ATO combination regimen for relapsed APL

Currently, there are few data on the management of patients who relapse following first-line treatment with ATO-based therapy. In a presentation by Dr. Vikram Mathews, the mechanistic basis of relapse following ATO therapy and a clinical trial investigating a new therapeutic regimen in the relapsed setting were discussed.

With the goal of exploring the clinical, cellular, and molecular changes occurring at relapse, a study led by Dr. Vikram Mathews found that several genes involved in cell adhesion and cytokine signalling were upregulated in patients with relapsed APL compared with newly diagnosed patients. These pathways have previously been reported to be involved in microenvironment-mediated drug resistance (EM-DR) in...
other malignancies, leading to the hypothesis that EM-DR may play a role in relapse following ATO therapy. To support this hypothesis, stromal cells were found to provide a survival advantage to malignant promyelocytes against ATO in in vitro co-culture assays. This advantage was mediated by the nuclear factor-kappa B (NF-κB) pathway.

Based on the gene expression data collected from this study, a panel of inhibitors was screened in a co-culture assay to assess their ability to rescue malignant promyelocytes from EM-DR. Of the drugs screened, the proteasomal inhibitor bortezomib sparked interest as it is easily accessible and is widely used to treat other malignancies. In previous studies, bortezomib has been found to have direct cytotoxicity on promyelocytic leukemia cells. In a follow-up study by Dr. Mathews and his colleagues, bortezomib was also found to restore the sensitivity of malignant promyelocytes to ATO at pharmacologically relevant concentrations. The combination of both ATO and bortezomib had synergistic effects in vitro in both ATO-sensitive and ATO-resistant APL cell lines. This effect involved downregulation of the NF-κB pathway, an increase in unfolded protein response, and an increase in reactive oxygen species generation. Despite proteasome inhibition by bortezomib, the combination of ATO and bortezomib was able to clear the promyelocytic leukemia-retinoic acid receptor alpha (PML-RARα) oncoprotein, which has been proposed to be mediated by a p62-dependent autophagy pathway. The efficacy of ATO and bortezomib was validated in an APL mouse model, where the combination was effective in reducing leukemic burden and improving survival. This study also reported preliminary data from two patients from India with APL at second relapse, who received an ATO and bortezomib-based induction regimen on a compassionate basis with informed consent. The combination was well tolerated and both patients remain in molecular remission at approximately 5 years since the second relapse.

This preliminary experience led to the rationale and design of a phase II trial examining the combination of bortezomib, ATO, ATRA, and mitoxantrone as induction therapy in patients with relapsed APL (NCT01950611). After confirmed molecular remission, patients would either receive autologous stem cell transplant (SCT) or maintenance therapy consisting of bortezomib, ATO, ATRA, and intrathecal methotrexate, based on their available resources. Eighteen patients with hematological relapse were enrolled in the trial and completed treatment between September 2013 and June 2016. The median age of patients was 24 years (range: 9–53) and all patients had previously received ATO upfront. The median time from diagnosis to first relapse was 21 months (range: 8–128).

After initiation of treatment, the median time to hematological remission was 45 days (range: 42–63). All patients achieved CRm and 17 patients (94%) were RT-qPCR–negative post induction. No patients had any major bleeding or thrombotic events and only one patient had a differentiation syndrome. The majority of adverse events were grade ≤2, transient, and did not require dose interruption. Grade 4 peripheral neuropathy was seen in one patient, who discontinued bortezomib after three maintenance cycles. No additional in-patient admissions were required post induction. After consolidation therapy, eight patients (44.4%) received autologous SCT and 11 (60.6%) received maintenance therapy. Compared to a historical control of 29 patients receiving the same therapeutic regimen with the exception of bortezomib, there was a statistically significant reduction in the amount of fresh frozen plasma used. Though not statistically significant, a reduction in coagulopathy and consumption of blood bank products was also observed. OS and EFS outcomes were significantly superior with the bortezomib regimen compared to historical controls. (Figure 2)

**Figure 2.** Comparison of survival outcomes between historical control (Group 1) and patients with APL enrolled in a phase II study with additional bortezomib (Group 2).
Early results from this trial suggest that the combination of ATO and bortezomib is well tolerated; however, the optimal dose and schedule for bortezomib needs to be defined. A larger study with longer follow-up is required, particularly to evaluate whether the OS and EFS results for patients not receiving autologous SCT are maintained, which may provide insight on whether SCT is needed in the relapsed setting. This finding would have a significant impact on patients with APL living in India who often do not have the funds to receive an SCT. Finally, with the availability of more potent proteasome inhibitors, future studies to evaluate the efficacy of these agents in combination with ATO for patients with relapsed APL are warranted.

**An update on AML17**

Dr. Nigel Russell presented updated results from the AML17 trial initiated by the National Cancer Research Institute acute myeloid leukemia (AML) working group. The AML17 trial was a randomized, controlled, multicentre study comparing a chemotherapy-free ATO and ATRA regimen with the standard ATRA and idarubicin (AIDA) chemotherapy-based regimen in patients with high- or low-risk APL. In total, 235 patients were randomized to receive either ATO and ATRA (n = 116) or AIDA (n = 119) therapy. In the ATO and ATRA arm, iv ATO was given at 0.3 mg/kg on Days 1–5 of the first week of induction and consolidation, followed by 0.25 mg/kg twice weekly for 7 weeks in induction and for 3 weeks in consolidation. This attenuated ATO schedule decreased the total days of ATO therapy from 140 to 63 days and the dose from 1,470 mg to 1,190 mg for a 70 kg patient, compared with the GIMEMA-AMLSG-SAL protocol. Of note, high-risk patients randomized to the ATO and ATRA arm could receive an initial dose of the immunoconjugate gemtuzumab ozogamicin (GO; iv, 6 mg/m²) within the first four days of therapy. Maintenance treatment was omitted from the AIDA arm due to previous reports of treatment-related AML and myelodysplastic syndrome. Minimal residual disease (MRD) was strictly monitored and centrally analyzed by RT-qPCR in all patients every three months until three years from diagnosis. Patients who had a molecular relapse after AIDA could receive the same schedule of ATO. In addition, 70 patients received AIDA after randomization was closed (due to ATO supply issues), and were available for the study of ATO at relapse.

The median age of patients in this trial was 47 years (range: 16–77), 99% of patients had newly diagnosed APL, and approximately 25% of patients had high-risk APL. The median time to molecular remission was 83 days in the AIDA arm and 111 days in the ATO and ATRA arm. The rate of RT-qPCR negativity at 60 days was significantly higher in the AIDA versus ATO and ATRA arm (73% vs. 56%; \( p = 0.03 \)). For the three patients in the ATO and ATRA arm who failed to achieve an early molecular remission, treatment was intervened with AIDA cycles and/or GO. At a median follow-up of approximately six years, the ATO and ATRA arm produced significantly higher 5-year rates for EFS, frank relapse-free survival (RFS), and molecular RFS compared to the AIDA arm. (Table 1) The 5-year cumulative incidences of hematological and molecular relapse were also significantly better in the ATO and ATRA arm. OS was not significantly different between treatment arms in the total population or when stratified by high- and low-risk disease.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>AIDA (%)</th>
<th>ATO + ATRA (%)</th>
<th>HR/OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>91</td>
<td>96</td>
<td>0.46 (0.17–1.27)</td>
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<tr>
<td>Molecular negativity</td>
<td>90</td>
<td>93</td>
<td>0.67 (0.27–1.66)</td>
<td>0.4</td>
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<tr>
<td>30-day mortality</td>
<td>6</td>
<td>4</td>
<td>0.72 (0.23–2.31)</td>
<td>0.6</td>
</tr>
<tr>
<td>Resistant disease</td>
<td>3</td>
<td>0</td>
<td>0.14 (0.02–0.97)</td>
<td>0.05</td>
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<tr>
<td>60-day mortality</td>
<td>9</td>
<td>5</td>
<td>0.55 (0.21–1.43)</td>
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<tr>
<td>5-year survival</td>
<td>87</td>
<td>93</td>
<td>0.61 (0.27–1.35)</td>
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<tr>
<td>5-year EFS</td>
<td>79</td>
<td>93</td>
<td>0.38 (0.19–0.77)</td>
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</tr>
<tr>
<td>5-year frank RFS</td>
<td>87</td>
<td>97</td>
<td>0.33 (0.13–0.85)</td>
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<tr>
<td>5-year molecular RFS</td>
<td>77</td>
<td>98</td>
<td>0.19 (0.09–0.41)</td>
<td>&lt;0.0001</td>
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<td>5-year CIDCR</td>
<td>2</td>
<td>2</td>
<td>1.72 (0.18–16.6)</td>
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<td>5-year CIHR</td>
<td>10</td>
<td>1</td>
<td>0.16 (0.05–0.48)</td>
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<td>5-year CIMR</td>
<td>21</td>
<td>0</td>
<td>0.12 (0.05–0.30)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>5-year CITAML</td>
<td>1</td>
<td>0</td>
<td>0.15 (0.003–7.48)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

AIDA = all-trans retinoic acid, idarubicin; ATO + ATRA = arsenic trioxide and all-trans retinoic acid; CI = confidence interval; CIDCR = cumulative incidence of death in complete remission; CIHR = cumulative incidence of hematologic relapse; CIMR = cumulative incidence of molecular relapse; CITAML = cumulative incidence of treatment-related myelodysplastic syndrome or acute myeloid leukemia; CR = complete remission; EFS = event-free survival; HR = hazard ratio; OR = odds ratio; RFS = relapse-free survival
Of the 189 patients who were treated with AIDA during or after randomization, 30 patients relapsed following therapy, including 18 molecular relapses. The attenuated ATO and ATRA schedule was administered to 29 of these patients (one patient died before salvage therapy could be initiated), all of whom achieved CRm on salvage treatment. Following molecular remission, 13 patients underwent an SCT (autologous = 10 patients, allogeneic = 3 patients), including four of five patients with central nervous system disease. The remaining 16 patients were treated with a full course of ATO and ATRA alone (without chemotherapy). Three of these 16 patients experienced a second molecular relapse, with one of the patients receiving a later SCT. All patients treated with ATO and ATRA salvage therapy alone remain alive.

The updated analysis of the AML17 trial confirms the superior 5-year EFS results for the ATO and ATRA regimen compared to AIDA. Notably, no patient in the ATO and ATRA arm who achieved molecular negativity experienced relapse compared with 21% of patients in the AIDA arm. This low risk of relapse negates the need for MRD monitoring after CRm is achieved; however, molecular surveillance for three years remains important in relapsed patients treated with ATO and ATRA. A survival benefit for ATO and ATRA was not observed in this study; however, this may be attributed to the excellent results of salvage therapy with ATO and ATRA in the AIDA arm, and the fact that many of these patients received this salvage therapy at molecular relapse. Overall, results from the AML17 trial show that the attenuated ATO schedule was safe and effective in the front-line and relapsed setting for patients with APL. In addition to the efficacy and safety, the increased convenience to patients and cost implications of this attenuated ATO regimen are important considerations that may help influence regulatory bodies to make ATO available to patients in the first-line setting.

Clinical trials in patients with high likely success rates

In a disease such as APL, where the combination of all-trans retinoic acid (ATRA) and chemotherapy (AIDA) results in cure rates of 90%–95%, ethical issues arise when trying to improve therapy for these patients with an investigational drug. This was the case when researchers were looking to evaluate arsenic trioxide and ATRA in patients with APL. In this type of population, it is important to consider the cost of using an investigational drug. Dr. Estey described a statistical design to help quantify the cost in lives lost or lost benefit if a trial with an investigational drug is unsuccessful. In this design, cohorts of six patients would be treated, and if there was a $\geq 90\%$ probability that the rate of complete remission (CR) was $<90\%$ (the historical CR rate for AIDA), trial accrual would be stopped. With this design, if the true CR rate of the investigational therapy was 60%, a median of 12 patients would be enrolled, resulting in seven patients achieving CR. If comparing to AIDA, a CR rate of 90% would result in 11 patients achieving a CR, leaving four patients with lost benefit to therapy. If the true CR rate was $<60\%$, accrual would stop earlier and the cost in terms of lost benefit would be the same. This type of study design is an oversimplification if the accrual is quicker than patients can be evaluated and one must be willing to accept the high-false negative rates inherent to this design.

If positive results are achieved with this trial design, the next step would be to evaluate the investigational drug in a randomized clinical trial compared to the standard of care. It is difficult to justify a randomized study design when the standard of care has a high success rate. One method to overcome this problem is through adaptive randomization, which uses a Bayesian design rather than the sequential group design typically used in randomized clinical trials. This type of study uses interim data to repeatedly compute the probability that one treatment is better than the other, allowing randomization to be unbalanced to favour the better treatment.

One of the disadvantages to this method is the inherent subjectivity of Bayesian prior probabilities; however, it is important to note that $p$-values can also be subjective. This type of Bayesian design can also lead to higher type 1 or 2 errors due to a small sample size if the trial is stopped early or if treatment groups have unequal sizes. In addition, the study may not be feasible if adequate computing facilities are unavailable or if accrual is quick compared to the length of time required to observe the desired outcome. An advantage of the adaptive randomization design is that it operates in agreement with how patients believe physicians practice, where a physician will continuously learn from each patient they treat and adjust their practice accordingly.

Clinical trials in small patient subsets

As new molecular subgroups continue to be identified in AML, it is important to consider how to account for the heterogeneity of patients in clinical trials. At one extreme, patient heterogeneity can be ignored, as in the Simon 2-stage design, and at the other extreme, separate trials can be created for each subgroup. The current practice in clinical trials is to design a large trial with a two-sided $p$-value of 0.05 that can detect a small difference with a power of 80%. However, it is often not feasible to design a large trial to evaluate the effect of a drug on a specific subgroup as it would take a long time to accrue enough patients to achieve the statistical power desired. Additionally, in this scenario, data from one trial cannot be used to adaptively affect the conduct of other trials. To overcome this limitation a third method, which considers subgroup-treatment interactions, can adaptively use data to see to what extent subgroups can be combined (“borrowing strength”).
A seamless phase II-phase III trial design could also help to obtain mature data in a shorter timeline. The conventional practice of initiating a phase III randomized trial following a phase II study fundamentally wastes information, as the most mature data comes from the phase II study (which often is not randomized). Even in instances where phase II trials are randomized, the decision to move forward to a phase III study rests on the response data, assuming a correlation between response and survival exists. This leads to a large delay between the phase II trial and the initiation of a phase III trial.

In a seamless phase II-III design, randomization of the experimental and standard arm would occur from the beginning. In this type of design, repeated interim decisions would be made based on response and survival and the relation between these two outcomes. For example, a decision to stop the trial could be made based on the conclusions that the experimental arm is better or worse than the standard therapy, or a decision to continue the trial and expand to a phase III trial could be made without interruption in accrual. Simulations show that this method results in much shorter trials with fewer patients compared to the phase II Simon 2-stage and subsequent phase III group sequential design, with no increase in type 1 or 2 errors. Given the knowledge gained in AML over the years, Dr. Estey suggests it is time to move away from the conventional trial designs of the past and towards new adaptive methods.

**The value of minimal residual disease detection in AML**

Dr. Francesco Lo-Coco was the first to treat patients at molecular relapse in APL with gemtuzumab ozogamicin. Following this study, several questions were raised regarding the value of minimal residual disease (MRD) in AML. One of these questions is whether MRD can improve disease prognosis. In a study by Jourdan et al., which investigated the predictive factors of relapse in AML patients with the translocation between chromosomes 8 and 21, a 3-log reduction in MRD was more predictive of relapse than other pre-treatment factors such as white blood cell count and receptor tyrosine kinase mutations. However, models to predict long-term outcomes in patients with AML remain limited. In the SWOG SO106 study, addition of multiparameter flow cytometry (MFC) data to evaluate MRD improved the prognostication model for relapse-free survival and overall survival; however, the c-statistic values (0.66 and 0.70, respectively) still showed only a fair ability for the model to predict outcomes.

Whether MRD monitoring can replace morphology in the future is another question of interest in AML. One advantage to evaluating molecular relapse over morphologic relapse is that the methods used to predict MRD are more sensitive than morphology methods. MRD also has a high positive predictive value for morphologic relapse and there is a short interval between MRD and morphologic relapse.

In order to address this question, a study from the University of Washington and Fred Hutchinson Cancer Research Center (FHCRC) aimed to determine the frequency with which morphologic relapse (≥5% blasts) in AML is accompanied by a negative MFC test. In this study, ten-color flow cytometry was performed in 87 patients with morphological relapse (≥5% blasts). MFC was abnormal in 86 of these patients, with one ‘suspicious’ result, indicating a false-negative rate of 0% (95% CI: 0–4). Results from this study led to a new policy at the FHCRC, whereby if MFC results are negative, morphology will only be performed in situations with declining blood counts. Identifying an MFC level above which morphology will invariably show >5% blasts may eliminate the need for morphology entirely in the future.

A caveat to using MFC to detect MRD is that this method is not standardized; however, it is important to note that morphology is also not standardized. With the examination of 500 cells, as recommended by the European LeukemiaNet, a discordance between pathologists on the identification of only 10 cells is needed to convert a report of 6% blasts (relapse) to 4% blasts (no relapse). Additionally, the 95% confidence intervals for 20/500 blasts (4%) and 30/500 (6%) blasts overlap (2%–6% and 4%–8%, respectively). In this situation, MFC has the advantage of having the ability to evaluate several orders of magnitude more cells than morphology, resulting in smaller confidence intervals.

The question of whether defining relapse by MRD will result in a clinical benefit also remains to be answered. Currently, the AML-19 trial is evaluating the outcomes of patients with AML who are randomized to either receive or not receive MRD monitoring in CR. To understand the value of MRD reduction in AML, future studies must randomize between administering a new treatment when MRD is detected versus only when morphologic relapse is detected. This would require the availability of more new therapies to treat MRD, which is currently rare in registered clinical trials. This may be due to the effect that defining relapse by MRD may have on drug approvals, since the time to relapse will be reduced compared to current morphology-based criterion. Nonetheless, clinical trials for patients with MRD are important as they may facilitate the discovery of new drug activity and be associated with a favourable benefit-to-risk ratio depending on the treatment chosen.
Background
In elderly patients with acute promyelocytic leukemia (APL), conventional treatment with all-trans retinoic acid (ATRA)-anthracycline-based chemotherapy regimens is associated with very few relapses, but high death rates. ATRA and arsenic trioxide (ATO) combinations are at least as effective as ATRA plus chemotherapy, while being less myelosuppressive.1,2 At the 7th International Symposium on APL, results from the APL 2006 trial were presented, where ATO was combined with ATRA and chemotherapy was reduced in patients aged >70 and with standard-risk APL.3

Study design
- Between 2006 and 2015, 124 elderly patients received induction treatment with ATRA and idarubicin on Days 3, 5, and 7 until complete remission (CR).
- This was followed by a first consolidation course with three doses of idarubicin and ATO, and a second consolidation course with ATO and ATRA.
- Finally, maintenance was carried out with intermittent ATRA, mercaptopurine plus methotrexate, and ATO.
- After the inclusion of 55 patients, due to high mortality rate in CR, consolidation therapy was amended on September 2010 as follows:
  - One dose of idarubicin and ATO for the first course.
  - ATO and ATRA for the second course.
- A further 68 patients were included in the study post September 2010.
- The inclusion criteria were:
  - Newly diagnosed patients with APL, subsequently confirmed by conventional cytogenetic and/or presence of promyelocytic leukemia-retinoic acid receptor alpha transcript;
  - Aged >70 years;
  - White blood cell (WBC) count <10 G/L; and
  - No contraindication to intensive chemotherapy or arsenic trioxide.
- Analysis was made at the reference date of January 1, 2016.

Key findings

Baseline characteristics and disposition
- The median age of the patients was 73.5 years (interquartile range [IQR]: 71.8–77.9).
- The median WBC and platelet counts were 1.1 G/L (IQR: 0.8–1.8) and 44.0 G/L (IQR: 22.5–87.5), respectively.
- The median fibrinogen count was 2.3 g/L (IQR: 1.6–3.3).
- Of the total patient population, 5% had an M3 variant morphology, and 35% had a previous cancer.
- The median follow-up was 44 months.

Study design

<table>
<thead>
<tr>
<th>Induction</th>
<th>Idarubicin 9 mg/m² x 3</th>
<th>ATRA until CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consolidation 1</td>
<td>Idarubicin 9 mg/m² x 3</td>
<td>ATO 25 days</td>
</tr>
<tr>
<td></td>
<td>ATO 25 days</td>
<td>ATO 25 days</td>
</tr>
<tr>
<td>Consolidation 2</td>
<td>ATO 25 days</td>
<td>ATRA</td>
</tr>
<tr>
<td>Maintenance</td>
<td>Two-year maintenance with intermittent ATRA and continuous MTX + 6MP</td>
<td></td>
</tr>
</tbody>
</table>

15 days ATO cycles every 3 months during first year

6MP = mercaptopurine; ATO = arsenic trioxide; ATRA = all-trans retinoic acid; CR = complete remission; MTX = methotrexate
**Efficacy**

- The CR rate post induction was 91.1%.
- Of the patients with CR, 3 relapsed, all after the amendment.
- The 2-year cumulative incidence of relapse was 2.9% (95% CI: 0.8–7.5).
- The incidence of relapse was 0% before the amendment and 5.5% (95% CI: 1.4–13.8) after the amendment.
- The reduction of idarubicin had no impact on the incidence of relapse.
- The 2-year overall survival (OS) rate was 82.4% (95% CI: 75.8–89.5). (Figure 1)
  - The 2-year OS was not significantly different before and after the amendment.
- The 2-year event-free survival rate was 80.6% (95% CI: 73.8–88.1), with no significant difference according to period. (Figure 2)

**Safety**

- A total of 14 (12%) patients died in CR, including four (4%) accrued after the amendment versus 10 (20%) accrued before the amendment ($p = 0.045$).
- Causes of death in CR were:
  - Sepsis (four patients before and two after the amendment);
  - Bleeding (five before and one after the amendment);
  - General deterioration (one before the amendment); and
  - Prostate cancer (one after the amendment).
- Hematological toxicities are outlined in Table 1.

**Figure 1. Overall survival**

![Overall survival chart](chart1)

**Figure 2. Event-free survival**

![Event-free survival chart](chart2)

**Table 1. Hematological toxicities after first consolidation**

<table>
<thead>
<tr>
<th></th>
<th>Before September 2010</th>
<th>After September 2010</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days with antibiotics</td>
<td>6.2</td>
<td>3.8</td>
<td>0.22</td>
</tr>
<tr>
<td>RBC transfusion</td>
<td>2.9</td>
<td>1.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time to platelet &gt;50 G/L</td>
<td>5.6</td>
<td>4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time to ANC &gt;1 G/L</td>
<td>16.2</td>
<td>11.9</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

$ANC =$ absolute neutrophil count; $RBC =$ red blood cell

**Key conclusions**

- In elderly patients with standard-risk APL, the addition of ATO to ATRA and the reduction of chemotherapy was associated with:
  - High CR rates; and
  - No increase in rates of relapse when compared to investigators’ previous experience with ATRA plus chemotherapy protocols.
- A reduction of mortality in CR was seen when consolidation chemotherapy was reduced to one single-day dose of idarubicin.

De Luca ML, et al. APL 2017:PO038

APL in patients aged >70 years: Real-life results

**Background**

In the treatment of very elderly patients with acute promyelocytic leukemia (APL), very few cases have been described in a real-life setting. Therefore, at the 7th International Symposium on APL, De Luca and colleagues evaluated the clinical features and followed up with patients aged >70 years who were treated with arsenic trioxide (ATO) plus all-trans retinoic acid (ATRA), idarubicin plus ATRA, or ATRA alone.¹

**Study design**

- Patients aged >70 years were consecutively diagnosed and treated at the *Università “La Sapienza” di Roma* from January 1991 to June 2017.
- Patients’ clinical features were examined and followed up throughout the treatment process.
- Patients received induction therapy consisting of idarubicin plus ATRA, ATO plus ATRA, or ATRA alone.
- After the induction phase, patients who achieved complete remission (CR) received consolidation therapy with chemotherapy, chemotherapy plus ATRA, ATO plus ATRA, or ATRA alone.

**Key findings**

**Clinical features**

- A total of 22 patients were evaluated for clinical features.
- The median age at diagnosis was 74.9 years (range: 70.0–85.4).
- There were 17 patients with the M3 APL subtype and five patients with the M3 variant subtype.
- The median white blood cell count was 1.3 x 10⁹/L (range: 0.6–286).
- According to the Sanz risk score, nine patients were at low risk, eight patients were at intermediate risk, and five patients were at high risk.
- In terms of major comorbidities, 6 of the 22 patients had concomitant pulmonary diseases, 10 had arterial hypertension, 7 had a concomitant cardiologic disease, 3 had diabetes mellitus, and 9 had a previous malignancy.

**Induction**

- Two patients (9.0%) died very early after admission from gastrointestinal bleeding and fatal cerebral hemorrhage, respectively, and did not receive induction therapy.
- A total of 20 patients received induction therapy:
  - Twelve patients received idarubicin plus ATRA; of which, five patients required idarubicin dose reduction.
  - Three patients received ATO plus ATRA.
  - Five patients received ATRA alone, but two patients needed to add chemotherapy (mitoxantrone and cytarabine) to the treatment due to hyperleukocytosis.
  - There were 18 patients (90%) who achieved morphological CR after a median time of 45 days (range: 28–66).
  - A total of 16 patients also achieved molecular CR after a median time of 118 days (range: 51–239).
  - The remaining two patients had not yet had a molecular evaluation.
- Infective complications were observed in 16 of the 20 patients (five episodes of fever of unknown origin, six sepsis cases, three cystitis cases, four pneumonitis cases, and one oral abscess case).
- ATRA syndrome occurred in 6 of the 20 patients.
- There were three episodes of respiratory failure, five episodes of arrhythmia (two paroxystic atrial fibrillations and one QT prolongation), and one episode of cardiac ischemia.

**Consolidation and maintenance**

- A total of 16 patients in CR received consolidation therapy:
  - Seven patients received chemotherapy alone;
  - Five patients received chemotherapy plus ATRA;
  - Three patients received ATO plus ATRA; and
  - One patient received ATRA alone.
- After consolidation, 9 of the 16 patients received maintenance treatment.
• The remaining two patients in CR who did not receive consoli-
dation therapy directly underwent maintenance treatment.
• Four patients had a hematological relapse after 7, 8, 11, and 35 months, respectively; two patients had a molecular relapse after 12 and 56 months, respectively.
• At present, 12 patients are still alive; four patients died due to disease progression (three patients) or senectus while in CR (one patient); two patients were lost to follow-up while in molecular CR.
• The 3-year cumulative event-free survival for all patients was 58.9% (95% CI: 36.5–81.3). (Figure 1)
• The 3-year cumulative overall survival for all patients was 63.2% (95% CI: 40.8–85.6). (Figure 2)

Figure 1. Three-year cumulative event-free survival for all patients

Figure 2. Three-year cumulative overall survival for all patients

Key conclusion

• ATRA-based treatment of APL is safe and effective in elderly patients over 70 years old, with long-lasting disease-free and overall survival.


Cicconi L, et al. APL 2017:CO032

Prolonged ATO and ATRA therapy for relapsed APL

Background
Arsenic trioxide (ATO) combined with all-trans retinoic acid (ATRA) is the standard salvage regimen for relapsed acute promyelocytic leukemia (APL); however, the optimal consolidation strategy remains undefined. The approach of giving prolonged ATO and ATRA with repeated cycles has not been investigated in relapsed APL. A retrospective analysis of patients with relapsed APL who were treated with prolonged ATO and ATRA at two Italian institutions was presented at the 7th International Symposium on APL.

Study design
• The objective of this retrospective study was to verify the efficacy of a prolonged ATO and ATRA therapy without subsequent stem cell transplant (SCT) in a cohort of patients with relapsed APL.
• This study included 22 adult patients with relapsed APL who were treated at two Italian Institutions between 2006 and 2017.

• All patients received ATO and ATRA during both induction and consolidation, with or without subsequent SCT, as per dosing and scheduling in previous studies.²

• Molecular analysis of the promyelocytic leukemia-retinoic acid receptor alpha translocation was performed by real-time quantitative polymerase chain reaction.

**Key findings**
• The median age of patients was 43.5 years (range: 18–80) and the median duration of previous complete remission (CR) was 32.5 months (range: 5–120).

• Of the 22 patients evaluated, 18 were being treated at first relapse and four were being treated at second or subsequent relapse.

• The breakdown of relapse by type was as follows:
  ○ Hematological (n = 7);
  ○ Molecular (n = 14); and
  ○ Extramedullary (n = 3).

• Front-line therapy included ATRA plus idarubicin (AIDA) in 20 patients and an amended AIDA regimen for two patients defined as elderly.

• After two cycles of ATO and ATRA salvage therapy, molecular remission was achieved in 20 patients (90%).

  ○ Of these patients, one received subsequent autologous SCT and one received subsequent allogeneic SCT.

  ○ Of the 18 patients who did not receive an SCT, nine patients had a long previous molecular CR, five patients were unfit/elderly, two patients refused SCT, and two patients lacked a donor.

  ○ The median number of ATO and ATRA cycles was 5.

• At a median follow-up of 58 months, 14 patients (68%) remained alive and in molecular remission, seven patients (32%) relapsed or were resistant to therapy, and one patient died while in molecular remission. (Table 1)

• The Kaplan-Meier curve for disease-free survival is presented in Figure 1.

<table>
<thead>
<tr>
<th>Table 1. Patient outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
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<tr>
<td>21</td>
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<tr>
<td>22</td>
</tr>
</tbody>
</table>

Auto = autologous; Allo = allogeneic; CRm = molecular complete remission; HSCT = hematopoietic stem cell transplant; PCR = polymerase chain reaction

**Key conclusions**

• Data from this analysis suggest that prolonged ATO and ATRA therapy without SCT intensification may be an option for relapsed APL.

• A long first remission is associated with a higher probability of long-term molecular CR with prolonged ATO and ATRA.

• Prospective studies investigating prolonged ATO and ATRA therapy in relapsed APL are warranted to confirm this preliminary data.

**Background**

The European acute promyelocytic leukemia (APL) group identified an increased risk of relapse in pediatric patients with APL less than 5 years of age. At the 7th International Symposium on APL, survival and relapse outcomes from a cooperative group trial of pediatric patients with newly diagnosed APL were presented.

**Study design**

- The AAML0631 study was a phase III, nonrandomized, cooperative group trial using arsenic trioxide (ATO) consolidation in pediatric patients with APL.
- Data from pediatric patients in the Italian AIDA0493 trial were used as a historical control.
- Eligibility criteria included age ≥2 to <22 years, de novo APL as confirmed by promyelocytic leukemia (PML)-retinoic acid receptor alpha (RARα) translocation by polymerase chain reaction (PCR), and no prior therapy.
- There were no exclusions based on organ function or performance score.
- Diagnostic white blood cell (WBC) count was used to define risk groups:
  - Standard risk (SR): WBC <10,000/µL; and
  - High risk (HR): WBC ≥10,000/µL.
- For SR patients with no Consolidation 4 treatment, 355 mg/m² daunorubicin equivalents were used (assuming 5:1 conversion ratio for both idarubicin and mitoxantrone to daunorubicin), resulting in a 45% reduction in anthracycline when compared with the AIDA0493 study.
- For HR and SR patients with positive results in real-time quantitative reverse transcriptase PCR (RQ-PCR; i.e., with Consolidation 4 treatment), 405 mg/m² daunorubicin equivalents were used, resulting in a 38% reduction in anthracycline when compared with the AIDA0493 study.

**Key findings**

- Trial accrual was open between March 9, 2009 and November 9, 2012.
- A total of 108 patients were enrolled in the study, with 101 patients (66 SR patients and 35 HR patients) evaluable for treatment outcome.
- There were seven exclusions: four that were PML-RARα PCR negative and three that had local consent issues.
- In the current analysis, patients were stratified by the following age groups:
  - Young children (2 to <5 years; n = 6); and
  - Older children (5 to <13 years; n = 27); and
  - Adolescents (13 to <22 years; n = 68).
- Sixty-seven percent of young children, 22% of older children, and 37% of adolescents enrolled were in the HR group (three-way comparison of HR proportion: p = 0.096).

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**ATO consolidation results in excellent survival in pediatric patients with newly diagnosed APL: A report from the Children’s Oncology Group Study AAML0631**

Kutny MA, et al. APL 2017:CO023

**Study design**

- **Induction**
  - Standard: 12 mg/m² x 3 doses (D1, 3, 5; HR: D1, 3, 5)
  - ATRA* D1–30

- **Consolidation 1**
  - 2 Dominoes cycle
  - ATO 0.15 mg/kg for 5 days x 5 weeks, ATRA D1–14

- **Consolidation 2**
  - AraC 1,000 mg/m² q12h D1–3
  - Mitoxantrone 10 mg/m² D3, 4
  - ATRA D1–14
  - IT AraC D1

- **Consolidation 3**
  - Standard: 1 mg/m² D1, 3, 5, ATRA D1–14, IT AraC D1

- **Consolidation 4**
  - If hematological CR not reached: Off-protocol therapy
  - AraC 1,000 mg/m² q12h D1–3, 5
  - Idarubicin 5 mg/m² on D4
  - ATRA D1–14

- **Maintenance**
  - 6 mercaptopurine 50 mg/m² oral daily: Maintenance and if needed, ATRA D1–14 every 3 weeks x 9 cycles, IT AraC D1 at cycle 3 only

* Pediatric dosing of 25 mg/m²/day, divided bid.

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**APL = acute promyelocytic leukemia; AraC = cytarabine; ATO = arsenic trioxide; ATRA = all-trans retinoic acid; bid = twice a day; CR = complete response; D = day; HR = high risk; IT = intrathecal; q12h = every 12 hours; RQ-PCR = real-time quantitative reverse transcriptase polymerase chain reaction; SR = standard risk; WBC = white blood cell.**
• The classic PML-RARα translocation between chromosomes 15 and 17 (t[15;17]) was present in five young children (83%), 11 older children (42%), and 46 adolescents (70%).
• Complex cytogenetics (PML-RARα t[15;17] in combination with other cytogenetic abnormalities) were identified in one young child (17%), 15 older children (58%), and 20 adolescents (30%) (three-way comparison of complex cytogenetics: $p = 0.028$).

• The 3-year overall survival rate was 100% for both young and older children, and 91% for adolescents ($p = 0.324$).
• The 3-year event-free survival was 100%, 96%, and 88% for young children, older children, and adolescents, respectively ($p = 0.540$).
• The 3-year risk of relapse (from the end of consolidation) was 0% for young children, 4% for older children, and 3% for adolescents ($p = 0.888$).

Key conclusions

• Although limited by small numbers, data from this analysis show similar outcomes in all pediatric age groups treated in the study.
• This suggests young age should not be used for risk stratification in APL when therapy includes ATO consolidation.
• Incorporating ATO consolidation allows dose reduction of anthracyclines while maintaining excellent outcomes in pediatric APL.


A Canadian Perspective on the Treatment of APL in Pediatric Patients by Dr. Oussama Abla

Acute promyelocytic leukemia (APL) is a rare disease in the pediatric population. Historically, pediatric patients with APL have been treated with anthracyclines and all-trans retinoic acid (ATRA), which has resulted in excellent survival outcomes. However, in this young population, there is a great concern about acute and late cardiac toxicity caused by anthracyclines. The previous Acute Myeloid Leukemia-Berlin-Frankfurt-Münster trials (AML-BFM 93 and AML-BFM 98) evaluated more than 1,000 children with acute myeloid leukemia (AML; including APL), and showed that 5% of them had late cardiomyopathy after receiving a cumulative dose of anthracycline of 300–450 mg/m². In fact, a few pediatric patients with APL have been reported with late heart failure requiring cardiac transplantation. Due to the cardiac toxicity associated with anthracyclines, there was a need to find a substitute to these drugs. Arsenic trioxide (ATO) has been shown to be well tolerated in adult patients with APL. Based on the efficacy and safety profile of ATO in adults, pediatric oncologists began to introduce it in clinical trials a few years ago.

In Canada, the standard of care for pediatric patients with APL depends on the risk stratification. Patients with APL are stratified into standard risk (white blood cell [WBC] count at diagnosis of <10,000/µL) and high risk (WBC ≥10,000/µL). At our institution and in most pediatric centres worldwide, the current standard of care for children with standard-risk APL is ATRA and ATO, without chemotherapy.

The use of ATRA and ATO is based on the excellent results of the Italian-German APL0406 trial, in which adult patients with standard-risk APL received ATRA plus ATO or ATRA plus chemotherapy. In this study, the event-free survival (EFS) and overall survival (OS) in patients receiving ATRA plus ATO versus ATRA plus chemotherapy were 97.3% versus 80%, and 99.2% versus 92.6%, respectively ($p <0.001$ and $p = 0.0073$, respectively). Moreover, the relapse rate was very low in the ATRA plus ATO group compared to ATRA plus chemotherapy (1.9% vs. 13.9%). Based on these results, most Canadian centres adopted the ATRA plus ATO regimen for pediatric patients with standard-risk APL a few years ago.

In pediatric patients with high-risk APL, the current standard of care is ATRA, ATO, and low-dose chemotherapy. This treatment protocol is based on the Australasian Leukaemia and Lymphoma Group (ALLG) APML4 study led by Dr. Harry Iland, which showed excellent survival outcomes and five-year relapse-free rates in adult patients with high-risk APL who received this regimen.
At the 7th International Symposium on APL, Dr. Matthew Kutny presented a study of the safety and efficacy of ATO and reduced chemotherapy in pediatric patients with newly diagnosed APL. It was the first large prospective pediatric trial using ATO in consolidation. The aim of this study was to greatly reduce the dose of anthracyclines and to substitute for this reduction with ATO. In the study, two cycles of ATO were used in combination with ATRA in the first consolidation phase, and the treatment regimen used 38% to 45% less daunorubicin. Most deaths in this study occurred during induction and were due to differentiation syndrome, complications from the disease, or coagulopathy. One patient died from infection in the consolidation phase, which could be explained by the addition of mitoxantrone (an anthracycline that is quite myelosuppressive) in consolidation. These safety results were better than those in the previous studies, although there were still some toxic deaths from anthracyclines.

In terms of cardiac toxicity, ATO did not result in heart failures or cardiac deaths on this trial. There were a few patients with QT prolongation on electrocardiogram, which is a common adverse event associated with ATO, but these events were low grade (grades 1 and 2); hence, ATO was generally well tolerated. Adverse events associated with ATO contained ATO. With the established efficacy and safety profile already been endorsed in our practice. However, we still need to assess the late effects of ATO, and the Children’s Oncology Group is currently investigating the long-term safety of ATO (e.g., neurocognitive effect) in pediatric patients with APL. It is also important to examine the relapse risk when maintenance chemotherapy is eliminated from regimens that contain ATO. With the established efficacy and safety profile of ATO, the future direction in APL treatment is to cure the disease without chemotherapy.


Creutzig U, et al. APL 2017:PO037

First experience with ATO and ATRA treatment in pediatric patients with low-risk APL

Background

Studies in adults with low-risk acute promyelocytic leukemia (APL) showed high cure rates and reduced toxicities after treatment with all-trans retinoic acid (ATRA) and arsenic trioxide (ATO); however, the study of this regimen in pediatric patients is limited.1 At the 7th International Symposium on APL, Creutzig et al. reported on the outcomes of 13 pediatric patients with low-risk APL treated with an ATO and ATRA regimen.2

Study design

- Since 2013, 13 patients with low-risk APL, aged 1–17 years, were treated with an ATO and ATRA regimen in nine hospitals in Germany and Austria (part of the acute myeloid leukemia [AML]–Berlin-Frankfurt-Münster consortium).

- A detailed outline of the treatment regimen is described in Figure 1.

- The following changes were made to the original treatment scheme:
  - ATO was given at a later start (Day 10) to avoid a hyperleukocytosis burst due to simultaneous ATO and ATRA at onset;
  - Patients received a one-week break from ATRA after the first 14 days; and
  - Seven intrathecal therapies with cytarabine (in age-dependent doses) were given every four weeks starting at Day 10 (after blast cell reduction).
Two patients received chemotherapy induction because either therapy was started in a hospital not involved in the consortium or the case was initially misdiagnosed as AML with level 2 maturation as classified by the French-American-British system.

Key findings
- The median follow-up was 2.4 years (range: 1.0–3.8).
- All patients experienced an increase of white blood cells (WBC) >10,000/µL during the first four weeks.
- The peak of WBC values was on Day 14 of treatment.
- In six patients, hyperleukocytosis with clinical signs of differentiation syndrome (DS) occurred.
- This occurred after starting ATO treatment in four patients (6–9 days after initiation).
- DS was managed with breaks of ATO, dexamethasone, hydroxyurea, and low-dose cytarabine.
- One patient experienced posterior reversible encephalopathy syndrome and aseptic osteonecroses, and one patient experienced temporary abducens paresis.
- Transient grade 1 hepatic toxicities occurred in four patients, temporary grade 1 corrected QT time prolongation occurred in two patients, and facial eczemas were reported in two patients.
- Only one patient reported a long-term toxicity (psychological problems with headache and partial hair loss, two years after diagnosis).
- Generally, in-patient treatment duration was one week and all patients required only out-patient care after the induction phase.
- All patients achieved molecular remission after 7–20 weeks (median 10 weeks).
- One patient (an infant) was polymerase chain reaction-positive after 16 weeks.

Figure 1. Treatment Regimen

<table>
<thead>
<tr>
<th>APL-BFM RECOMMENDATION FOR STANDARD RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAB M3 (PML/RARα): ATO + ATRA IN PATIENTS WITH WBC &lt;10,000/µL</td>
</tr>
</tbody>
</table>

**Induction**
- Day 1–14
- ATRA
- IT starting Day 10, every 4 weeks, in total 7x
- MRD
- Day 1

**Maintenance**
- Day 10 to Day 42
- 2-week break
- ATO
- 4 weeks
- CR
- ATO
- IT every 4 weeks, in total 7x
- MRD
- Day 28

**Molecular remission**
- Day 78–90
- ATO
- 4-week break
- 4 weeks
- ATO
- 14 days, 14-day break

**Total 4x ATO following CR**

**BMP**
- Next BMP every 3 months until Month 12

**If PML/RARα remains positive, perform another cycle.**
- If still positive, additional therapy is required.

**In case of symptoms of differentiation syndrome, immediately start dexamethasone 10–15 mg/m²;**
- In case of rising WBC values, low-dose cytarabine (40 mg/m²/day) or hydroxyurea (2 x 20 mg/kg/day) is recommended.

Key conclusions
- Therapy with ATO and ATRA in pediatric patients with standard-risk APL was well tolerated.
- Similar to the Lo-Coco trial, prophylactic prednisone 0.5 mg/kg/day is recommended during induction to prevent DS.
- Due to the rising leukocyte counts observed, frequent blood count monitoring is recommended until blood counts drop.
- The best strategy for the introduction of ATO, whether starting cautiously on Day 10 or at an earlier start with ATRA, remains unclear.
- This new ATO and ATRA treatment regimen should only be applied in the pediatric setting by experienced clinics, while accompanied by expert consultation.

References:
Background
Acute promyelocytic leukemia (APL) accounts for about 5%–10% of all cases of childhood acute myeloid leukemia, with the disease being significantly more frequent in children of Mediterranean origin.\textsuperscript{1} Recent studies with adult patients with standard-risk APL have shown that combined therapy with arsenic trioxide (ATO) and all-trans retinoic acid (ATRA) leads to impressive cure rates and has a milder toxicity profile than standard chemotherapy regimens.\textsuperscript{2} However, data on the use of ATO and ATRA in childhood APL are scarce. At the 7\textsuperscript{th} International Symposium on APL, Gurnari and colleagues presented results from a collection of cases of pediatric patients with APL given the ATO and ATRA regimen.\textsuperscript{3}

Study design
• From April 2014 onwards, 17 children with APL were treated in seven Italian centres.
• They were given the ATO and ATRA combination regimen, as reported by the Gruppo Italiano Malattie Ematologiche dell’Adulto, the German-Austrian Acute Myeloid Leukemia Study Group, and Study Alliance Leukemia.

Key findings
Baseline characteristics
• The median age at diagnosis was 13 years (range: 4–17).
• Sixteen of the 17 children belonged to the standard-risk group (white blood cell [WBC] count ≤10,000/µL), while the remaining child had high-risk APL (WBC count >10,000/µL).

Efficacy
• All patients achieved hematological complete remission (CR) after induction therapy.
• All 14 patients who completed treatment achieved molecular CR.
• Neither hematological nor molecular relapses occurred during a median follow-up of 13 months (range: 2–41).
• Median hospital stay was 30 days (range: 15–43) during the induction phase.
• Consolidation courses were administered on an outpatient basis.
• Patient characteristics are presented in Table 1.

Safety
• Coagulopathy was present at diagnosis in 12 of 17 patients, and resolved during induction with no major complications.
• Hyperleukocytosis during therapy occurred in 10 of 16 standard-risk patients, with a median peak on Day 7.
• There were no cases of differentiation syndrome.
• Liver toxicity (a temporary increase in alanine aminotransferase/aspartate aminotransferase levels) occurred in nine patients:
  ▶ Grade 1 in four patients;
  ▶ Grade 2 in four patients; and
  ▶ Grade 3 in one patient.
• Two patients experienced transient corrected QT (QTc) interval prolongation (0.5 seconds).
• Pseudotumor cerebri was observed in one patient during consolidation.
• Hematological toxicities of varying severity were observed in all patients. (Table 1)
• Temporary treatment discontinuation was necessary in seven patients because of:
  ▶ Grade 3 liver toxicity;
  ▶ Prolonged QTc interval;
  ▶ Fever; and
  ▶ Pseudotumor cerebri.
### Table 1. Patient characteristics and treatment-related side effects

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<th>Patient number</th>
<th>Gender</th>
<th>Age (years)</th>
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<th>Coagulopathy</th>
<th>Initial WBC Peak WBC count</th>
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<td>F</td>
<td>17</td>
<td>3</td>
<td>Yes</td>
<td>1,840/μL 21,000/μL (Day 3)</td>
<td>Yes</td>
<td>Yes</td>
<td>Pseudotumor cerebri, TTD</td>
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<td>3</td>
<td>F</td>
<td>14</td>
<td>1</td>
<td>No</td>
<td>2,580/μL &lt;10,000/μL</td>
<td>No</td>
<td>Yes</td>
<td>Grade 2 liver toxicity</td>
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<td>4</td>
<td>F</td>
<td>15</td>
<td>1</td>
<td>Yes</td>
<td>1,960/μL 65,000/μL (Day 7)</td>
<td>Yes</td>
<td>No</td>
<td>Fever, QTc 0.5 seconds, grade 2 liver toxicity, TTD</td>
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<tr>
<td>5*</td>
<td>M</td>
<td>8</td>
<td>3</td>
<td>Yes</td>
<td>33,700/μL 86,940/μL (Day 7)</td>
<td>Yes</td>
<td>No</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>11</td>
<td>3</td>
<td>Yes</td>
<td>2,290/μL 23,000/μL (Day 8)</td>
<td>No</td>
<td>Yes</td>
<td>Fever, grade 1 liver toxicity</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>17</td>
<td>1</td>
<td>No</td>
<td>1,740/μL &lt;10,000/μL</td>
<td>No</td>
<td>Yes</td>
<td>Fever, grade 1 liver toxicity</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>17</td>
<td>1</td>
<td>No</td>
<td>860/μL &lt;10,000/μL</td>
<td>Yes</td>
<td>Yes</td>
<td>Grade 1 liver toxicity</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>14</td>
<td>3</td>
<td>Yes</td>
<td>1,500/μL &lt;10,000/μL</td>
<td>No</td>
<td>Yes</td>
<td>Fever</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>10</td>
<td>1</td>
<td>Yes</td>
<td>2,260/μL 113,700/μL (Day 11)</td>
<td>Yes</td>
<td>No</td>
<td>Grade 2 liver toxicity</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>11</td>
<td>3</td>
<td>Yes</td>
<td>2,420/μL 37,900/μL (Day 16)</td>
<td>Yes</td>
<td>No</td>
<td>Fever, grade 2 liver toxicity, TTD</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>15</td>
<td>2</td>
<td>Yes</td>
<td>5,790/μL 88,590/μL (Day 5)</td>
<td>No</td>
<td>No</td>
<td>Fever, TTD</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>4</td>
<td>3</td>
<td>No</td>
<td>2,100/μL &lt;10,000/μL</td>
<td>No</td>
<td>Yes</td>
<td>–</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>13</td>
<td>2</td>
<td>Yes</td>
<td>1,250/μL 39,070/μL (Day 19)</td>
<td>No</td>
<td>No</td>
<td>–</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>13</td>
<td>1</td>
<td>Yes</td>
<td>9,420/μL 86,750/μL (Day 7)</td>
<td>Yes</td>
<td>No</td>
<td>Fever, infection, TTD, infection</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>11</td>
<td>1</td>
<td>Yes</td>
<td>2,300/μL 17,400/μL (Day 5)</td>
<td>No</td>
<td>No</td>
<td>–</td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>13</td>
<td>3</td>
<td>Yes</td>
<td>7,500/μL &lt;10,000/μL</td>
<td>No</td>
<td>Yes</td>
<td>QTc 0.5 seconds, TTD</td>
</tr>
</tbody>
</table>

*BCR = breakpoint cluster region; F = female; M = male; QTc = corrected QT interval; TTD = temporary treatment discontinuation; WBC = white blood cell

*High-risk patient.

### Key conclusions

- The results presented indicate that the ATO and ATRA combination is safe and highly effective in childhood APL.
- The observed acute treatment-related side effects were transient and manageable.
- Although only one child with high-risk APL was treated, the favourable outcome suggests that this subset of patients may also benefit from this combination treatment.

**Background**

Information on the true incidence of therapy-related acute promyelocytic leukemia (t-APL) is scarce. However, the incidence appears to have increased in recent years, with some studies suggesting that the outcomes are similar to patients with de novo APL.¹ The combined regimen of arsenic trioxide (ATO) and all-trans retinoic acid (ATRA) is effective in de novo low- to intermediate-risk APL, but it has not been evaluated in a large cohort of patients with t-APL.² At the 7th International Symposium on APL, Kayser and colleagues presented an analysis of outcomes in patients with t-APL according to different treatment strategies.³

**Study design**

- A total of 103 patients with APL were retrospectively studied.
  - The patients had been treated between 1991 and 2015 across 11 study groups/institutions in the U.S. and Europe.
- Patients had received one of the following four treatments:
  - Chemotherapy (CTX)/ATRA (n = 53);
  - ATO/ATRA (n = 24);
  - CTX/ATO/ATRA (n = 19); and
  - ATRA only (n = 7).

**Key findings**

**Baseline characteristics**

- The median age of all patients was 59 years (range: 18–80).
- There were no differences in baseline characteristics by gender, hemoglobin levels, lactate dehydrogenase levels, white blood cell count, and peripheral blood and bone marrow blasts. (Table 1)
- A total of 87 (84%) patients had solid cancer (breast: 38, prostate: 14, head and neck: 9, gastrointestinal: 9, and other: 14).
- Five patients had non-Hodgkin lymphoma, while three had Hodgkin lymphoma.
- Eight patients had autoimmune disease.
- The median latency period from prior disease to the onset of t-APL was 3.5 years (range: 0.4–26.2).

**Efficacy**

- Patients receiving ATO/ATRA had the highest complete remission rate at 100%, while patients received ATRA only had the highest early death rate at 43%. (Table 2)
- The patients receiving CTX/ATRA had the highest number of competing events in remission.
  - Two had relapses of the prior malignancy, two had infections, two had therapy-related acute myeloid leukemia, three had relapses of t-APL, one developed diffuse large B-cell lymphoma, and one had a competing event of unknown cause.
- Of the patients receiving ATO/ATRA, one patient had relapse of the prior malignancy, one patient had an infection, and one suffered cardiopulmonary arrest during therapy.

---

**Table 1. Baseline characteristics**

<table>
<thead>
<tr>
<th></th>
<th>CTX/ATRA</th>
<th>ATO/ATRA</th>
<th>CTX/ATO/ATRA</th>
<th>ATRA only</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>57.0</td>
<td>60.0</td>
<td>56.0</td>
<td>69.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Cytogenetics (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(15;17) sole</td>
<td>77</td>
<td>57</td>
<td>87</td>
<td>75</td>
<td>0.20</td>
</tr>
<tr>
<td>t(15;17) &amp; abnormality</td>
<td>23</td>
<td>43</td>
<td>13</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Risk categorization* (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low/intermediate</td>
<td>80</td>
<td>87</td>
<td>79</td>
<td>71</td>
<td>0.63</td>
</tr>
<tr>
<td>High</td>
<td>20</td>
<td>13</td>
<td>21</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>FLT3-ITD (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutated</td>
<td>74</td>
<td>57</td>
<td>29</td>
<td>33</td>
<td>0.10</td>
</tr>
<tr>
<td>Unmutated</td>
<td>26</td>
<td>43</td>
<td>71</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>M3 (%)</td>
<td>94</td>
<td>87</td>
<td>100</td>
<td>86</td>
<td>0.23</td>
</tr>
<tr>
<td>M3v (%)</td>
<td>6</td>
<td>13</td>
<td>–</td>
<td>14</td>
<td></td>
</tr>
</tbody>
</table>

* Prognostic score of APL (Sanz score): WBC <10.0 g/L (low- to intermediate-risk) vs. WBC ≥10 g/L (high-risk).

APL = acute promyelocytic leukemia; ATO = arsenic trioxide; ATRA = all-trans retinoic acid; CTX = chemotherapy; FLT3-ITD = FMS-like tyrosine kinase 3-internal tandem duplication; M3 = APL subtype according to French-American-British classification of acute myeloid leukemia; M3v = microgranular variant; t(15;17) = translocation between chromosomes 15 and 17; WBC = white blood cell.
One patient receiving CTX/ATO/ATRA and three receiving ATRA had relapses of the prior malignancy.

The 2-year event-free survival (EFS) rates were 78% (95% CI: 64–87) in patients treated with CTX/ATRA, 89% (95% CI: 64–97) in the ATO/ATRA group, and 95% (95% CI: 68–99) in the CTX/ATO/ATRA group. (Figure 1)

The estimated 2-year overall survival rates for patients receiving CTX/ATRA were 84% (95% CI: 71–92), 89% (95% CI: 64–97) for ATO/ATRA, and 95% (95% CI: 68–99) for CTX/ATO/ATRA. (Figure 1)

None of the patients treated with ATRA alone survived beyond one year.

When excluding death due to primary malignancy, the estimated 2-year modified EFS rate was significantly higher in patients treated with ATO-based therapy, including both ATO/ATRA and CTX/ATO/ATRA (95%; 95% CI: 82–99), when compared with patients treated with CTX/ATRA (78%; 95% CI, 64–87; \(p = 0.045\)). (Figure 2)

Cumulative incidence of relapse in intensively-treated patients showed a strong trend towards a higher cumulative incidence of relapse after treatment with CTX/ATRA when compared with ATO-based regimens \(p = 0.07\).

**Table 2. Response to induction therapy***

<table>
<thead>
<tr>
<th>% (n)</th>
<th>CTX/ATRA</th>
<th>ATO/ATRA</th>
<th>CTX/ATO/ATRA</th>
<th>ATRA only</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>78 (40)</td>
<td>100 (23)</td>
<td>95 (18)</td>
<td>57 (4)</td>
</tr>
<tr>
<td>PR</td>
<td>10 (5)*</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>ED</td>
<td>12 (6)</td>
<td>–</td>
<td>5 (1)</td>
<td>43 (3)</td>
</tr>
</tbody>
</table>

ATO = arsenic trioxide; ATRA = all-trans retinoic acid; CR = complete remission; CTX = chemotherapy; ED = early death; PR = partial remission

* Response data were available in 100 of 103 (97%) patients.

† All patients went on to consolidation and achieved CR thereafter.

**Figure 1. Event-free and overall survival**

**Figure 2. Event-free survival excluding death due to primary malignancy**

**Key conclusions**

- The distribution of clinical and biological characteristics in t-APL is comparable with what has been described in patients with *de novo* APL.
- There was an excellent and sustained response, as well as favourable survival profile, following ATO-based regimens as first-line treatment.
- ATO, when combined with ATRA or CTX/ATRA, is a feasible treatment and leads to better outcomes than CTX/ATRA alone.

References:
Background

All-trans retinoic acid (ATRA) in combination with anthracycline-based chemotherapy has obtained high response rates, but is associated with potential long-term sequelae in patients with acute promyelocytic leukemia (APL). The combination of arsenic trioxide (ATO) and ATRA was introduced in an attempt to obviate these complications. The aim of this study was to compare the number of hospitalization days and number of transfusions in patients with APL who received ATO plus ATRA to those who received ATRA plus chemotherapy. Results were presented at the International Symposium on APL 2017.1

Study design

• Twelve patients with APL were treated with ATO plus ATRA according to the GIMEMA protocol APL0406.2

• The control group consisted of 12 patients who were treated with chemotherapy plus ATRA according to AIDA-2000.3

Key findings

Baseline characteristics and disposition

• Patient characteristics are summarized in Table 1.

• In the ATO plus ATRA group, there were patients for whom chemotherapy was not applicable because of prior chemotherapy (secondary APL), intracerebral hemorrhage, or massive pulmonary embolism at the onset of disease.

Safety

• All patients started ATRA immediately and were admitted to the hospital for the induction phase.

• The median length of first hospitalization after ATRA plus ATO therapy was 34 days (range: 28–47) and was 31 days (range: 25–46) in the ATRA plus chemotherapy group.

• In the ATRA plus ATO group, the mean number of units of red blood cells (RBCs), platelets, and fresh frozen plasma (FFP) transfused during induction was 4.5, 7, and 3, respectively; in the ATRA plus chemotherapy group it was 4, 6, and 10, respectively.

• In the ATRA plus ATO arm, 11 patients received the consolidation phase as outpatients.

• In the ATRA plus chemotherapy arm, all patients were hospitalized during the first two consolidations. The median time of first consolidation recovery was six days (range: 5–7).

– Ten patients needed a second admission for neutropenia and other complications that lasted a median of nine days (range: 7–15).

– During the second admission, three patients received RBC and platelet transfusions.

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics</th>
<th>ATO plus ATRA (n = 12)</th>
<th>Chemotherapy plus ATRA (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>45.5 (24–62)</td>
<td>42 (17–60)</td>
</tr>
<tr>
<td>Gender, n (Male/Female)</td>
<td>9/3</td>
<td>7/5</td>
</tr>
<tr>
<td>WBC count, /mm³ (range)</td>
<td>1,070 (650–9,770)</td>
<td>3,350 (800–117,000)</td>
</tr>
<tr>
<td>Hemoglobin, g/dL (range)</td>
<td>9.1 (6.1–12.8)</td>
<td>9.9 (5.3–14.5)</td>
</tr>
<tr>
<td>Platelet count, /mm³ (range)</td>
<td>25.5 (9–136)</td>
<td>23 (7–119)</td>
</tr>
<tr>
<td>Risk category, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Intermediate</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Low</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

ATO = arsenic trioxide; ATRA = all-trans retinoic acid; WBC = white blood cell
During the second consolidation, the median time of first recovery was seven days (range: 6–9).

- This was followed by a second admission of 11 days (range: 8–18).
- Eight patients received platelet transfusions and six patients received RBC transfusions during this phase.

Two patients were admitted to the hospital for the third consolidation.

- Five patients required hospitalization for complications during this phase, and one patient received a platelet transfusion.

Key conclusions

- The ATRA plus ATO regimen allowed for the treatment of patients in whom chemotherapy could not be used.
- Analyses showed that the ATRA plus ATO regimen reduced hospitalization and transfusion support.
  - Patients treated with ATRA plus chemotherapy received more FFP transfusions during induction ($p = 0.003$), received more RBC and platelet transfusions during consolidation ($p < 0.001$), and experienced a higher number of hospital readmissions ($p < 0.001$) compared to those treated with ATRA plus ATO.
- The association of ATO to ATRA is an efficacious chemotherapy-free regimen and seems to reduce costs in terms of hospitalization and transfusion support.

References:

Long-term follow-up of first-line ATO in combination with ATRA compared to chemotherapy in combination with ATRA in patients with APL: Monocentric experience

**Background**

At the 7th International Symposium on APL, Autore and colleagues presented their experience of patients with acute promyelocytic leukemia (APL) treated with arsenic trioxide (ATO) plus all-trans retinoic acid (ATRA) compared to those treated with chemotherapy plus ATRA in the long term.¹

**Study design**

- From January 2009, patients with APL were treated with ATO plus ATRA according to the GIMEMA protocol in the APL0406 trial (first arm),² or with chemotherapy plus ATRA according to the AIDA-2000 study (second/control arm).³

**Key findings**

- There were 12 patients in the first arm and 12 patients in the control arm.
- Patients’ characteristics were as follows:
  - The median age in the first and control arms was 45.5 and 42 years, respectively.
  - The white blood cell count was 1,070 mm⁻³ (range: 650–9,770) in the first arm and 3,350 mm⁻³ (range: 800–117,000) in the control arm.
  - There were four patients in the control arm with high-risk APL, compared to no patients in the first arm.
• During treatment, brief interruptions of ATO were registered in seven patients, and ATRA syndrome was described in five patients in the first arm; ATRA syndrome was also reported in six patients in the control arm.
• Adverse events (AEs) in the induction phase were reported as follows:
  ◦ In the first arm, two thrombotic events, two herpes simplex virus (HSV) infections, and one ATRA myopathy were reported.
  ◦ In the control arm, eight fever cases requiring antibiotics, five hemorrhagic complications, one thrombophlebitis, and one benign endocranial hypertension were reported.
• Molecular remission was achieved in all patients after a median time of 3 months in both groups.
• AEs in the consolidation phase were reported as follows:
  ◦ In the first arm, two patients required dose reduction of ATO due to corrected QT prolongation; one patient experienced benign endocranial hypertension; one patient experienced mild hepatotoxicity; and one patient had HSV infection.
  ◦ In the control arm, nine patients showed neutropenic fever; two patients had a thrombotic event; and one patient experienced mild hepatotoxicity.
• During the maintenance phase, hepatotoxicity of different grades and neutropenia were common in both arms.
• All patients in the first arm remained in molecular response at a median time of 16 months (range: 2–91), with the exception of one patient, who showed the reappearance of promyelocytic leukemia-retinoic acid receptor alpha in the bone marrow after 11 months.
  ◦ This patient restarted ATO plus ATRA, and achieved molecular complete remission at the three-month control.
• All patients in the control arm were in molecular response for a median time of 43.5 months (range: 30–97), but two patients developed myelodysplastic syndrome (MDS) after a few months and three years after the maintenance phase, respectively.
  ◦ All patients in the first arm remain alive and in response at a median follow-up of 19 months (range: 4–94), with no late effects registered.
  ◦ In the control arm, all patients remain alive after a median time of 47 months (range: 35–100), except for two patients who developed MDS and died.
  ◦ Only nine patients in the first arm required platelet or red blood cell transfusion, whereas all patients in the control arm required transfusion support and fresh frozen plasma.
  ◦ During the consolidation phase, no patients in the first arm versus nine patients in the control arm required transfusion support.

Key conclusions

• The treatment of ATO plus ATRA was well tolerated, and showed advantages in comparison to chemotherapy plus ATRA.
• The ATO plus ATRA regimen reduced the need for transfusion support during treatment.
• ATO plus ATRA also reduced the risk of MDS.

Background
The APL-2005 study was started as an Acute Myeloid Leukemia Cooperative Group (AMLCG) trial with the intention to be part of an acute promyelocytic leukemia (APL) intergroup study with the PETHEMA LPA99 protocol as a common standard arm. Results from this study were presented at the 2017 International Symposium on APL.1

Study design
• Patients with genetically confirmed, newly diagnosed APL were randomized to receive either the AMLCG protocol or the PETHEMA LPA99 study protocol between November 2005 and December 2015.
• Primary endpoint was comparison of the kinetics of minimal residual disease.
  ◇ This was defined as the first negative reverse transcription polymerase chain reaction (RT-PCR) of promyelocytic leukemia-retinoic acid receptor alpha (PML-RARα) after induction or consolidation.
• Secondary endpoints included toxicity, overall survival (OS), event-free survival, relapse-free survival, and cumulative incidence of relapse (CIR).

Key findings
Baseline characteristics and disposition
• A total of 102 patients were assessed for eligibility.
  ◇ Fifteen patients were excluded prior to randomization for death (n = 3), no informed consent (n = 2), medical contraindication (n = 5), APL diagnosed after the start of acute myeloid leukemia therapy (n = 4), and secondary APL (n = 1).
• Eighty-seven patients were randomized to the AMLCG (n = 44) or PETHEMA (n = 43) groups.
  ◇ Six patients were excluded after randomization to the AMLCG group for protocol violation (n = 1), withdrawn consent (n = 1), or incorrect diagnosis of APL (n = 4).
  ◇ One patient was excluded after randomization to the PETHEMA group for protocol violation.
• Of the 38 evaluable patients in the AMLCG group, 14 were low risk, 18 were intermediate risk, and six were high risk.
• Of the 42 evaluable patients in the PETHEMA group, 14 were low risk, 19 were intermediate risk, and nine were high risk.
  ◇ The numbers of patients in each risk group were statistically similar to those in the AMLCG group (p = 0.875).

AC = cytarabine, cyclophosphamide; AD = cytarabine, daunorubicin; AT = cytarabine, 6-thioguanine; ATRA = all-trans retinoic acid; HAM = cytarabine, mitoxantrone; TAD = 6-thioguanine, cytarabine, daunorubicin

AC = cytarabine, cyclophosphamide; AD = cytarabine, daunorubicin; AT = cytarabine, 6-thioguanine; ATRA = all-trans retinoic acid; HAM = cytarabine, mitoxantrone; TAD = 6-thioguanine, cytarabine, daunorubicin

**Study design**

<table>
<thead>
<tr>
<th>Induction</th>
<th>Consolidation</th>
<th>Maintenance 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A (AMLCG)</td>
<td>TAD</td>
<td>Idarubicin + ATRA</td>
</tr>
<tr>
<td>Randomization</td>
<td></td>
<td>Methotrexate/mercaptopurine + ATRA</td>
</tr>
<tr>
<td>Arm B (PETHEMA, LPA99)</td>
<td></td>
<td>Idarubicin + ATRA, Mitoxantrone + ATRA</td>
</tr>
</tbody>
</table>

Induction
- ATRA plus idarubicin
- Idarubicin + ATRA
- Mitoxantrone + ATRA
- Idarubicin + ATRA

Consolidation
- TAD
- AC + ATRA
- AT + ATRA
- AT + ATRA
- ATRA plus TAD/HAM

Maintenance 2 years
- ATRA plus idarubicin
- Idarubicin + ATRA
- Mitoxantrone + ATRA
- Idarubicin + ATRA
- Methotrexate/mercaptopurine + ATRA
Baseline patient characteristics were similar between groups.

- Median age was 56 years in the AMLCG group and 49.5 years in the PETHEMA group ($p = 0.391$).
- The majority of patients were male (58% and 50% in the AMLCG and PETHEMA groups, respectively; $p = 0.509$), had an L/V transcript type (54% vs. 69%; $p = 0.339$), and had translocation between chromosomes 15 and 17 (62% vs. 60%; $p = 1$).
- White blood cell counts were similar between groups (23 x $10^9$/L in the AMLCG group and 12 x $10^9$/L in the PETHEMA group; $p = 0.583$).

**Efficacy**

- Complete hematological remission was observed in 33 patients (87%) in the AMLCG group and in 35 patients (83%) in the PETHEMA group ($p = 0.76$).
- After induction, significantly more patients in the AMLCG group achieved RT-PCR negativity ($p = 0.0124$). (Table 1)
- Following consolidation, RT-PCR negativity was similar between groups. (Table 1)
- Cumulative incidence of RT-PCR conversion from positive to negative was also similar between groups ($p = 0.12$). (Figure 1)
- Long-term outcomes were similar between groups with the exception of CIR, as there were no incidences of relapse in the AMLCG group compared to a 12% relapse rate in the PETHEMA group ($p = 0.04$). (Table 2)

**Safety**

- Toxicities during induction therapy were similar between groups with the exception of the median duration of critical cytopenia, which was longer in the AMLCG group ($p = 0.02$). (Table 3)
- Events during follow-up are summarized in Table 4.

### Table 1. RT-PCR results for patients with complete response

<table>
<thead>
<tr>
<th></th>
<th>AMLCG</th>
<th>PETHEMA</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>After induction, n (%)</td>
<td>29/31 (94)</td>
<td>23/34 (68)</td>
<td>0.0124</td>
</tr>
<tr>
<td>Negative</td>
<td>2/31 (6)</td>
<td>11/34 (32)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>27/29 (93)</td>
<td>2/29 (7)</td>
<td></td>
</tr>
<tr>
<td>Mean time until control after induction, days (SD)</td>
<td>63 (27)</td>
<td>47 (25)</td>
<td></td>
</tr>
<tr>
<td>After consolidation, n (%)</td>
<td>24/25 (96)</td>
<td>27/29 (93)</td>
<td>1</td>
</tr>
<tr>
<td>Negative</td>
<td>1/25 (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>2/29 (7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RT-PCR = reverse transcription polymerase chain reaction; SD = standard deviation

### Table 2. Long-term outcomes

<table>
<thead>
<tr>
<th>Outcome at 6 years (%)</th>
<th>AMLCG</th>
<th>PETHEMA</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>75</td>
<td>78</td>
<td>0.92</td>
</tr>
<tr>
<td>EFS</td>
<td>75</td>
<td>68</td>
<td>0.29</td>
</tr>
<tr>
<td>RFS</td>
<td>86</td>
<td>81</td>
<td>0.28</td>
</tr>
<tr>
<td>CIR</td>
<td>0</td>
<td>12</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Subgroup analysis

<table>
<thead>
<tr>
<th>OS at 6 years (%)</th>
<th>AMLCG</th>
<th>PETHEMA</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60 years</td>
<td>83</td>
<td>86</td>
<td>0.90</td>
</tr>
<tr>
<td>≥60 years</td>
<td>57</td>
<td>62</td>
<td>0.75</td>
</tr>
<tr>
<td>RFS at 6 years (%)</td>
<td>Low/intermediate risk</td>
<td>87</td>
<td>92</td>
</tr>
<tr>
<td>High risk</td>
<td>65</td>
<td>43</td>
<td>0.28</td>
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</table>

CIR = cumulative incidence of relapse; EFS = event-free survival; OS = overall survival; RFS = relapse-free survival

### Table 3. Results of induction therapy

<table>
<thead>
<tr>
<th></th>
<th>AMLCG</th>
<th>PETHEMA</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete hematological remission, n (%)</td>
<td>33 (87)</td>
<td>35 (83)</td>
<td>0.76</td>
</tr>
<tr>
<td>Early death, n (%)</td>
<td>5</td>
<td>13</td>
<td>0.12</td>
</tr>
<tr>
<td>Suspected or manifest ADS (treated with steroids), n (%)</td>
<td>16 (42)</td>
<td>17 (40)</td>
<td>1</td>
</tr>
<tr>
<td>Toxicities WHO grade ≥3, n (%)</td>
<td>Bleeding</td>
<td>1 (3)</td>
<td>2 (5)</td>
</tr>
<tr>
<td></td>
<td>Infection/fever</td>
<td>21 (55)*</td>
<td>15 (36)</td>
</tr>
<tr>
<td></td>
<td>Hepatotoxicity</td>
<td>5 (13)</td>
<td>1 (2)</td>
</tr>
<tr>
<td></td>
<td>Cardiotoxicity</td>
<td>1 (3)</td>
<td>3 (7)</td>
</tr>
<tr>
<td></td>
<td>Mucositis</td>
<td>2 (5)</td>
<td>4 (10)</td>
</tr>
<tr>
<td></td>
<td>Median duration of critical cytopenia, days (range)</td>
<td>32 (17–59)</td>
<td>27 (19–48)</td>
</tr>
</tbody>
</table>

ADS = acute differentiation syndrome; WHO = World Health Organization

* Ten patients had infections in both induction cycles. Infections during consolidation: 31% in the AMLCG group and 19% in the PETHEMA group ($p = 0.68$).
Table 4. Events during follow-up

<table>
<thead>
<tr>
<th></th>
<th>AMLCG (n = 38)</th>
<th>PETHEMA (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total deaths, n (%)</td>
<td>8 (21)</td>
<td>9 (21)</td>
</tr>
<tr>
<td>Early death, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding (n)</td>
<td>5 (13)</td>
<td>7 (17)</td>
</tr>
<tr>
<td>Infection (n)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonary embolism (n)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Multiorgan failure (n)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Death in CR, n (%)</td>
<td>3 (8)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Pancreatic cancer (n)</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Secondary AML/MDS (n)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Relapse, n (%)</td>
<td>0</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Secondary malignancy, n (%)</td>
<td>4 (11)</td>
<td>5 (12)</td>
</tr>
<tr>
<td>MDS (n)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Solid tumour (n)</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Key conclusions

- The randomized comparison of AMLCG and PETHEMA regimens shows similar OS and indicates the limitations of ATRA and chemotherapy.
- A lower relapse rate was seen with the more intensive regimen (AMLCG), but this was associated with more toxicity.
- In comparison with the literature, the results indirectly support the application of ATRA plus arsenic trioxide in standard-risk APL.
- Small patient number is a limitation of this study.


Labrador J, et al. APL 2017:CO017

Clinical significance of complex karyotype at diagnosis in patients with APL treated with ATRA and chemotherapy-based PETHEMA trials

Background

In acute promyelocytic leukemia (APL), the presence of the promyelocytic leukemia-retinoic acid receptor alpha translocation between chromosomes 15 and 17 (t[15;17]/PML-RARα) predicts sensitivity to treatment with all-trans retinoic acid (ATRA) and arsenic trioxide. Up to 30% of patients with APL will have chromosomal abnormalities in addition to conventional t(15;17). The majority of studies have not shown a prognostic impact of additional chromosomal abnormalities (ACAs) in patients with APL treated with ATRA and chemotherapy-based front-line therapies. Results from a study that further explored this relationship were presented at the International Symposium on APL 2017.

Study design

- Between 1996 and 2012, 1,559 consecutive adult and pediatric patients were enrolled in the PETHEMA LPA 96, 99, and 2005 trials.
- All patients had de novo genetic diagnosis of PML-RARα APL.
- Treatment consisted of ATRA and idarubicin induction followed by risk-adapted consolidation.
- Cytogenetic analyses in bone marrow samples at diagnosis were performed in local laboratories.
- ACAs were classified as follows:
  - Normal karyotype or t(15;17) alone was considered as no ACA.
  - Multiple rearrangements (i.e., triple rearrangements involving chromosome 15, 17, and other) were considered as one ACA.
  - Abnormalities detected in fluorescence in situ hybridization were considered as ACA.
  - A complex karyotype was defined as ≥2 ACAs.
  - A very complex karyotype was defined as ≥3 ACAs.
Key findings

Baseline characteristics and disposition

- Cytogenetic reports were available for 1,128 patients (72%).
  - From this group, 842 patients (75%) had no ACA, 197 (17%) had 1 ACA, 48 (4%) had 2 ACAs, and 41 (4%) had ≥3 ACAs.
- Baseline characteristics were similar in the group of patients with <2 ACAs (n = 1,039) compared to the group of patients with ≥2 ACAs (n = 89).
  - Median age was 42 years in the <2 ACA group and 40 years in the ≥2 ACA group (p = 0.18).
  - The majority of patients were male (51% in the <2 ACA group and 52% in the ≥2 ACA group; p = 0.98) with a platelet count ≤40 x 10^9/L (75% vs. 79%; p = 0.55) and intermediate relapse risk (52% vs. 64%; p = 0.10).
  - White blood cell counts were ≥10 x 10^9/L in 28% of patients in the <2 ACA group and in 21% of patients in the ≥2 ACA group (p = 0.31).
- The only clinical or biological characteristic associated with a complex karyotype was cluster of differentiation-34 antigen negativity in leukemic blasts (p = 0.04).

Efficacy

- Induction death rates were similar between groups (8% in the <2 ACA group vs. 7% in the ≥2 ACA group; p = 0.74).
- Number of ACAs did not significantly affect overall survival. (Figure 1)
- Cumulative incidence of relapse was lower in the <2 ACA group versus the ≥2 ACA group (12% vs. 18%; p = 0.09) and in the <3 ACA group versus the ≥3 ACA group (12% vs. 27%; p = 0.003). (Figure 2)
- Multivariate analysis confirmed that a very complex karyotype was significantly associated with incidence of relapse. (Table 1)
- Female gender, higher relapse-risk group, and enrolment in the PETHEMA LPA 96 or 99 trials were also predictors of relapse.

Figure 1. Overall survival stratified by number of ACAs

<table>
<thead>
<tr>
<th>Time after diagnosis (months)</th>
<th>OS probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>12</td>
<td>0.75</td>
</tr>
<tr>
<td>24</td>
<td>0.50</td>
</tr>
<tr>
<td>36</td>
<td>0.25</td>
</tr>
<tr>
<td>48</td>
<td>0.00</td>
</tr>
</tbody>
</table>

| Number at risk | <2 ACA 1,058 901 839 769 679 585 497 417 383 292 241 | ≥2 ACA 89 80 75 72 62 54 47 40 35 29 25 |
|----------------|------------------------------------------------------|

ACA = additional chromosomal abnormalities; OS = overall survival

Figure 2. Cumulative incidence of relapse

<table>
<thead>
<tr>
<th>Time after CR (months)</th>
<th>Cumulative probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>12</td>
<td>0.75</td>
</tr>
<tr>
<td>24</td>
<td>0.50</td>
</tr>
<tr>
<td>36</td>
<td>0.25</td>
</tr>
<tr>
<td>48</td>
<td>0.00</td>
</tr>
</tbody>
</table>

| Number at risk | <2 ACA 945 817 772 700 611 519 452 396 325 269 213 | ≥2 ACA 81 77 75 64 51 47 39 32 29 24 20 |
|----------------|------------------------------------------------------|

ACA = additional chromosomal abnormalities; CR = complete remission
APL in the obese: Should we treat it differently?

**Background**

Differentiation syndrome (DS) is a life-threatening complication in acute promyelocytic leukemia (APL). Studies have reported that a high body mass index (BMI) is the most powerful predictor of DS, with an odds ratio of 7.24.1,2 At the 2017 International Symposium on APL, a case study was presented which further examined this relationship.3

**Study design**

- Eighteen patients with low- to intermediate-risk APL received induction therapy with all-trans retinoic acid and arsenic trioxide according to the GIMEMA protocol on an in-patient basis in the last two years.

**Key conclusions**

- This study shows an increased risk of relapse for patients with very complex karyotype (≥3 ACAs) among patients with APL treated with ATRA plus chemotherapy front-line regimens.
- This increased risk did not influence overall survival.
- It should be noted that only 4% of patients with an evaluable cytogenetic profile had a very complex karyotype.

**References**


**Table 1. Multivariate analysis of cumulative incidence of relapse**

<table>
<thead>
<tr>
<th>Variable</th>
<th>p - multivariate</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>0.008</td>
<td>0.6 (0.4–0.9)</td>
</tr>
<tr>
<td>Higher relapse-risk group</td>
<td>&lt;0.0001</td>
<td>2.1 (1.5–2.9)</td>
</tr>
<tr>
<td>Very complex karyotype (≥3 ACA)</td>
<td>0.0009</td>
<td>2.7 (1.5–4.9)</td>
</tr>
<tr>
<td>PETHEMA LPA 96 and 99 trials</td>
<td>0.05</td>
<td>1.4 (1.0–2.1)</td>
</tr>
</tbody>
</table>

ACA = additional chromosomal abnormalities; CI = confidence interval; HR = hazard ratio

**Key conclusions**

- The two most difficult cases to manage during induction were obese patients (BMI >30).
  - Case 1 was a 25-year-old male with intermediate-risk APL and a BMI of 33 kg/m².
  - Case 2 was a 52-year-old female with intermediate-risk APL and a BMI of 31 kg/m².

**Key findings**

- Baseline characteristics and clinical summaries of the obese and non-obese patients are summarized in Table 1.
- Both obese patients died of DS. Their disease progressions are summarized in Figure 1.
Table 1. Clinical summary and results

<table>
<thead>
<tr>
<th>Category</th>
<th>Obese (BMI &gt;30), n = 2</th>
<th>Non-obese (BMI ≤30), n = 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (range)</td>
<td>38.5 (25–52)</td>
<td>18.5 (11–26)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1 (50)</td>
<td>8 (50)</td>
</tr>
<tr>
<td>Female</td>
<td>1 (50)</td>
<td>8 (50)</td>
</tr>
<tr>
<td>Mean BMI (kg/m²)</td>
<td>31.5</td>
<td>22.4</td>
</tr>
<tr>
<td>Development of DS, n (%)</td>
<td>2 (100)</td>
<td>7 (43.75)</td>
</tr>
<tr>
<td>Days of onset of DS after initiation</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Mean duration of DS (days)</td>
<td>11.5</td>
<td>4</td>
</tr>
<tr>
<td>DS-related mortality, n (%)</td>
<td>2 (100)</td>
<td>0</td>
</tr>
<tr>
<td>Mortality due to fungal pneumonia, n (%)</td>
<td>0</td>
<td>1 (6.25)</td>
</tr>
</tbody>
</table>

BMI = body mass index; DS = differentiation syndrome

Figure 1. Event chart

Case 1

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>1. ATRA (45 mg/m²)</td>
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<td>2. ATO (0.15 mg/kg)</td>
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<tr>
<td>3. WBC count &gt;50,000/mm³</td>
<td>2</td>
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<td>11. Dexamethasone therapeutic</td>
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Case 2

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<td>2. ATO (0.15 mg/kg)</td>
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<td>3. WBC count &gt;10,000/mm³</td>
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<td>6. Daunorubicin</td>
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<td>7. Fever</td>
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<td>9. Antifungal</td>
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<td>10. Prednisolone prophylaxis</td>
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<td>11. Dexamethasone therapeutic</td>
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<td>6</td>
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</tbody>
</table>

1. ATRA/ATO kept on hold due to symptoms of DS; 2. TC >10,000, hydroxyurea started at 1 g/day (2*: dose increased to 4 g/day); 3. Unexplained fever, respiratory distress, weight gain, pulmonary infiltrate on HRCT thorax; 4. Hyperleukocytosis, TC >100,000, daunorubicin at a dose of 60 mg/m²; 5. DS: prednisolone prophylaxis changed to therapeutic dose of dexamethasone; 6. Tapering of dexamethasone started; 7. Patient succumbed to respiratory failure and arrhythmia.

Key conclusions

- The association of obesity with DS has important clinical implications.
- More intense DS prophylaxis might be necessary in obese patients during induction.
- Aggressive correction of increased leukocyte count with anthracyclines should be considered earlier in obese patients.
- Urgent initiation of therapeutic dosing of steroid at the earliest clinical suspicion of DS may be effective.

Acute promyelocytic leukemia (APL) is a rare subtype of acute myeloid leukemia (AML) characterized by the promyelocytic leukemia-retinoic acid receptor alpha (PML-RARα) translocation between chromosomes 15 and 17. Historically, the combination of all-trans retinoic acid (ATRA) and an anthracycline has been regarded as the standard of care in APL. However, it is associated with an appreciable relapse rate and significant toxicity, such as cardiomyopathy. In recent years, arsenic trioxide (ATO) has been shown to be effective in combination regimens that are chemotherapy-free (“chemo-free”) or chemo-reduced.3,4 Most centres in Canada are moving towards a chemo-free approach, which includes ATO in the regimen.

At the 7th International Symposium on APL, various aspects of APL treatment were discussed, including long-term and “real-world” outcomes, treatment in older patients and in children, management of relapse, therapy-related APL (t-APL), and early death (ED).

Long-term outcomes and real-world data

In Canada, the chemo-free approach (i.e., ATRA plus ATO) is widely used in most centres for adult patients with non–high-risk APL (white blood cell [WBC] counts <10 x 10⁹/L). This was based on the early and long-term results from the German-Italian study (APL0406) led by Dr. Francesco Lo-Coco, as well as a favourable recommendation by the Pan-Canadian Oncology Drug Review.3,5,6

High-risk patients (WBC >10 x 10⁹/L) represent a minor proportion of APL in Canada (20% to 30% of APL patients). High-risk patients are often treated with ATO plus ATRA along with systemic chemotherapy. They are not receiving chemo-free approaches because there is insufficient data to support the use of these regimens in high-risk APL. Currently, most centres in Canada are using one of the two ATO-containing regimens published for high-risk APL – the approach published in the Intergroup C9710 study by Powell et al., and the Australasian protocol published by Dr. Iland’s group.5,7

At the 7th International Symposium on APL, Ravandi et al. presented the long-term follow-up (47.6 months) of a large cohort of patients with APL at the M.D. Anderson Cancer Center.8 The treatment approach they used was similar to the German-Italian APL0406 protocol for the non–high-risk patients.3 The main difference of this study from the APL0406 trial is the addition of gemtuzumab ozogamicin (GO) in the treatment for high-risk patients. Although GO is currently unavailable in Canada, the study certainly demonstrated the feasibility of a “chemo-reduced” approach for high-risk patients. Of the 187 patients, 54 were high risk and 45 of them received GO (9 mg/m²) on Day 1. GO was also used in low-risk patients when WBC rose above 10 x 10⁹/L during induction. Compared to the recently published U.K. National Cancer Research Institute (NCRI) trial, GO was given at a slightly higher dose (in this study versus 6 mg/m² in the NCRI study).9

Most non–high-risk patients who experienced leukocytosis during induction (51/60) were treated with GO. Specific concerns in those who develop leukocytosis during induction are APL differentiation syndrome and coagulopathy; we often treat patients with hydroxyurea or idarubicin to reduce this leukocytosis. Although the use of GO is sensible, I think there needs to be a proven advantage to using GO for physicians to shift away from using conventional cytotoxics such as hydroxyurea, with the latter being well tolerated and less costly compared to GO.

The outcomes in the long-term follow-up of this cohort were excellent. The early death (ED) rate was low (3.7%) and relapse occurred in only 7 patients. Older patients (aged ≥50 years) had poorer outcomes compared to younger patients likely because of a combination of higher ED, treatment-related toxicities, or relapse. The five-year event-free survival (EFS) and overall survival (OS) in older vs. young patients were 74% vs. 89% and 74% vs. 93%, respectively. However, their results in older patients are better than what we have demonstrated in historical population-based outcomes in Canada (ED rate of 36% and five-year OS of 29% in patients aged ≥50 years old).10

Overall, the results from the study by Ravandi et al. reinforce previous data from the APL0406 study, which used a well-tolerated regimen in both young and older patients.5,15 The study also consolidates the NCRI data of using GO in high-risk patients; however, although there may be an advantage to the use of GO, the current data is insufficient to adopt GO if and when it becomes available in Canada.

APL in elderly patients

The median age of patients with APL is approximately 50 years. From our Canadian experience, patients with APL who are aged >50 years had significantly poorer outcomes compared to younger patients.15 The current standard of care for older patients with APL is the same as that for younger adult patients. We treat older, low-risk patients with a chemo-free approach (ATO plus ATRA),5,6 paying very close attention to the possibility of toxicities. This is because these patients are often on other medications with attendant risks of drug-drug interactions and complications such as cardiac arrhythmias and metabolic abnormalities. For older patients with high-risk APL, we would consider the Australian approach (ATO, ATRA, and idarubicin),4 but would favour a chemotherapy-free regimen1 if concerns about tolerability of chemotherapy exist, especially that of cardiac toxicity from anthracyclines.
At the 7th International Symposium on APL, Dr. Adès presented a subgroup analysis of the APL 2006 study, which evaluated the use of ATO and ATRA with chemotherapy in elderly patients with standard-risk, newly diagnosed APL.1 This trial defined elderly patients as age >70 years.

In this study, the overall two-year OS was 82.4% and the complete response (CR) rate was 91.1%. The treatment schedule was amended to include fewer doses of idarubicin in consolidation due to the concern of high mortality rates in CR. The amendment resulted in a significantly lower post-remission death rate (20% vs. 4%; p = 0.045) and had no negative impact on relapse. There were 3% of elderly patients with resistant leukemia. The inherent weakness of this study is that it was designed in 2006, when treating physicians were not aware of the feasibility of a chemo-free approach. Thus, idarubicin was still used in induction and consolidation phases. I question the clinical significance of the approach used in this study as current treatment is moving towards a chemo-free approach. I suspect the same or better survival outcomes can be achieved without the aid of an anthracycline.

**APL in pediatric patients**

Since APL is predominantly seen in adults, pediatricians tend to look at the trials and outcomes in adult patients with APL when they model their approach in pediatric patients with APL. In Canada, anthracyclines have traditionally been used in the treatment of pediatric APL; however, in view of cardiotoxicity concerns, a chemo-free approach may be preferable. Recently, the Children's Oncology Group (COG) commenced a phase III trial (AAML1331), which examines the superiority of a chemo-free approach over standard chemotherapy in treating children with non-high-risk APL.12 In this trial, pediatric patients with non-high-risk APL receive ATO and ATRA for induction and consolidation, while patients with high-risk APL receive ATO, ATRA, and idarubicin. There is no maintenance therapy in the regimen. Many pediatric oncology centres in Canada will be embracing this trial.

At the 7th International Symposium on APL, Kutny et al. presented a study in which pediatric patients with APL were treated with a regimen containing anthracyclines in induction and consolidation.13 ATO was used in the first consolidation cycles, which resulted in a reduction of anthracycline use by 38% to 45%. The survival outcomes remained high in the study (3-year EFS: 100% for young children, 96% for older children, and only 88% for adolescents; p = 0.540), and the relapse risk was similar across all age groups (0% to 4%). The three-year EFS appeared to be lower in adolescents possibly due to lower compliance rates.

Overall, the results in this study are somewhat poorer than what has been observed in young adult patients with APL. Although the study used reduced chemotherapy, the study protocol is probably outdated compared to the current COG regimen or standard of care adult protocols.

**Management of relapse in APL**

With the emergence of ATO, relapses in APL have become extremely rare. Most relapses now happen in patients who completed treatment with a non-ATO-based regimen. In Canada, patients with relapsed APL are generally treated with ATO plus ATRA (with an anthracycline for high-risk patients). Once these patients achieve molecular remission, they may receive an autologous stem cell transplant because it is a preferred treatment for patients who have relapsed and are responsive to second-line treatment.14 In patients who have relapsed but fail to achieve a subsequent molecular response to second-line treatment, an allogeneic transplant would be considered. Prolonged exposure to ATO and ATRA can be considered if an autologous stem cell transplant could not be offered. As relapse cases are extremely rare, individualized, case-by-case collaborative decision making is needed.

The study by Cicconi et al. presented at the 7th International Symposium on APL was conducted in a reasonably large group of patients who relapsed after receiving front-line non-ATO-based regimens (e.g., ATRA plus idarubicin).15 These patients received prolonged ATO and ATRA therapy (without stem cell transplant), and 68% achieved molecular remission. The efficacy outcomes are better than expected, and they support the use of prolonged ATO and ATRA in patients with relapsed APL who cannot undergo a stem cell transplant.

**Therapy-related APL**

Therapy-related APL (t-APL) is rare worldwide. At the 7th International Symposium on APL, Kayser et al. presented a study on t-APL that followed a large group of patients with t-APL (103 patients) accrued over a very long period (~25 years of accumulated data).16 In this study, patients with t-APL were treated with a mix of different regimens. ATO and ATRA therapy resulted in 100% CR, while the chemotherapy with ATO and ATRA combination resulted in 95% CR, and chemotherapy and ATRA resulted in 78% CR. EFS excluding death due to primary malignancy was higher in patients treated with ATO and ATRA or chemotherapy with ATO and ATRA when compared with chemotherapy and ATRA. The ED rate was lower if patients received an ATO-based regimen for induction. The study demonstrated that ATRA plus ATO was a vital aspect to treating these patients.

The overall take-home message from this study is that patients with t-APL should be treated in the same way as de novo APL (i.e., using ATO plus ATRA). This study has also shown that stem cell transplant is not uniformly needed. For high-risk t-APL, the use of idarubicin should be cautioned because these patients may have received anthracyclines for their primary malignancy, such as breast cancer, and the cumulative doses of anthracyclines in these patients become a concern.

**Early death in APL**

The definition of ED remains controversial in the treatment of APL. We are most interested in deaths occurring in the first week of induction, but it is difficult to determine which day
the patient died using population-based data, as opposed to a prospective clinical trial or patient registry. Therefore, for practical purposes, ED should be defined as death occurring in the first 30 days during induction. This definition allows comparability between treatment centres and registries.

ED rates depend on the characteristics of treatment centres. From our Canadian experience, if patients with APL are treated at an experienced acute leukemia centre, ED rates are much lower than those reported in population-based cancer registry data. Recent U.S. SEER data showed that the presence of a trauma centre and an intensive care unit in the hospital where APL patients are treated is associated with improved ED rates. More importantly, prompt and familiar access to blood products and ATRA is a key characteristic of a successful APL treatment centre, as blood product support and ATRA are essential to rescuing patients with APL from ED. Overall, ED in APL can be largely reduced and it relies, at least in part, on the characteristics of treatment centres where APL care is delivered.

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