Lacutamab in Patients with Relapsed and/or Refractory Sézary Syndrome:
Translational Analysis from the TELLOMAK Phase 2 Trial

Poster # **1609**

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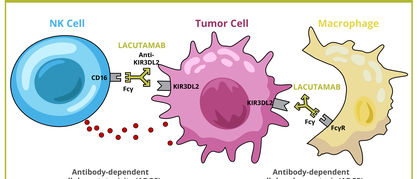
Introduction

Cutaneous T-cell lymphoma (CTCL) is a form of non-Hodgkin lymphoma, which includes Sézary Syndrome (SS), a rare, aggressive and advanced type of CTCL characterized by erythroderma, significant blood involvement, and lymphadenopathy. SS is associated with poor prognosis with a median patient survival of approximately 5 years. KIR3DL2 is expressed on circulating tumor cells (CTCs) of all SS patients and in the skin of more than 85% of SS patients. Lacutamab is a first-in-class monoclonal antibody designed to deplete KIR3DL2-expressing cells via antibody-dependent cell-cytotoxicity (ADCC) and phagocytosis (ADCP).

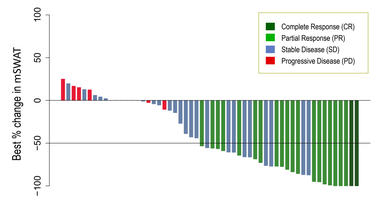
Figure 1: Lacutamab Mechanisms of Action



TELLOMAK is an international, open-label, multi-cohort Phase 2 trial investigating the safety and efficacy of single agent lacutamab in patients with relapsed/refractory (R/R) CTCL (NCT03902184). The SS patient cohort is characterized by advanced (IVA, IVB), highly refractory disease where patients received ≥2 prior systemic therapies including mogamulizumab.
Lacutamab showed robust activity with a global ORR of 37.5% [95% CI; 26.0-50.6; Figure 2], with a blood ORR of 48.2% [35.7-61.0; Figure 3] and a skin ORR of 46.4% [34.0-59.3; Figure 8] (*Porcu, ASH 2023*).

Here we report the results of translational analysis of this SS patient cohort exploring the association between blood and skin biomarkers and clinical outcomes. At the Data Cut-Off, May 1st 2023, 56 patients were enrolled, treated and evaluated.

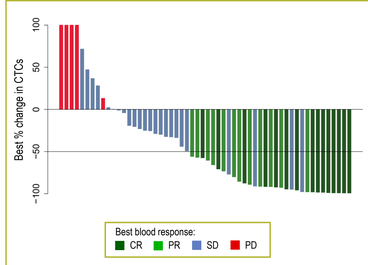
Figure 2: Best Global Response to Lacutamab (n=56)



- 21 (37.5%) patients achieved Global Response, including 2 CR and 19 PR.
- Median time to Global Response: 2.8 months (range: 1-9)

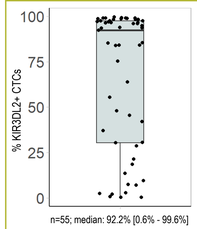
Translational Data in Blood

Figure 3: Best blood response (n=56)



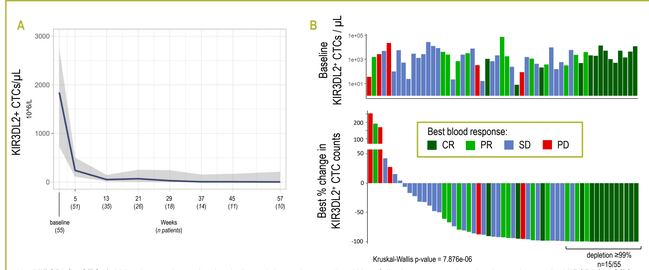
- Of the 27 (48.2%) patients that achieved a blood response,15 had a CR & 12 had PRs.
- Median time to Blood Response: 1.0 month (range 1-6)

Figure 4: KIR3DL2 is expressed on CTCs of all patients



- KIR3DL2 expression in CTCs by flow cytometry was detected on all patients at baseline. CTCs were defined as CD3+ CD4+ CD26-, CD3+ CD4+ CD7- or CD3+ CD4- CD8- cells for each patient. (Not Evaluable N=1).

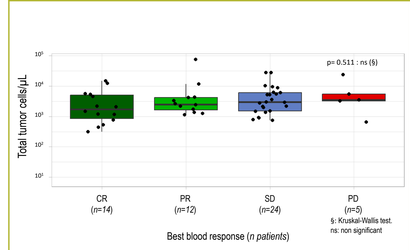
Figure 5: Lacutamab induces an early and deep depletion of KIR3DL2+ CTCs



A) KIR3DL2+ CTCs/µl blood were determined at indicated timepoints. Median value (blue line) and 95% confidence intervals (grey) are represented.The number of patient analyzed at each timepoint is indicated below each timepoints.

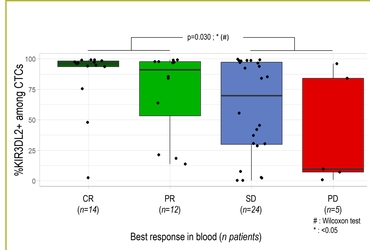
B) Waterfall plot representing the best change in KIR3DL2+ CTC counts in blood according to best blood response. Baseline blood KIR3DL2+ CTC burden is represented for each patient above the waterfall plot.

Figure 6: Blood response to lacutamab occurs irrespective of baseline CTC blood burden



- Baseline tumor cell burden was determined by flow cytometry.
- Blood response to lacutamab (CR/PR) is observed for patients with CTCs ranging from 311 to 74634 cells /µl.

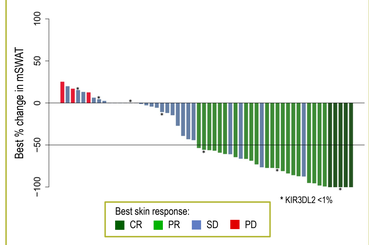
Figure 7: Blood response is associated with higher KIR3DL2 frequency on CTCs at baseline



- % KIR3DL2 expression among CTCs was determined by flow cytometry and represented according to blood response.

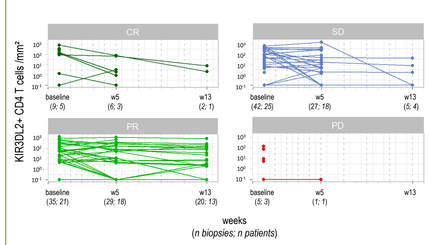
Translational Data in Skin

Figure 8: Best skin response (n=56)



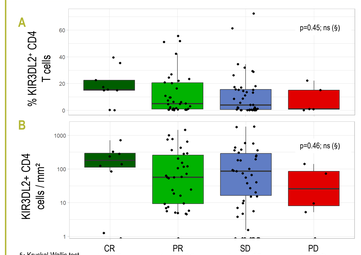
- 26 (46.4%) patients achieved a Skin Response; 5 CR & 21 PR. Median time to Skin Response: 2.8 months (range: 1-10)
- KIR3DL2 status (<1% or ≥1% KIR3DL2+ cells among mononucleated cells) was determined using an analytically validated FFPE test and demonstrated that KIR3DL2 ≥1% is observed in the skin of 87.5% of patients (49/56).

Figure 9: Lacutamab induces a decrease of CD4+ KIR3DL2+ cells in skin at week 5 post treatment, prior to median time to skin response



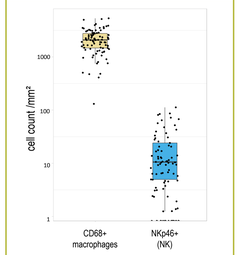
- One or two skin lesion biopsies were collected per patient at baseline, week 5 (W5) and week 13 (W13, optional). FFPE sections were stained with a multiplex IF panel (KIR3DL2, CD4, NKp46, CD16, CD68) and the density of KIR3DL2+ CD4+ T cells was determined. All biopsies are represented according to best skin response, determined by modified Severity-Weighted Assessment Tool (mSWAT).

Figure 10: Skin response to lacutamab occurs irrespective of baseline % and density of KIR3DL2+ CD4 T cells



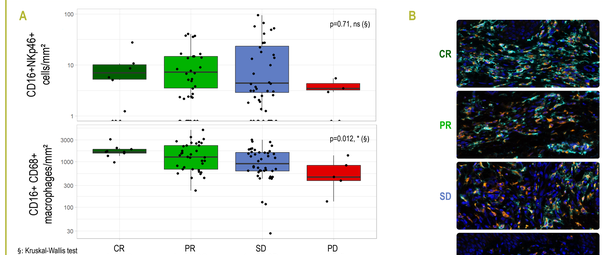
- %KIR3DL2 expression among CD4+ cells (A) and KIR3DL2+ CD4+ cell density (B) were determined by digital pathology. Data for each patient were distributed according to best skin response.

Figure 11: Baseline CD68+ macrophage infiltration is greater than that of NK cells



- CD68+ macrophage and NKp46+ NK cell densities were determined at baseline by digital pathology using the multiplex IF panel.

Figure 12: Patients responding to lacutamab in skin have higher baseline CD68+ CD16+ macrophage density suggesting ADCP is a mechanism of action of lacutamab in skin



A) CD16+ NKp46+ NK cell and CD16+ CD68+ macrophage densities were determined by digital pathology. Data for each patient were distributed according to best skin response.
B) A representative example of CD16+ CD68+ infiltration in each response group is shown.

Conclusions

Lacutamab monotherapy shows robust clinical activity with a favorable safety profile in a R/R SS population previously treated with 2 or more prior systemic therapies including mogamulizumab (*Porcu, ASH 2023*). The exploratory translational analyses from this cohort of n=56 SS patients indicate that:

- Lacutamab induces early and deep depletion of KIR3DL2-expressing CTCs, irrespective of the baseline blood tumor burden
- Lacutamab induces depletion of skin KIR3DL2+ CD4+ cells regardless of their density, which occurs prior to median time to skin response
- In the skin, CD68+ macrophage infiltration is largely higher than NK cell infiltration
- Association between CD16+ CD68+ macrophage densities with response to lacutamab suggest ADCP is involved in the mechanism of action of lacutamab in skin

These data confirm at a translational level the activity of lacutamab, and its potential as a compelling future treatment option for SS patients with high unmet medical need.

Acknowledgments

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- **Clinical study teams who made this trial possible, including the translational team who generated translational data.**

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