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Enhancing the Ability to Diagnose, Interpret and Apply Best Treatment Options for Cutaneous Lymphomas

Therapeutics/Preclinical Studies | #86

Durvalumab (Anti-PD-L1) & Lenalidomide is Superior to Single-Agent Durvalumab in Refractory/Advanced Cutaneous T Cell Lymphoma

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Disclosures

- Consultant/Advisor for Citius Pharmaceuticals, Inc., Helsinn, and Kyowa Kirin.
- Grant/Research Support from Helsinn and Kyowa Kirin.
- This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.
- This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.
- This presentation has been peer-reviewed and no conflicts were noted.
- **The investigational use of durvalumab and lenalidomide will be addressed.**

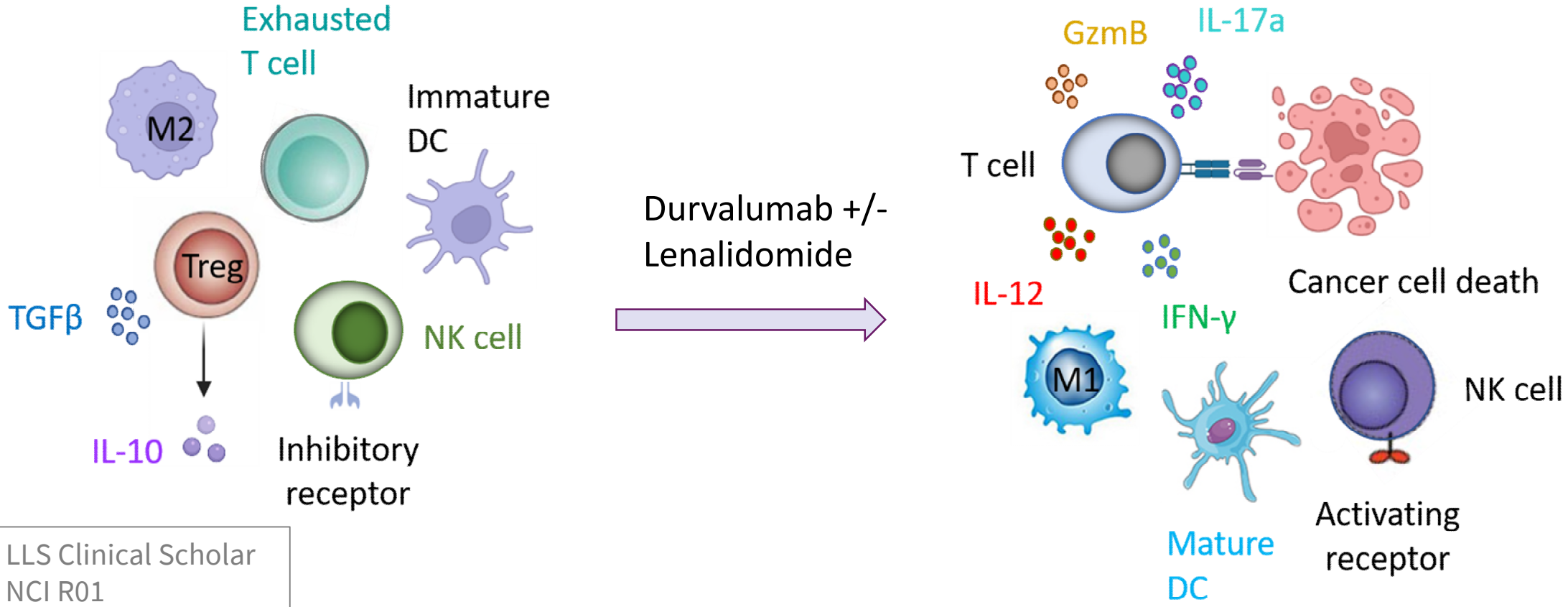
Introduction

- Advanced stages of mycosis fungoides (MF) and the leukemic variant Sézary syndrome (SS) have an unfavorable prognosis.
- We have shown that the malignant T cells escape immune surveillance via immune checkpoint signaling such as the PD-1/PD-L1 axis.
- We investigated the effects of PD-L1 blockade as a strategy for targeting both the innate and adaptive immune system in cutaneous T cell lymphoma in our randomized Phase 2 portion to compare single agent durvalumab to durvalumab & lenalidomide in relapsed/advanced CTCL (NCT03011814).
- The primary end point was objective response rate using the global composite response (based on skin, blood, nodes, and viscera) according to consensus guidelines.
- Secondary end points included duration of response, progression-free survival, and toxicity.
- Relationships between gene expression profile, tumor-microenvironment, and antitumor activity were exploratory end points.

Querfeld C et al. Cancer Immunol Res 2018; Han Z et al. J Invest Dermatol 2021

Treatment Regimen

- Single agent arm
  - 1500 mg IV durvalumab q 4 week
- Combination arm
  - 1500 mg IV durvalumab q 4 week
  - 10 mg lenalidomide starting dose up to MTD or 20 mg q daily for 21 days



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Clinical Features of Enrolled Patients

	Durvalumab (n =12)	Durvalumab/Lenalidomide (n= 13)
Age, median (range)	56 (26-79)	65 (32-88)
Gender		
▪ Female / Male	3 (25%) / 9 (75%)	6 (46%) / 7 (54%)
Stage		
▪ IB	2 (17%)	4 (31%)
▪ IIB	5 (42%)	3 (23%)
▪ IIIA	1 (8%)	2 (15%)
▪ IIIB	1(8%)	2 (15%)
▪ IVA1	0	1 (8%)
▪ IVA2	3 (25%)	1 (8%)
Subtype		
▪ Mycosis fungoides	11 (92%)	12 (92%)
▪ Sezary syndrome	1 (8%)	1 (8%)
▪ Erythroderma	4	4
▪ FMF	4	6
▪ LCT	5	4
Ethnicity/Race		
▪ Black	0	4
▪ Hispanic	4	2
▪ Asian	1	1
▪ White	6	6
▪ Pacific Islander	1	0
Median prior Tx (range)		
▪ Systemic	3 (2-4)	2 (2-4)
▪ Skin-directed	3 (1-4)	2 (1-4)

➢ **Median follow up time = 7.7 (range, 0.9-27.6) months**

	Durvalumab (n =12)	Durvalumab/Lenalidomide (n= 13)
Best Response	**5 (42%)**	**9 (75%)**
▪ CR	0	4 (33%)
▪ PR	5 (42%)	5 (42%)
▪ SD	5 (42%)	3 (25%)
▪ PD	2 (16%)	0
▪ Inevaluable	0	1
Number of Tx cycles Median (range)	3.5 (2-20)	6 (1-17)
PD or Lack of Response	7 (58%)	4 (31%)
Remain on Tx	3 (25%)	3 (23%)

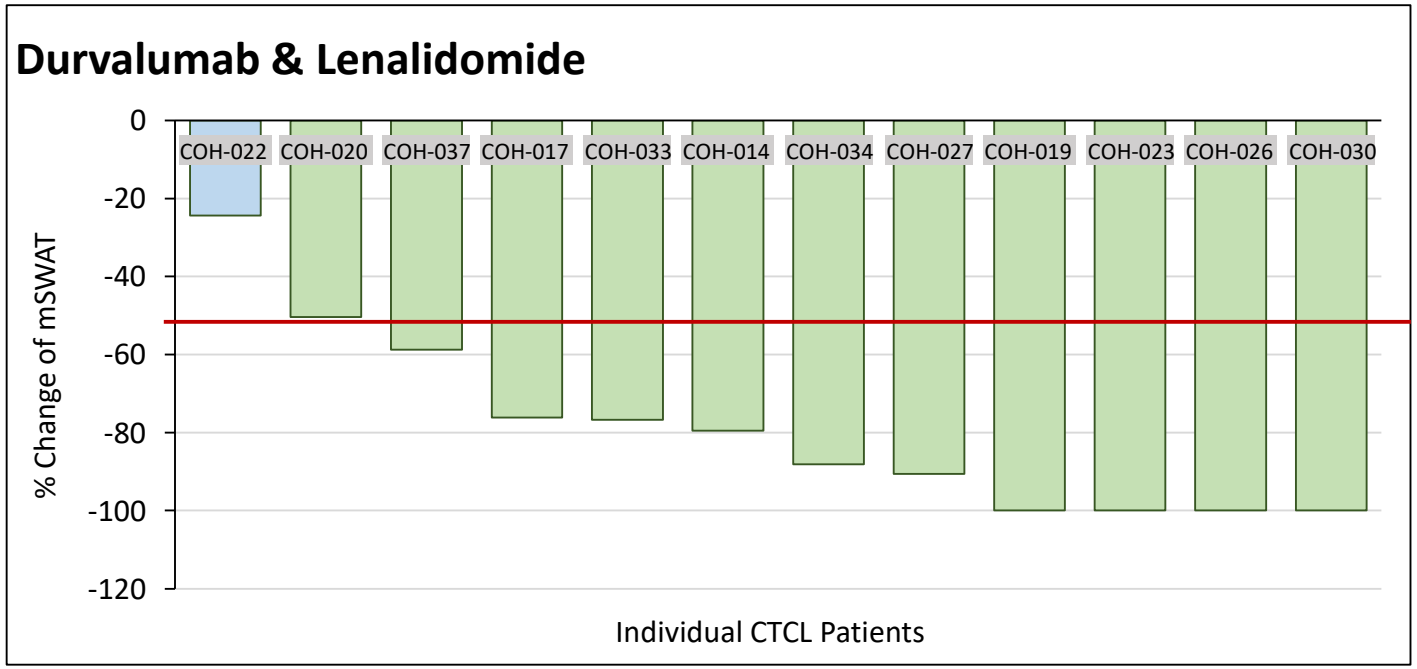
Skin Response

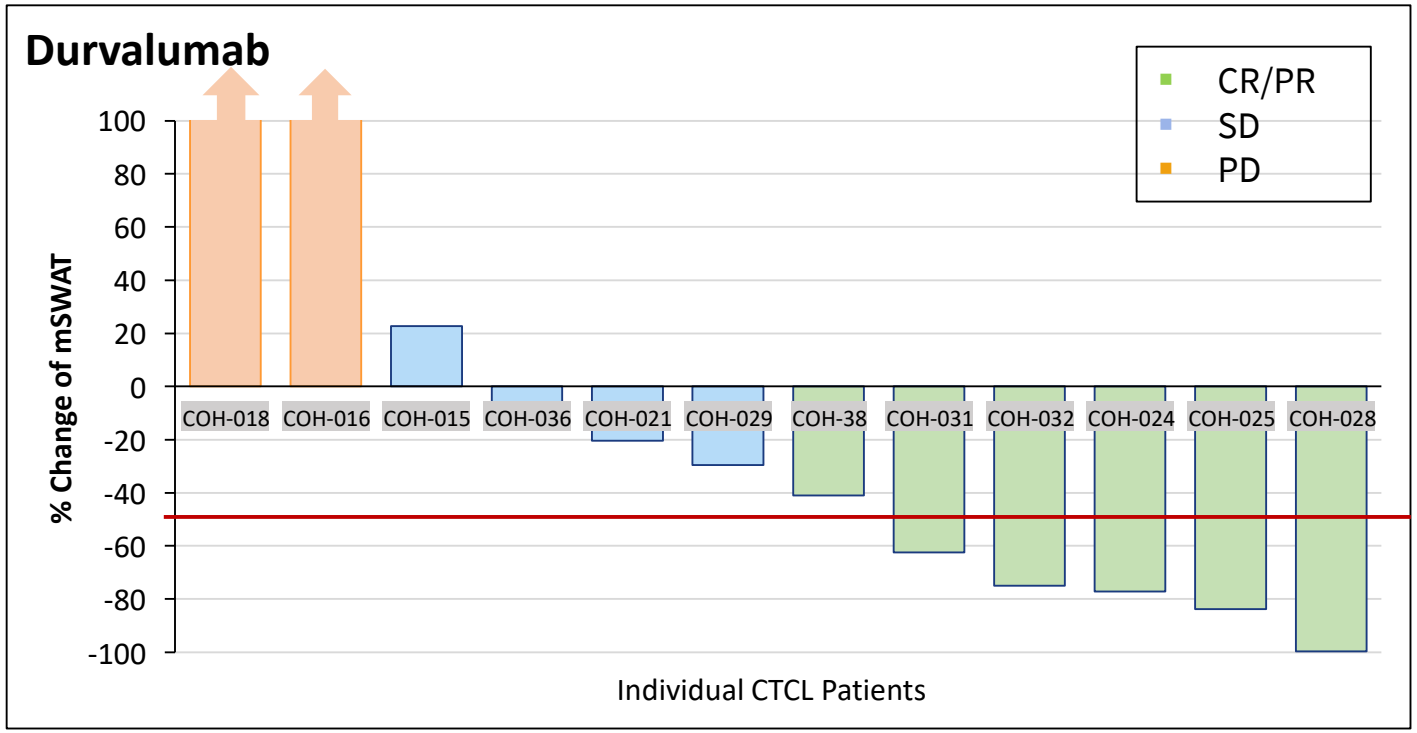
Combined durvalumab/lenalidomide:

- 11 pts with CR (4)/PR (5)
- 1 pt with SD

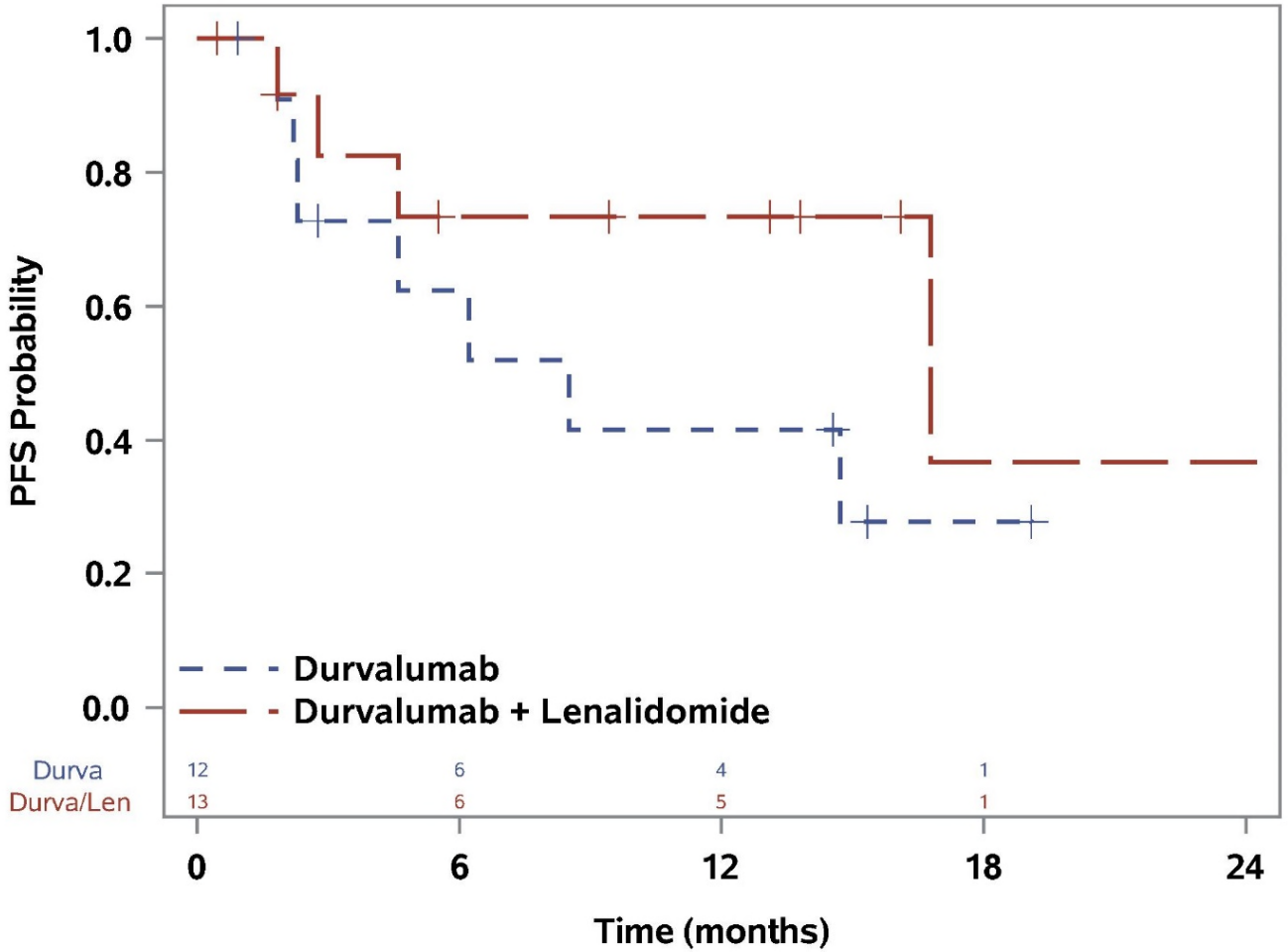
Single agent durvalumab:

- 5 pts with PR, no CR
- 4 pts with SD
- 2 pts with PD





Progression-Free Survival of Single Agent Durvalumab vs Durvalumab/Lenalidomide Combination



Median PFS: 8.5 (95% CI 2.2-NA) months for durva arm vs 16.8 (2.8-NA) months for durva/lenalidomide arm.

Most Common Treatment-Related Adverse Events

Adverse Event	Durva only (n=12)	Durva + Len (n=13)	Total (n)
Fatigue	4	10	14
Anemia	1	5	6
Thrombocytopenia	2	4	6
Diarrhea	1	5	6
Constipation	1	4	5
Leg edema	0	4	4
Leukopenia	0	3	3
Neutropenia	0	3	3

- AEs with attribution of possibly or higher and a total of 2+ events (any grade)
- Most common treatment-emergent Adverse Events are more frequent in the durvalumab/lenalidomide arm.

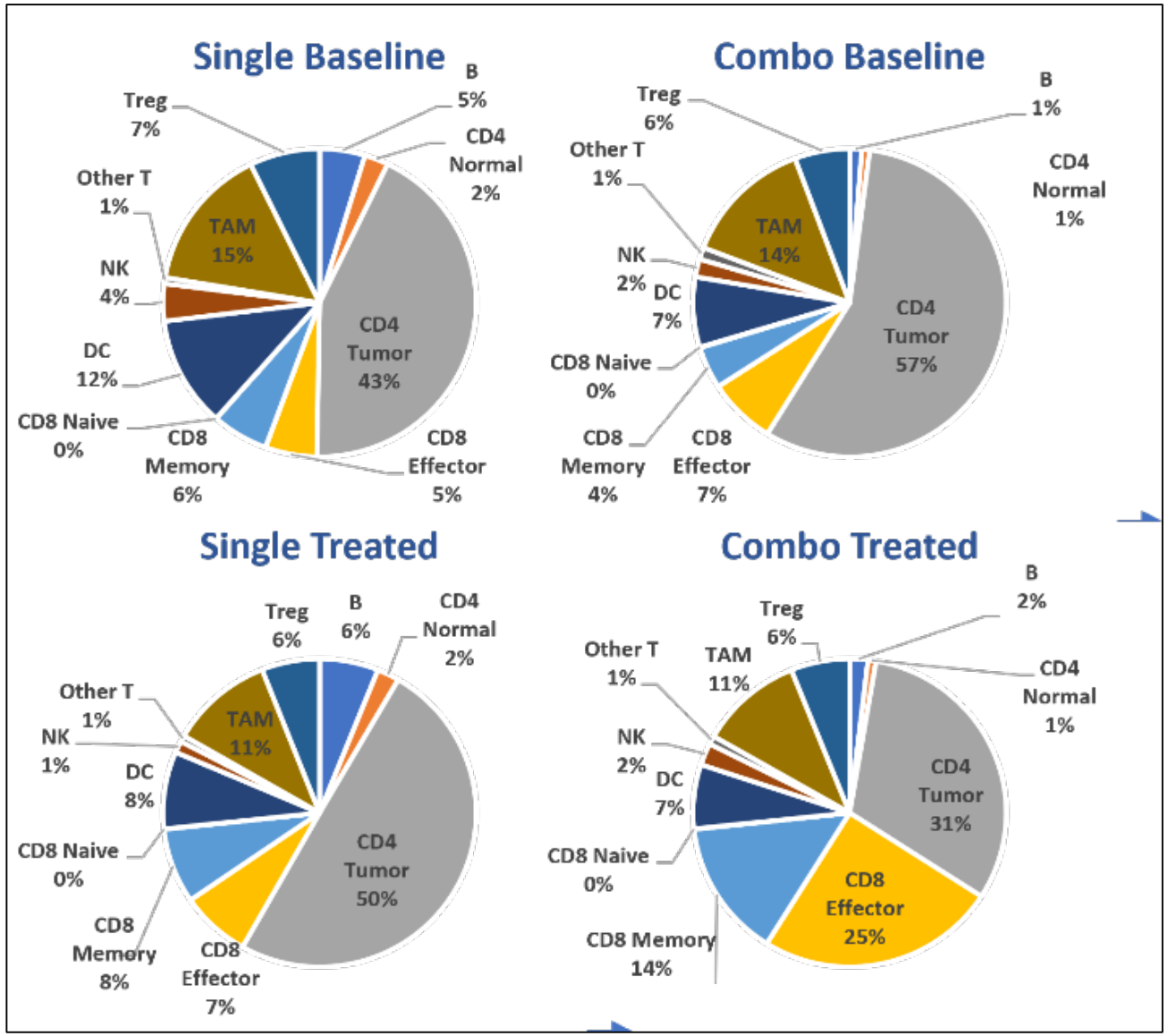
Immune-Related Adverse Events

Adverse Event	Durva only (n=12)	Durva + Len (n=13)	Total (n)
Tumor flare/rash/skin changes	1	6	7
Elevated TSH	2	0	2
Hypothyroidism	1	1	2
Hyperthyroidism	1	1	2
Elevated ALT	1	1	2
Elevated AST	0	1	1
Flu-like symptoms/body aches	1	1	2
Dysgeusia	0	1	1
Anosmia	1	0	1

- AEs with attribution of possibly treatment –related or higher and any grade
- Cutaneous events are most common
- Thyroid dysfunctions in ~ 25% of patients

Immune Cell Composition for each Treatment Arm at Baseline and Posttreatment Reveals Distinct Signatures

- Increase in tumor-infiltrating CD8+ T cells in combo arm
- Decrease in CD4+ tumor cells
- No change in TAMs for either treatment arm



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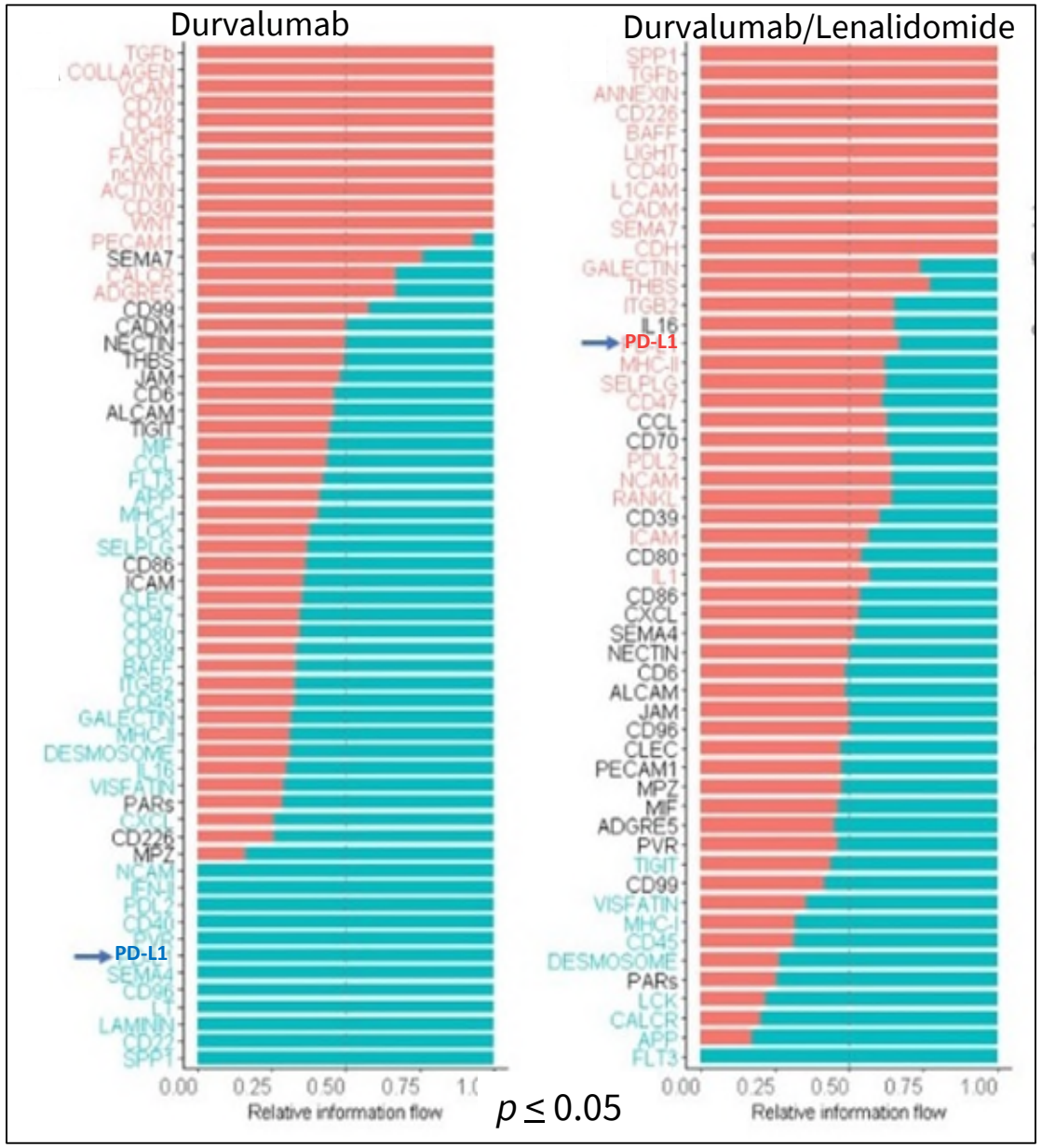
Differences in Cell-Cell Interaction Signals in Durvalumab Arm vs Durvalumab/Lenalidomide Arm

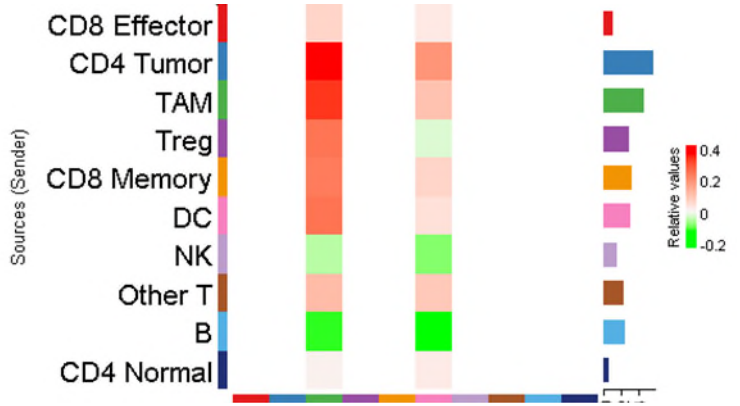


$p \leq 0.05$

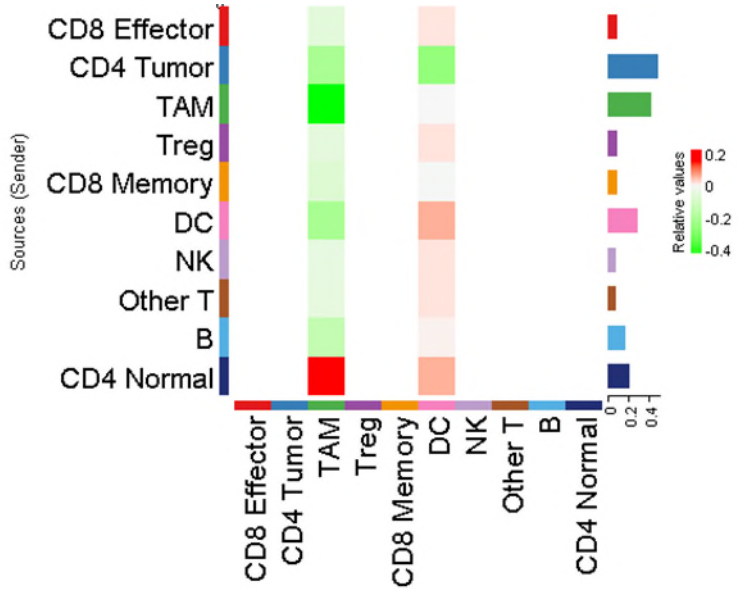
Baseline

Treated

Durvalumab



Durvalumab/Lenalidomide



- Cell-cell communication between CTCL cells & TAMs and other immune cells increased in post-treatment samples from durva arm contributing to an immunosuppressive TME

In Conclusion

- Combinatorial regimen of durvalumab (anti-PD-L1) & lenalidomide demonstrated superior clinical activity compared to single-agent durvalumab in refractory/advanced CTCL.
- Responses were durable and ongoing, and treatment was well tolerated.
- Molecular profiling using CIBERSORT and single cell analysis revealed distinct changes of immune cell signatures and cellular signaling interactions within the TME that occurred in each treatment arm when compared to baseline.

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Thank you!