NEWEVIDENCE

Idelalisib given front-line for the treatment of CLL results in frequent and severe immune-mediated toxicities

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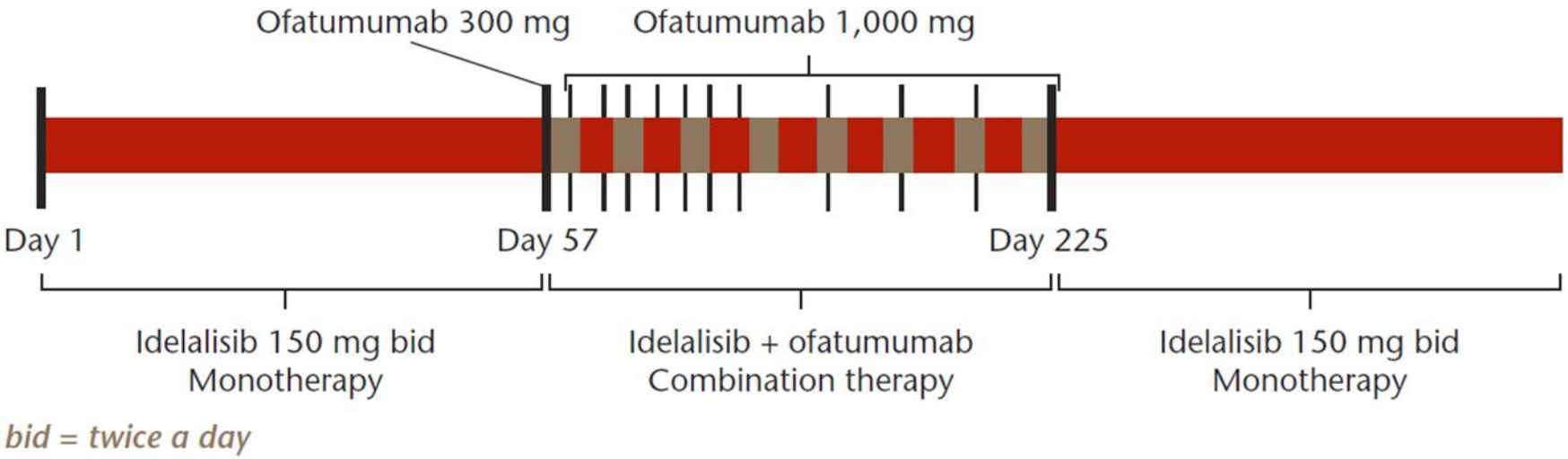
Background

- Idelalisib inhibits the p110δ isoform of PI3K
  - P110δ expression is primarily limited to leukocytes[1]
- P110δ integrates and transduces signals that are important for lymphocyte growth, survival, and migration
- The combination of idelalisib with rituximab improved ORR, PFS, and OS compared to rituximab monotherapy in patients with R/R CLL[2]

1. Sawyer C, et al. Cancer Res 2003;63(7):1667–75.
2. Sharman JP, et al. ASH Annual Meeting 2014:330.

CLL = chronic lymphocytic leukemia; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PI3K = phosphatidylinositol 3-kinase; R/R = relapsed/refractory

Study Design



bid = twice a day

- This was a phase II study of idelalisib plus ofatumumab in previously untreated CLL/SLL
- As of September 11, 2015, the trial was ongoing with 24 subjects enrolled
- Median time on therapy was 7.7 months (range: 0.7–16.1)

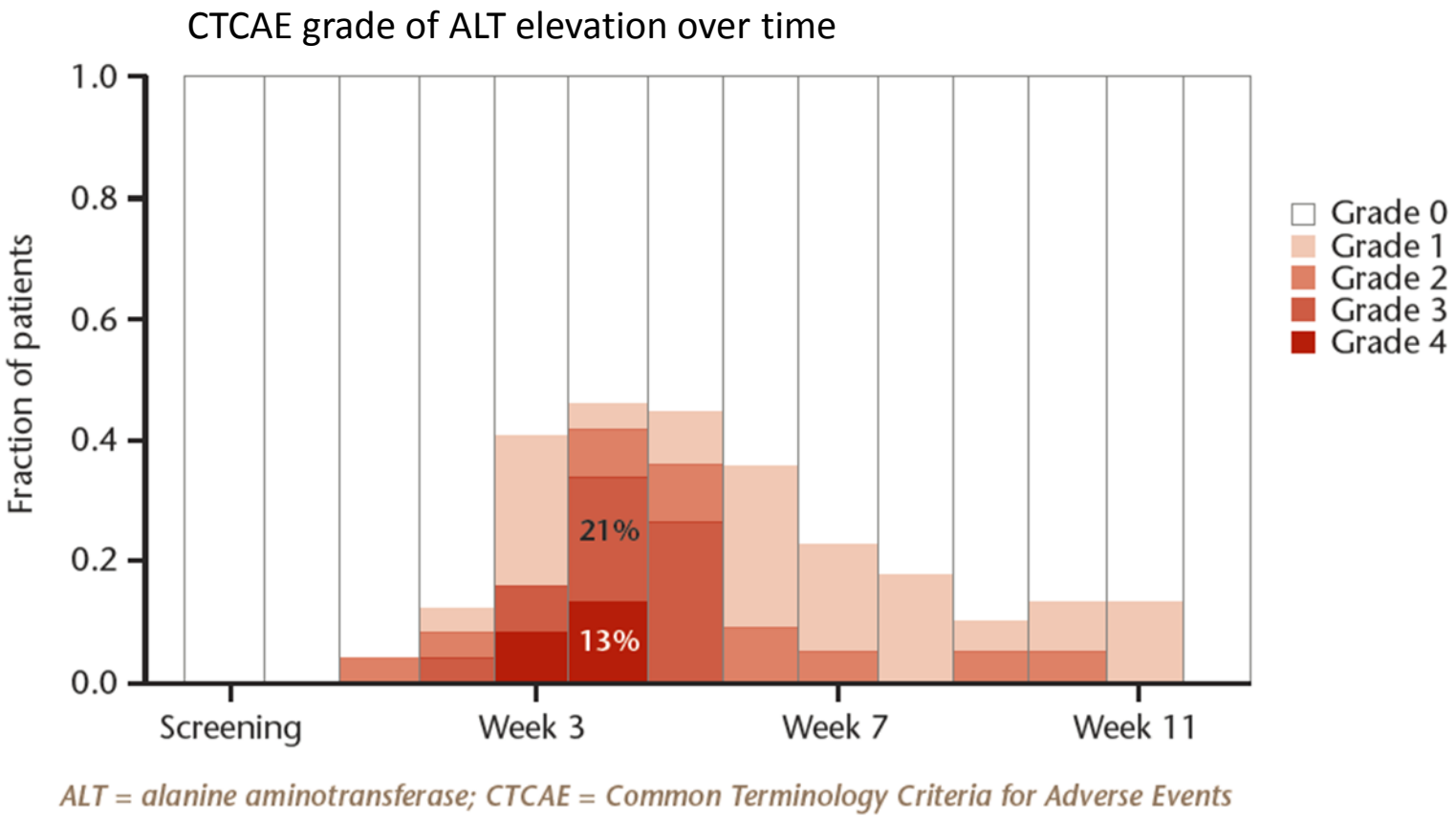
CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma

Baseline Characteristics

		Idelalisib + Ofatumumab
Total number of patients enrolled, n		24
Male gender, %		75
Median age, years (range)		67.4 (57.6–84.9)
Prior number of therapies		0
CLL genetics, n (%)	Unmutated IGHV Del(17p)/TP53 mutations Del(11q) Del(13q)	13 (54%) 4 (17%) 1 (4%) 13 (54%)

CLL = chronic lymphocytic leukemia; del(11q) = deletion 11q; del(13q) = deletion 13q; del(17) = deletion 17p; IGHV = immunoglobulin heavy chain variant; TP53 = tumour protein 53

Frequent and Severe Hepatotoxicity with Idelalisib



ALT = alanine aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events

- The majority of patients had grade ≥3 hepatotoxicity (52%)

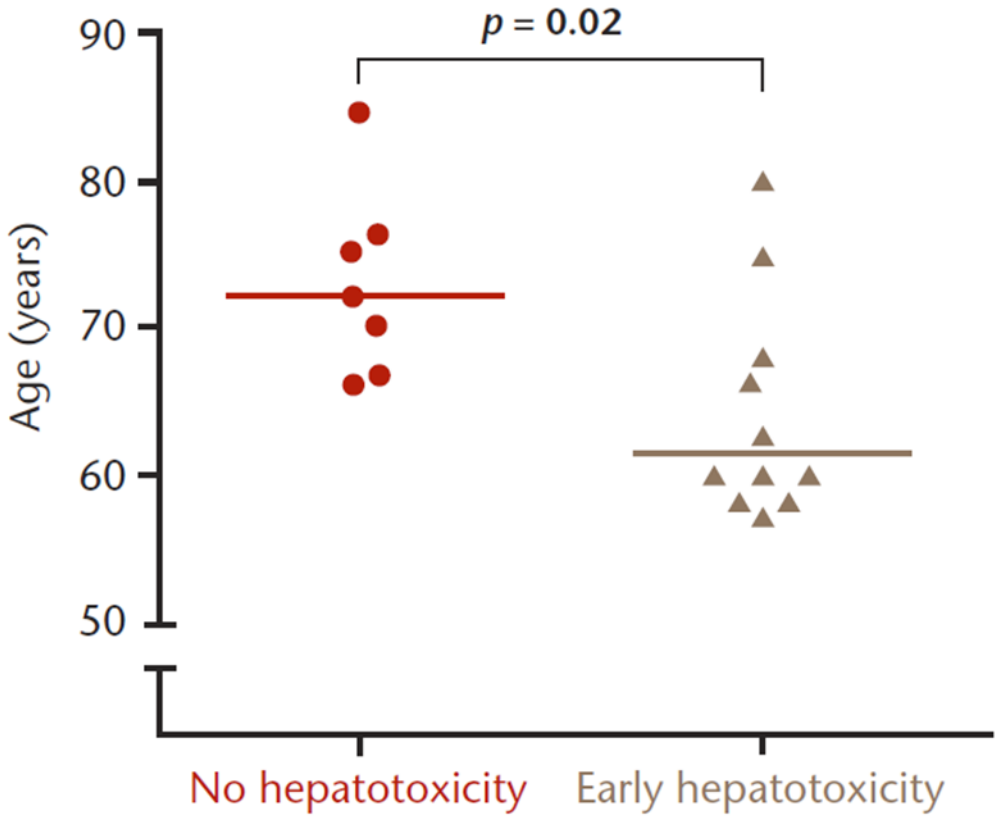
Incidence of Toxicities

	Toxicity frequency			
	Phase I	Overall relapsed	Upfront patients aged ≥65	Upfront idelalisib + ofatumumab
Number of subjects	54	760	64	24
Median prior therapies (range)	5 (2–14)	≥1	0	0
Median age, years (range)	63 (37–82)	66 (21–91)	71 (65–90)	67.4 (58–85)
Median time on therapy, months (range)	15 (0.2–48.7)	—	22.4 (0.8–45.8)	7.7 (0.7–16.1)
Grade ≥3 transaminitis, %	1.9	14	23	52
Grade ≥3 colitis/diarrhea, %	5.6	14	42	13
Any grade pneumonitis, %	5.6	3	3	13
Reference	Brown JR, et al. Blood 2014[1]	Coutre S, et al. EHA 2015[2]	O'Brien SM, et al. Blood 2015[3]	

- An analysis of previous studies suggested that toxicities were more common in less heavily pretreated patients

1. Brown JR, et al. Blood 2014;123:3390–7.
2. Coutre S, et al. EHA Congress Abstracts 2015:S433.
3. O'Brien SM, et al. Blood 2015;126:2686–94.

Age Was a Risk Factor for Early Hepatotoxicity



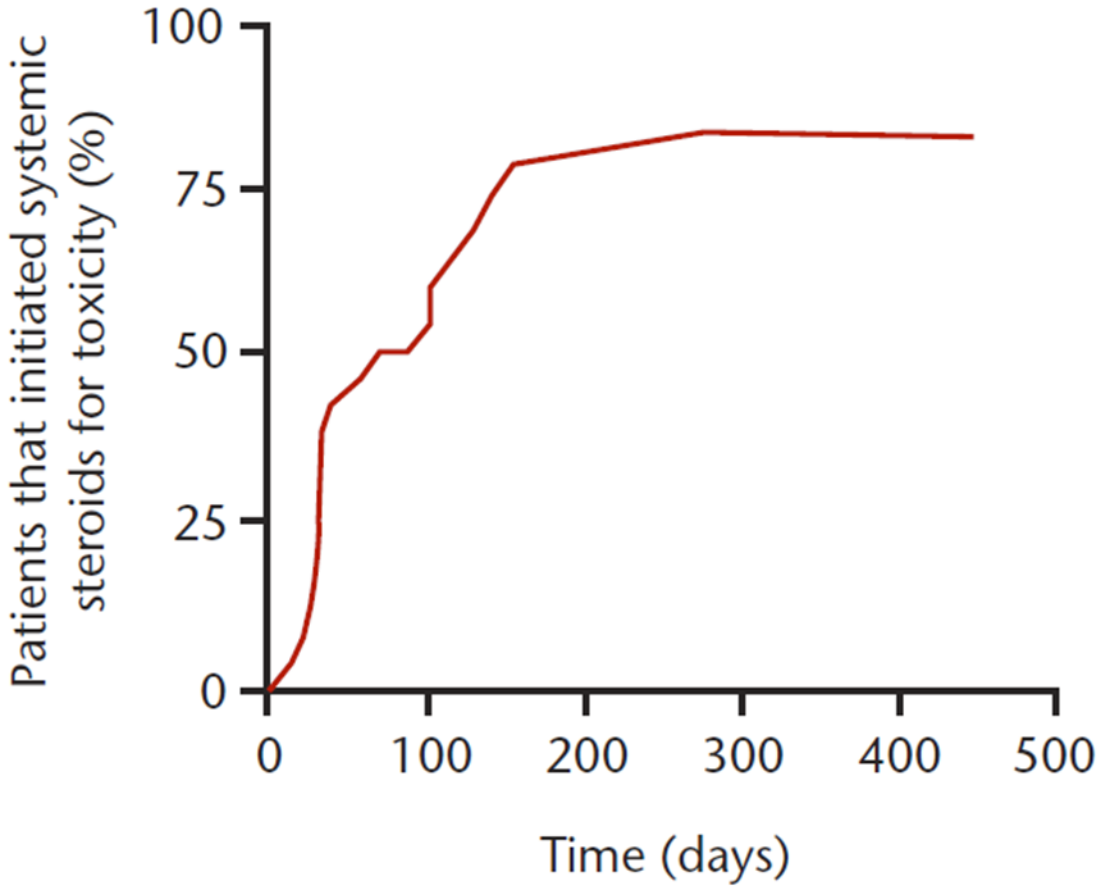
- All patients with age ≤65 years (n = 7) required systemic steroids for toxicities

Idelalisib Toxicities are Likely Due to On-Target Immune-Mediated Effects

- Activated immune infiltrate was found on liver biopsy
- Intestinal biopsies from patients with idelalisib-related colitis showed intraepithelial CD8+ lymphocytosis and crypt cell apoptosis

CD = cluster of differentiation

Responsiveness to Steroids: Kaplan-Meier Time to Initiation of Steroids



Delayed Development with Rapid Recurrence

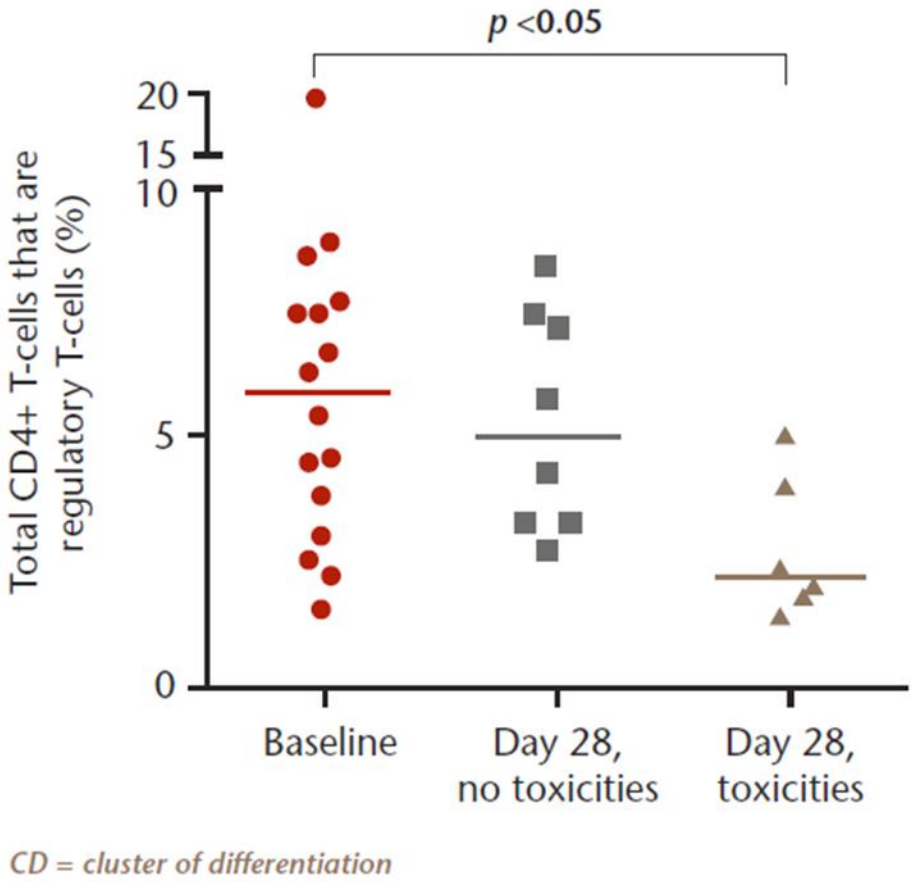
- Twelve subjects with grade ≥2 transaminitis were rechallenged with the drug after holding for toxicity
  - Five patients were rechallenged while off steroids; four developed recurrent transaminitis within 1–4 days (grade 2: n = 1; grade 3: n = 2; grade 4: n = 1)
  - Seven patients were rechallenged while on steroids; two developed recurrent transaminitis within 3–4 days (grade 2: n = 1; grade 3: n = 1)

The Connection between p110δ and Regulatory T-Cells

- Mice with genetic inactivation of p110δ developed autoimmune colitis[1]
- Mutations that disrupted the function of regulatory T-cells in mice and humans led to autoimmune syndromes with hepatitis, enteritis, and pneumonitis[2,3]
- Mice with genetic inactivation of p110δ had decreased numbers and function of regulatory T-cells[4]

1. Okkenhaug K, et al. Science 2002;297:1031–4.
2. Torgerson TR, et al. J Allergy Clin Immunol 2007;120:744–50.
3. Godfrey V, et al. Am J Path 1991;138:1379–87.
4. Patton DT, et al. J Immunol 2006;177:6589–602.

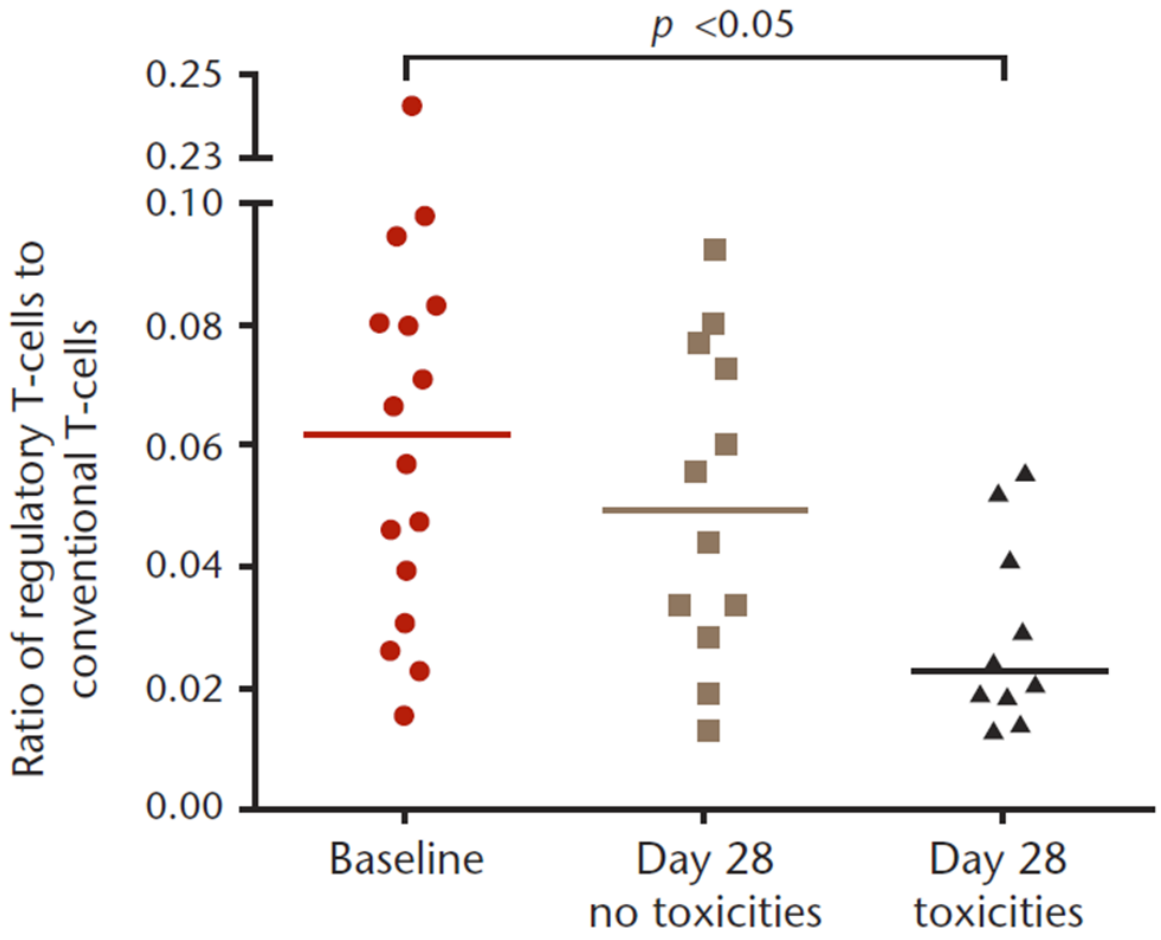
Decrease in Regulatory T-Cells While on Therapy



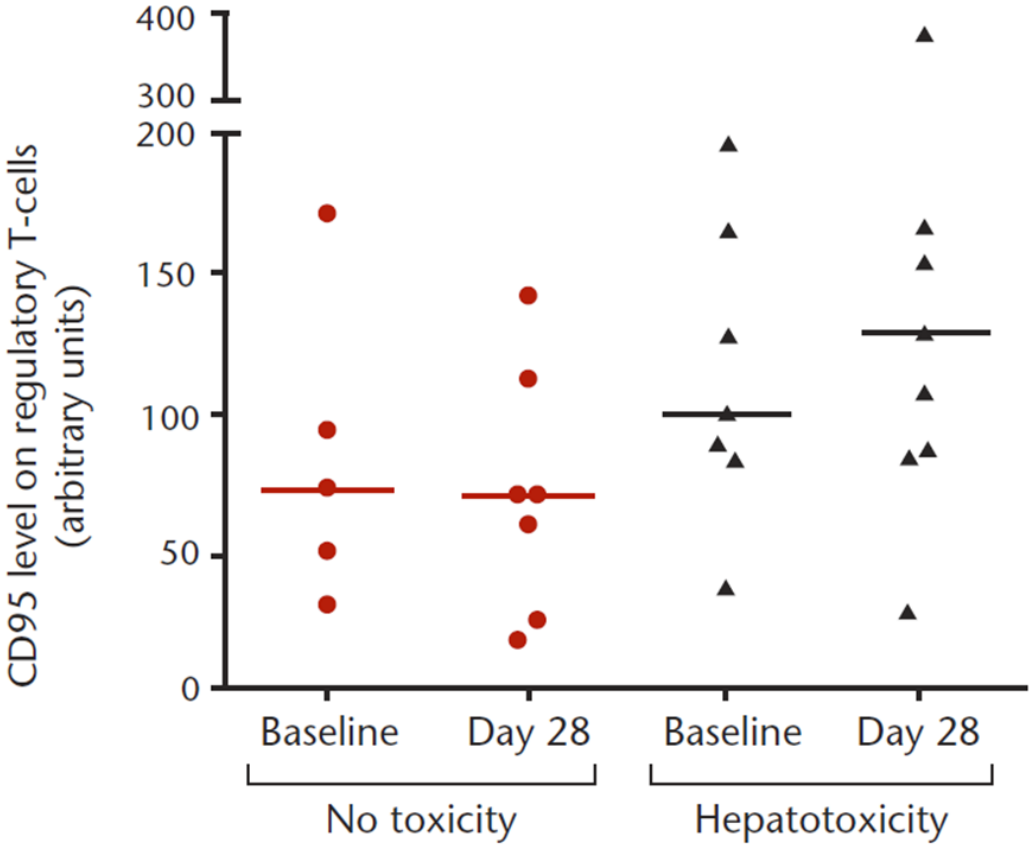
CD = cluster of differentiation

- Eleven out of 15 patients with matched samples (73%) had a decrease in the percentage of regulatory T-cells over time

Change in Ratio of Regulatory T-Cells to Conventional T-Cells



Change in CD95 Level on Regulatory T-Cells



- CD95 is a pro-apoptotic marker

CD = cluster of differentiation

Summary and Conclusion

- An early fulminant hepatotoxicity developed in a subset of primarily younger patients treated with idelalisib monotherapy in the front-line setting
- Multiple lines of evidence suggest that this early hepatotoxicity is immune-mediated
- The proportion of regulatory T-cells in the peripheral blood decreased on idelalisib therapy, providing a possible explanation for the development of early hepatotoxicity