Durvalumab & Lenalidomide Shows Superior Efficacy Versus Single-Agent Durvalumab in Refractory/Advanced Cutaneous T Cell Lymphoma in a Randomized Phase 2 Trial

Christiane Querfeld[1,2,7,8], Lu Chen[3,8], Xiwei Wu[4,5,8], Zhen Han[2,8], Ching-Yu Su[2,8], Liliana Crisan[2,8],Melissa Banez[6], Jeralyn Quach[6], Tiffanie Barnhizer[6], Steven T. Rosen[7,8], Jasmine Zain[7]

[1]Division of Dermatology, [2]Department of Pathology, [3]Division of Biostatistics, [4]Integrative Genomics and Bioinformatics Core, [5]Computational and Quantitative Medicine, [6]Clinical Trials Office, [7]Department of Hematology/Hematopoietic Cell Transplantation, and [8]Beckman Research Institute, City of Hope, Duarte, CA, USA

BACKGROUND

Advanced stages of cutaneous T cell lymphoma (CTCL) have an unfavorable prognosis. We have shown that CTCL escapes immune surveillance via immune checkpoint signaling such as the PD-1/PD-L1 axis. Selective targeting of the functionally exhausted malignant T cells in cutaneous T-cell lymphoma (CTCL) and distinct cells within the tumor microenvironment (TME) via PD1/PD-L1 blockade (durvalumab) may restore an anti-tumor immune response. We initiated the randomized Phase 2 portion to compare single agent durvalumab to durvalumab plus lenalidomide in relapsed/advanced CTCL (NCT03011814). The primary end point was objective response rate (ORR) 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 (TME), and antitumor activity were exploratory end points.

METHODS

Adult patients with histologically confirmed MF or SS, who had failed ≥2 systemic therapies were enrolled and randomized 1:1 to single agent durvalumab (1500 mg (day 1 of 28-day cycle) or durvalumab (same dose) & lenalidomide (10 mg for cycle 1, 15 mg for cycle 2, then 20 mg for subsequent cycles daily for 21 days of each 28-day cycle). The study used a “pick a winner” design based on ORR. Serial skin and blood samples were collected to assess the impact on the TME and anti-tumor activity. .

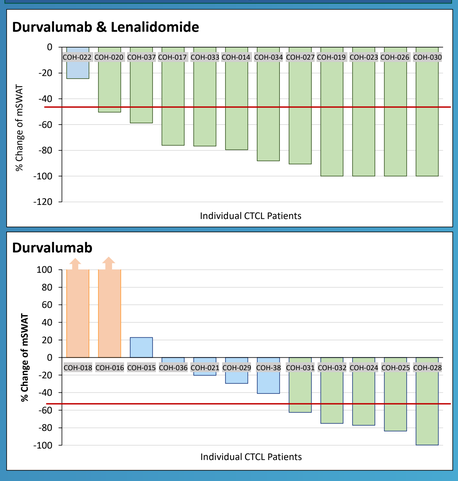
Clinical Characteristics of Enrolled Patients

	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%)
▪ Sézary syndrome	1 (8%)	1 (8%)
▪ Erythrodermic	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)	3 (2-4)	2 (2-4)
▪ Systemic	3 (1-4)	2 (1-4)
▪ Skin-directed		

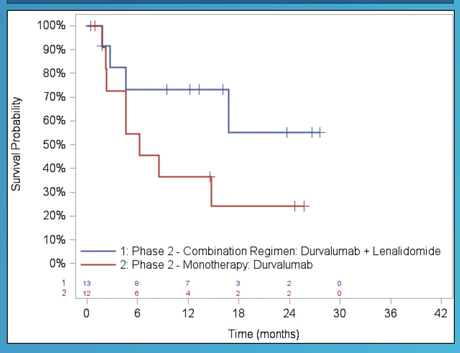


- Patient with mycosis fungoides, clinical stage IIB with large cell transformation
- Treated with durvalumab & lenalidomide combo
- Patient achieved CR., response is ongoing for ≥ 18 months

Skin Response Measured by mSWAT Change



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



GLOBAL RESPONSES

	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%)

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
Thrombocyto-penia	2	4	6
Diarrhea	1	5	6
Constipation	1	4	5
Leg edema	0	4	4
Leukopenia	0	3	3
Neutropenia	0	3	3

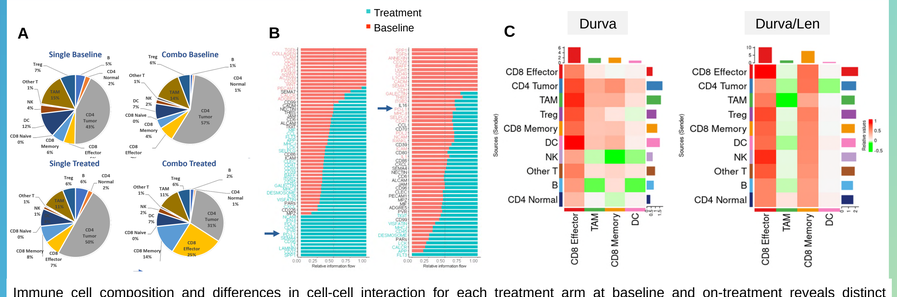
Immune-Related Adverse Events

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

RESULTS

- Median follow-up 14.5 (range 0.5 -29.7) months.
- ORR of 75% (9 pts) for durva/len arm vs. 42% (5 pts) for single agent durva.
- 12 months PFS of 73% (95% CI: 38%-91%) for durva/len vs. 36% (95% CI: 11%-63%) for durva.
- Median PFS: 8.5 (95% CI 2.2-NA) months for durva arm vs not reached (2.8-NA) months for durva/lenalidomide arm.
- The most common treatment-emergent adverse events were more frequent in the durvalumab/lenalidomide arm vs durvalumab arm.
- The majority of AEs with both treatment arms were mild to moderate in severity (grade I/II, 92%; grade III, 8 %).
- One grade IV neutropenia on combo arm was observed.

Immune Cell Composition and Cell-cell Interactions for Each Treatment Arm Reveals Distinct Signatures



Immune cell composition and differences in cell-cell interaction for each treatment arm at baseline and on-treatment reveals distinct signatures (A). The interactions between CD8+ T cells and TAMs are central to shaping immunosuppressive tumor microenvironment with increased/decreased communication dynamics observed across immune cell subsets. This maybe likely due to decreased PD-L1 expression (B). Increased interactions with CD8+ T cells are seen in both arms (C); communications with TAMs are increased in single agent arm but decreased in combo arm. Overall, findings demonstrate that durva/len shows stronger anti-tumor immunity in CTCL.

CONCLUSIONS

- Durvalumab (anti-PD-L1) & lenalidomide demonstrated superior clinical activity compared to single-agent durvalumab in refractory/advanced MF/SS.
- Responses are durable and ongoing, and treatment was well tolerated with a favorable safety profile in both arms.
- Molecular profiling 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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