LACUTAMAB IN PATIENTS WITH RELAPSED AND/OR REFRACTORY MYCOSIS FUNGOIDES: RESULTS FROM THE TELLOMAK PHASE 2 TRIAL

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Clinicaltrials.gov: NCT03902184

Mycosis Fungoides

- Most common type (50-60%) of cutaneous T-cell lymphoma (CTCL)
- Rare mature T-cell lymphoma first appearing in the skin
- About 25% of patients are diagnosed in advanced stage (IIB-IVB), with 5-year survival 15-25%

- Last approval (2018) in R/R CTCL is mogamulizumab[1] for patients with ≥1 prior systemic therapies
  - Objective response rate (ORR): 28% in SS+MF (21% in MF)
  - Median progression-free survival (PFS): 6.7 months, most patients relapse on mogamulizumab
  - Grade 3-4 adverse event in 41% of patients, 19% patients discontinued mogamulizumab for safety reasons
  - **A high medical need remains in this population**

- **TELLOMAK:** A phase 2 study (NCT03902184) evaluated the anti-KIR3DL2 antibody lacutamab in 2 CTCL subtypes:
  - **Sezary Syndrome** with ≥ 2 prior systemic therapies (must have received mogamulizumab)
  - Heavily pretreated population (median 5 prior therapies):
    - Global ORR 37.5% (26.0, 50.6); median DoR 12.3 months (5.2, NE); PFS 8.0 months (4.7, 21.2)[2].
  - **Mycosis Fungoides**: 2 cohorts according to KIR3DL2 expression in skin (≥1%, <1%), based on central evaluation by IHC

- We present data in all Mycosis Fungoides patients, according to KIR3DL2 expression in skin

ORR: Objective Response Rate; PFS: progression free survival

1. Kim Y et al, Lancet Oncol 2018; 2 Porcu et al, ASH 2023

Lacutamab KIR3DL2 targeted treatment in T-Cell Lymphoma

- **KIR3DL2** is a killer immunoglobulin-like receptor, expressed in approximatively 90% of SS pts and 50% of MF pts (expression threshold set to ≥ 1% of positive mononucleated cells in skin biopsy)

- **Lacutamab** is a first-in-class monoclonal antibody designed to specifically deplete KIR3DL2-expressing cells via antibody-dependent cellular cytotoxicity and phagocytosis.

- In recognition of high-unmet need and early potential demonstrated in phase 1[3], lacutamab has been granted key designations:
  - Orphan drug designation for the treatment of CTCL (EMA and FDA)
  - PRIME (EMA) and Fast Track (FDA) designation for SS patients who have received at least 2 prior systemic therapies

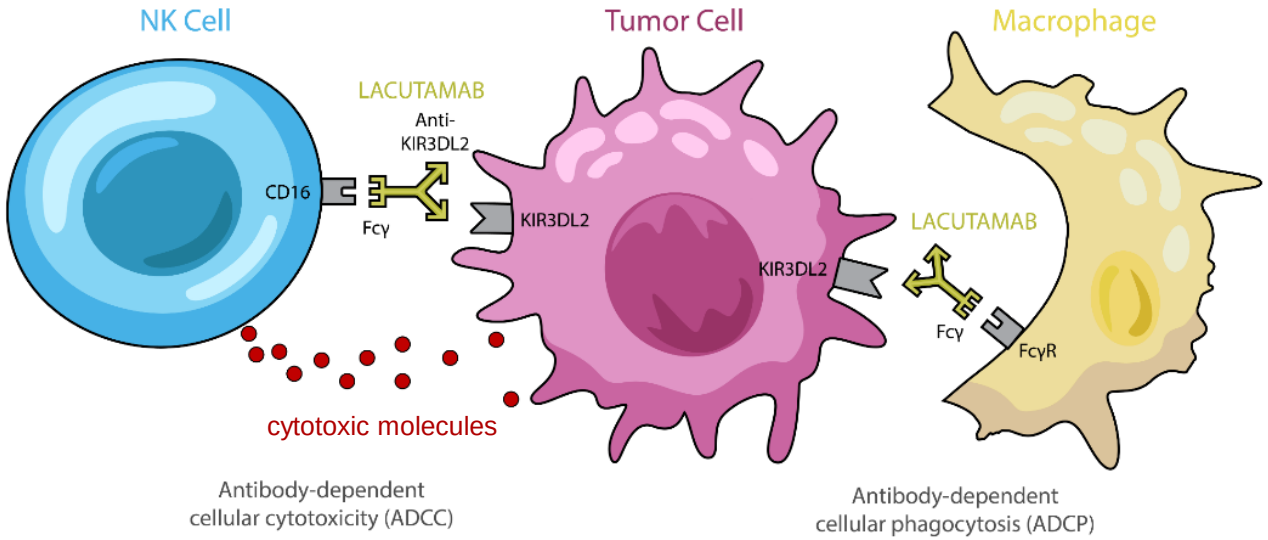


Figure 1: Lacutamab Mechanism of Action

3. Bagot M et al, Lancet Oncol 2019

TELLOMAK Study Design: Phase 2 Study in Two CTCL Subtypes

Sézary Syndrome (N~60)
≥ 2 prior systemic therapies

Cohort 1 SS

Sézary Syndrome ≥ 2 prior systemic therapies,

Must include mogamulizumab as prior therapy

Mycosis Fungoides (N~100)
≥ 2 prior systemic therapies

Cohorts MF

KIR3DL2 ≥ 1% KIR3DL2 <1%

Key Eligibility Criteria for MF Cohorts

- Relapsed and/or refractory stage IB-IV MF
- At least 2 prior systemic therapies
- No evidence of large cell transformation (LCT) based on central histologic evaluation at screening

Study Endpoints

- **Primary endpoint: global ORR**
- Secondary endpoints: PFS, OS, DoR, quality of life, safety and tolerability, PK & immunogenicity

Treatment

- Lacutamab is administered every week for 5 weeks then every 2 weeks for 10 administrations then every 4 weeks, by intravenous infusion, **until disease progression or unacceptable toxicity**

ORR: Objective Response Rate; DoR: duration of response; PFS: progression free survival

* KIR3DL2 expression based on central evaluation by immunohistochemistry (IHC) assay on FFPE skin biopsy

Demographic and Baseline Disease Characteristic

	All MF N=107	KIR3DL2 ≥ 1% N=48	KIR3DL2 <1% N=59
Age in years, Median (range)	62 (19-82)	59 (28-82)	65 (19-81)
Sex • Male, N (%) • Female, N (%)	 72 (67.3) 35 (32.7)	 28 (58.3) 20 (41.7)	 44 (74.6) 15 (25.4)
Stage at baseline, N (%) • I • II • III • IV	 44 (41.1) 38 (35.5) 15 (14.0) 10 (9.3)	 19 (39.6) 15 (31.3) 10 (20.8) 4 (8.3)	 25 (42.4) 23 (39.0) 5 (8.5) 6 (10.2)
Prior systemic lines, Median (range) Prior mogamulizumab, N (%)	4.0 (1-14) 34 (31.8)	4.5 (2-12) 13 (27.1)	4.0 (1-14) 21 (35.6)
Follow-up in months, Median (95%CI)	11.8 (9.9, 13.8)	12.7 (10.0, 16.6)	10.6 (8.3, 12.0)

Efficacy in MF patients with different KIR3DL2 expression levels

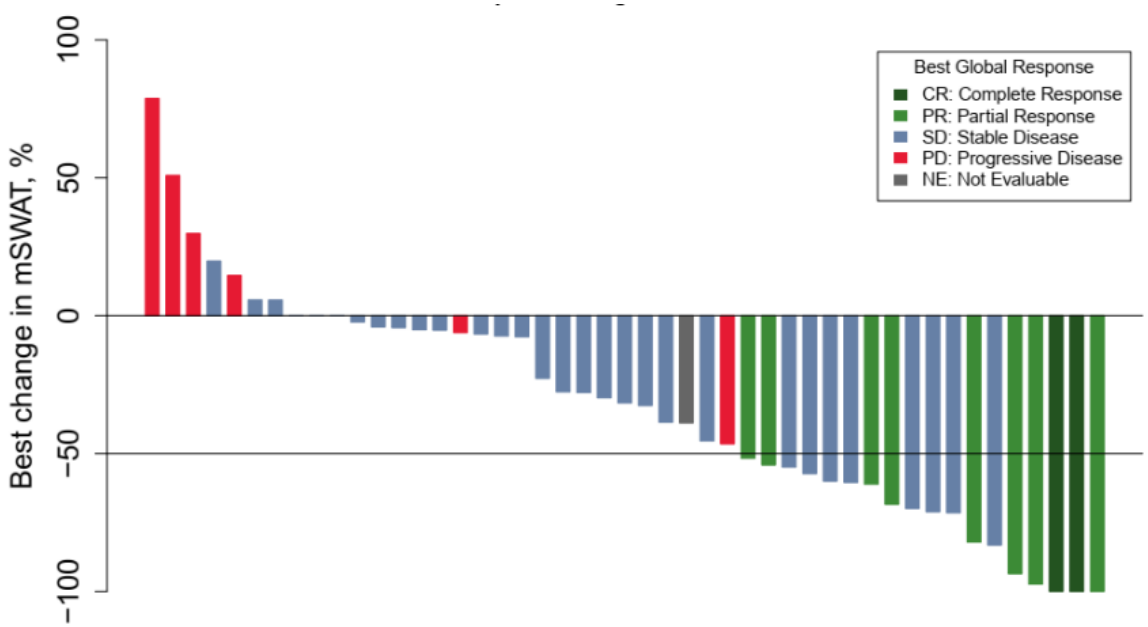
ITT set	All MF N=107	KIR3DL2 ≥ 1% N=48	KIR3DL2 <1% N=59
Olsen 2011 Global ORR % (95%CI)	**16.8% (10.9, 25.0)**	**20.8% (11.7, 34.3)**	**13.6% (7.0, 24.5)**
CR n (%)	2 (1.9)	2 (4.2)	0 (0.0)
PR n (%)	16 (15.0)	8 (16.7)	8 (13.6)
SD* n (%)	74 (69.2)	30 (62.5)	44 (74.6)
PD n (%)	13 (12.1)	6 (12.5)	7 (11.9)
NE n (%)	2 (1.9)	2 (4.2)	0 (0.0)
Time to global response (mo) median (range)	1.0 (1-5)	1.0 (1-5)	1.9 (1-4)
Skin response (n=107) % (95%CI)	29.0% (21.2, 38.2)	33.3% (21.7, 47.5)	25.4% (16.1, 37.8)
Olsen 2022 Global ORR % (95%CI)	**22.4% (15.6, 31.2)**	**29.2% (18.2, 43.2)**	**16.9% (9.5, 28.5)**

** SD includes 2 pts uPR confirmed after DCO & 1 new uPR after DCO*

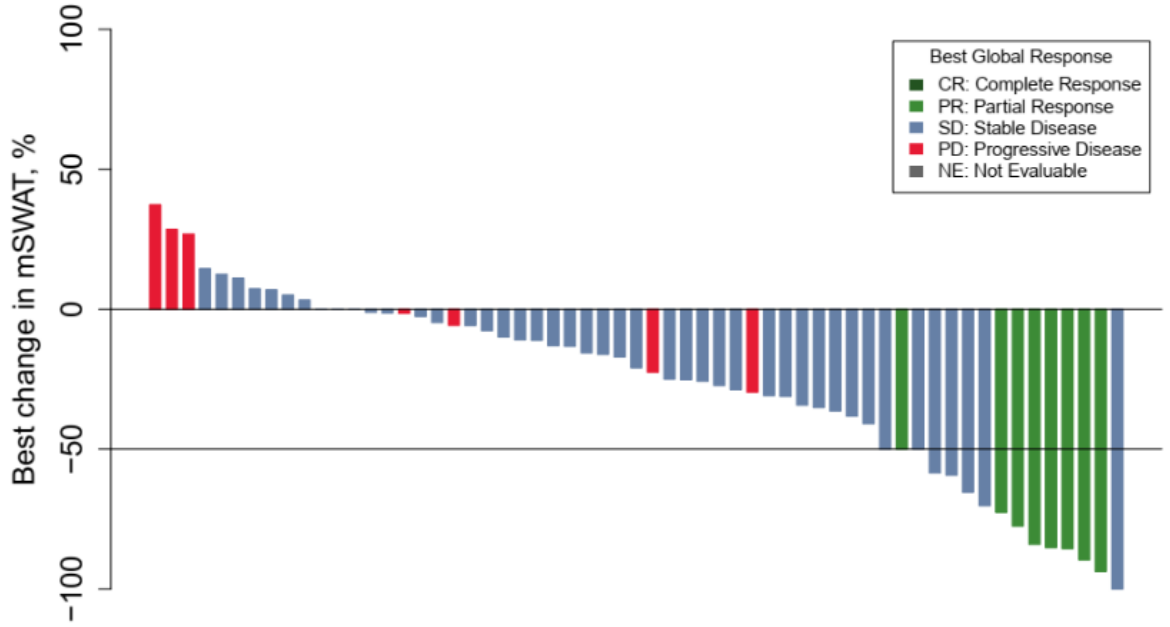
ORR: Objective Response Rate; CR complete response; PR partial response; SD stable disease; PD progression disease, NE not evaluable

Waterfall plot for best response in MF patients treated with lacutamab

KIR3DL2 ≥ 1%



KIR3DL2 <1%

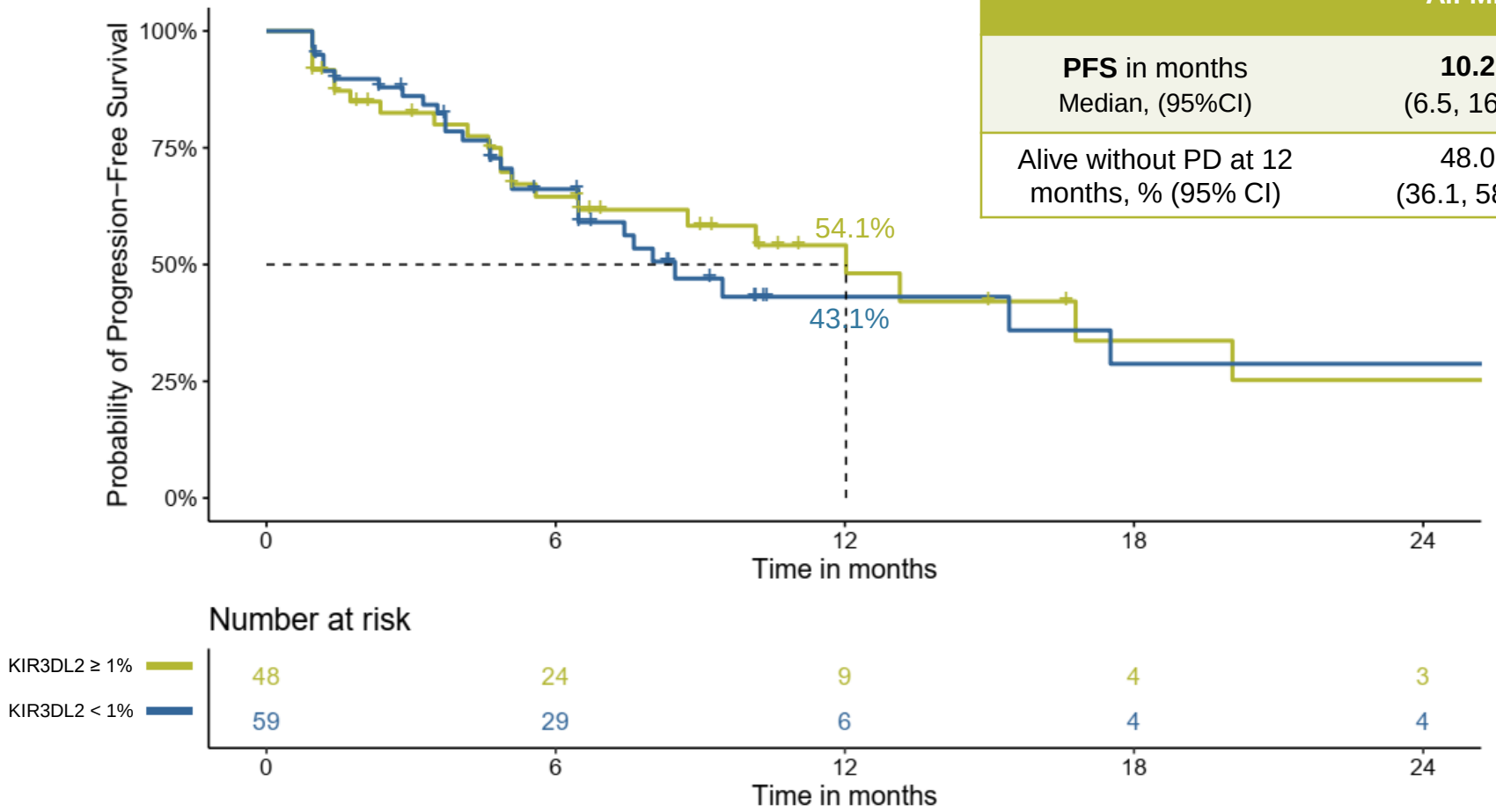


Early and deep responses observed in MF patients regardless of KIR3DL2 expression level

Data cut-off (DCO): 13 OCT 23

Progression Free Survival in MF patients treated with lacutamab

	All MF	KIR3DL2 ≥ 1%	KIR3DL2 <1%
PFS in months Median, (95%CI)	**10.2** (6.5, 16.8)	**12.0** (5.6, 20.0)	**8.5** (6.5, 17.5)
Alive without PD at 12 months, % (95% CI)	48.0 (36.1, 58.9)	54.1 (36.5, 68.8)	43.1 (27.2, 58.0)

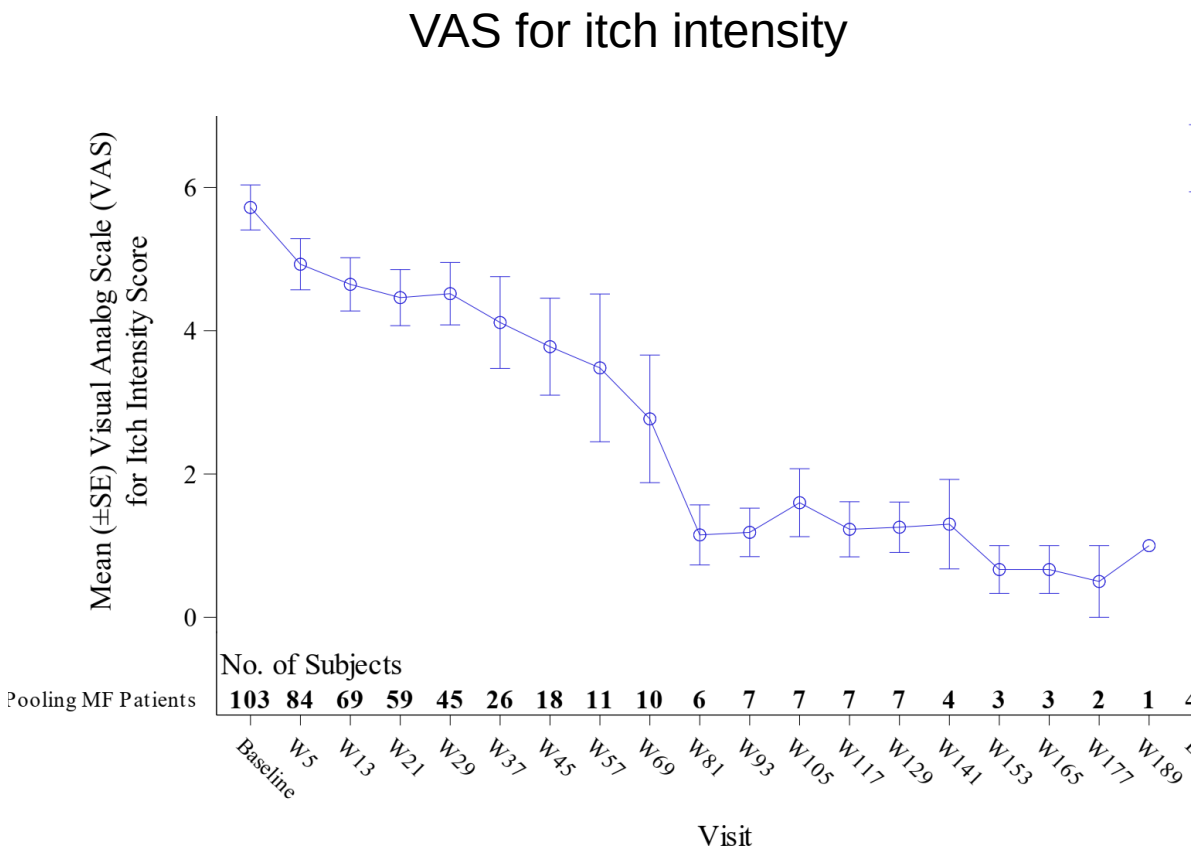


Kaplan-Meier estimate of time to progression, next treatment or death

PFS Progression free survival; PD progressive disease

Data cut-off (DCO): 13 OCT 23

Visual Analog Scale for Itch Intensity Score Over Time all MF

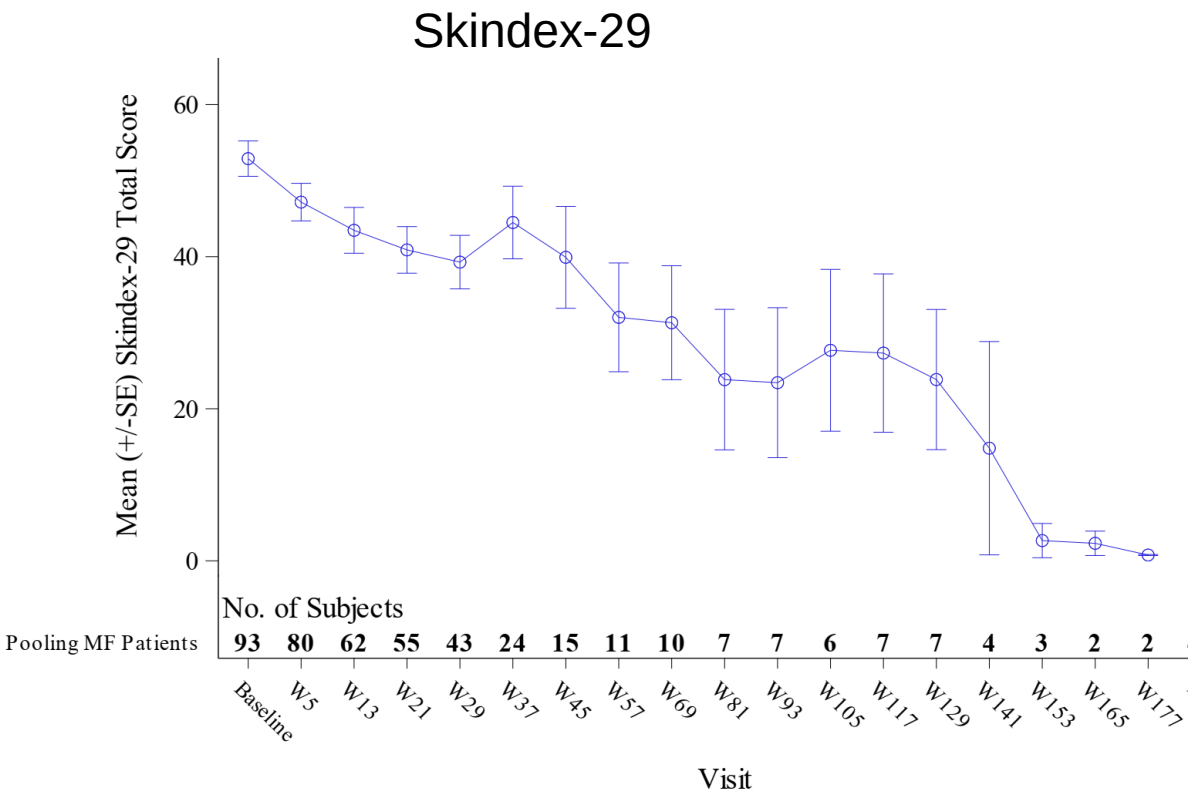


- The presence and severity of pruritus was assessed using a 10-point visual analogue scale (VAS) ranging from 0 (no itch) to 10 (worst imaginable itch)
- At baseline, median VAS was 6.0
- Early decrease of itch intensity over time starting from W5 (median VAS 5)
- Significant improvement ≥2 points decrease in itch intensity in VAS scale with median VAS<4 from W37

VAS Visual Analog Scale

Data cut-off (DCO): 13 OCT 23

Skindex-29 Total Score Over Time in all MF



- Skindex-29 questionnaire inquiries about how often (Never, Rarely, Sometimes, Often, All the time) during the previous 4 weeks the pt experienced the effect described in each item
- Overall score are expressed on a 100-point scale, with higher scores indicating lower levels of quality of life
- At baseline, median Skindex-29 global score was 56.3
- Early slight decrease of Skindex-29 starting from W5 (median Skindex 46.3)
- Later a deeper decrease (i.e. Skindex 38.8 at W29)

Summary of adverse events

Nb and (%) of pts with at least one	All MF N=107	KIR3DL2 ≥ 1% N=48	KIR3DL2 <1% N=59
TEAE	97 (90.7)	43 (89.6)	54 (91.5)
Related TEAE	**62 (57.9)**	**29 (60.4)**	**33 (55.9)**
TESAE	25 (23.4)	13 (27.1)	12 (20.3)
Related TESAE	**4 (3.7)**	**2 (4.2)**	**2 (3.4)**
Grade ≥3 TEAE	26 (24.3)	13 (27.1)	13 (22.0)
Related Grade ≥3	**4 (3.7)**	**2 (4.2)**	**2 (3.4)**
TEAE leading to discontinuation	6 (5.6)	3 (6.3)	3 (5.1)
Related TEAE leading to discontinuation	**3 (2.8)**	**1 (2.1)**	**2 (3.4)**
AE leading to death	2 (1.9)	1 (2.1)	1 (1.7)

TE(S)AE treatment emergent (serious) adverse event;

Most frequent related Adverse Events

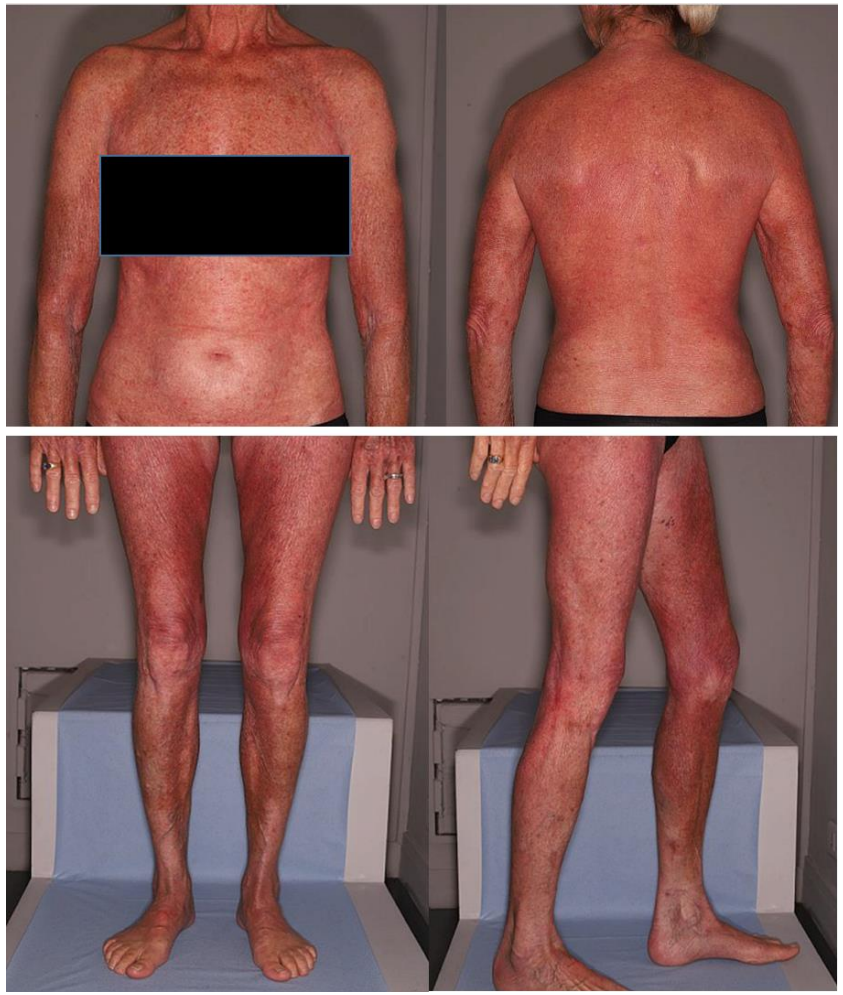
Related TEAE Most frequent (>5%) or of interest, n (%)	All MF N=107	KIR3DL2 ≥ 1% N=48	KIR3DL2 <1% N=59
Fatigue	12 (11.2)	7 (14.6)	5 (8.5)
Nausea	12 (11.2)	4 (8.3)	8 (13.6)
Asthenia	11 (10.3)	5 (10.4)	6 (10.2)
Arthralgia	11 (10.3)	5 (10.4)	6 (10.2)
Diarrhea	7 (6.5)	4 (8.3)	3 (5.1)
Skin infection	4 (3.7)	2 (4.2)	2 (3.4)
Adrenal insufficiency	2 (1.9)	1 (2.1)	1 (1.7)
Cholestasis	2 (1.9)	0 (0.0)	2 (3.4)
Hepatic cytolysis	1 (0.9)	0 (0.0)	1 (1.7)
Infusion related reaction	1 (0.9)	1 (2.1)	0 (0.0)
Interstitial lung disease	1 (0.9)	0 (0.0)	1 (1.7)

Patient Case

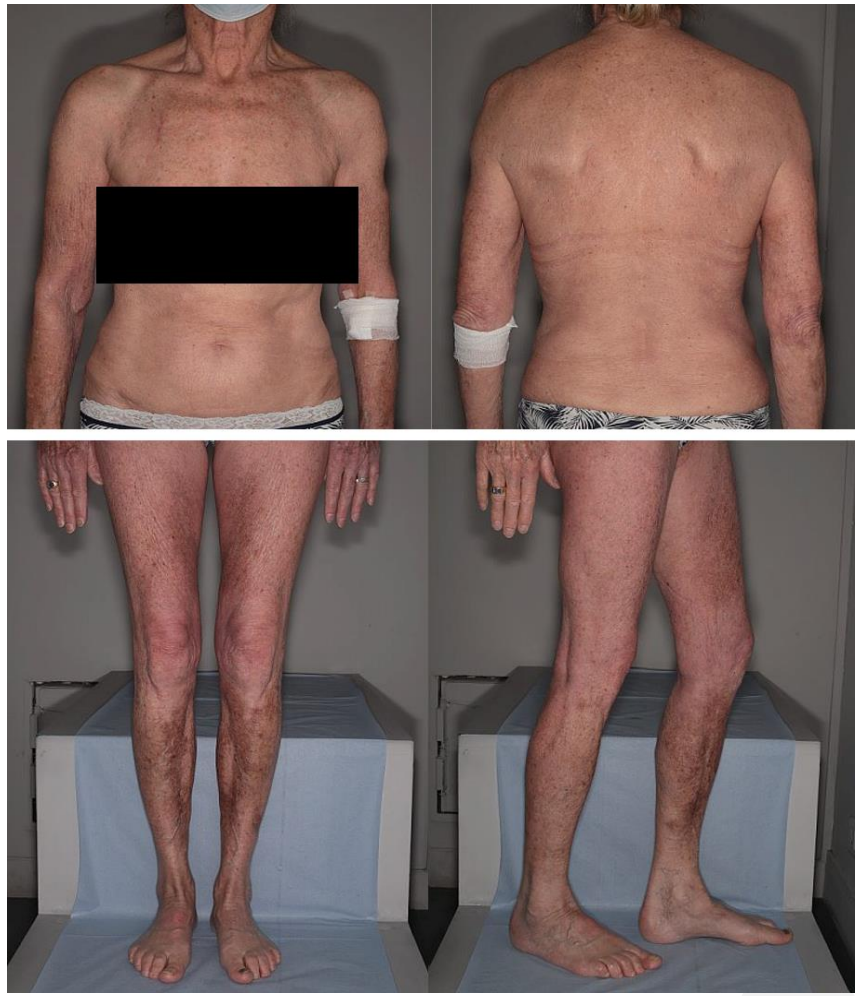
Patient characteristics

- 68-year-old female
- MF diagnosed in 2016
- 4 previous lines of therapy (PUVA therapy, bexarotene, interferon, methotrexate)
- T2N0M0B1 at baseline
- Response:
  - Skin: PR from W5, CR from W37
  - Blood: CR from W5
  - LN: Not involved (N0 at baseline)
  - Global: PR from W5 then **CR from W37**, still ongoing (last evaluation W153 in Jan 2024)

BASELINE
October 05, 2020



Week 57
March 29, 2022



Conclusions

- TELLOMAK is a Phase 2 study evaluating lacutamab monotherapy in CTCL. The study enrolled MF patients with ≥ 2 prior systemic therapies
- Lacutamab treatment induced early and durable responses and improvement in quality of life in heavily pretreated patients with MF
- We observed anti-tumor activity in patients who expressed KIR3DL2 ≥1% and < 1% at baseline
- The median PFS of 10.2 months (6.5,16.8) of the whole MF population results is very promising, considering the number of previous systemic lines and the lack of available drugs
- Importantly, no safety concerns nor delayed toxicities were identified and lacutamab was very well tolerated
- The excellent tolerability of lacutamab provides a strong rationale for further investigation in combination with other anti-lymphoma agents
- Though the trial was single arm, and one should be cautious with indirect comparison, these data support further development of lacutamab to bring improved treatments to patients with CTCL

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In total 53 active sites

USA (17)
France (10)
Germany (8)
Spain (6)
Italy (4)
Belgium (3)
Austria (2)
Poland (3)

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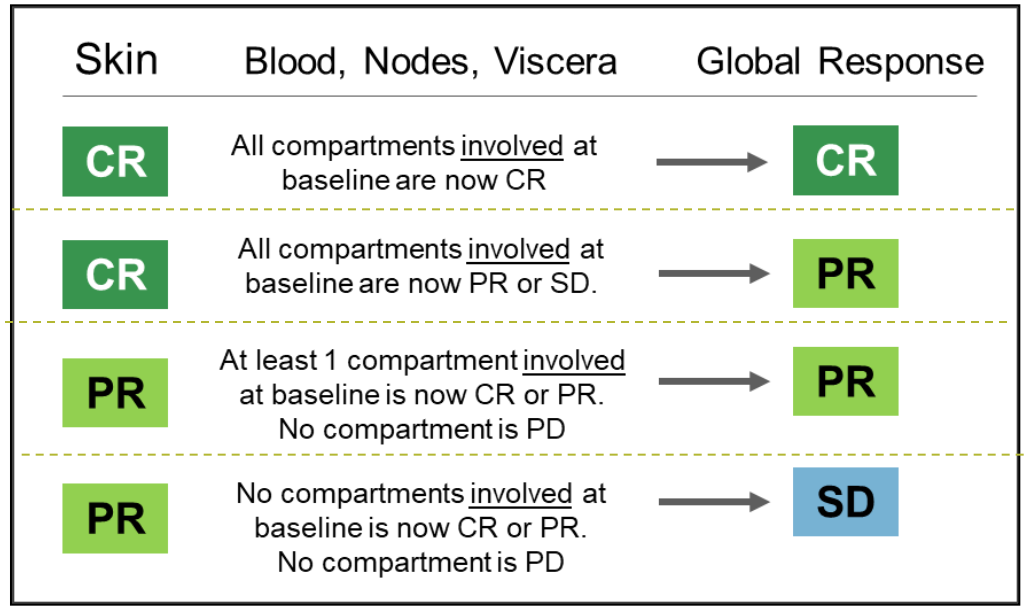
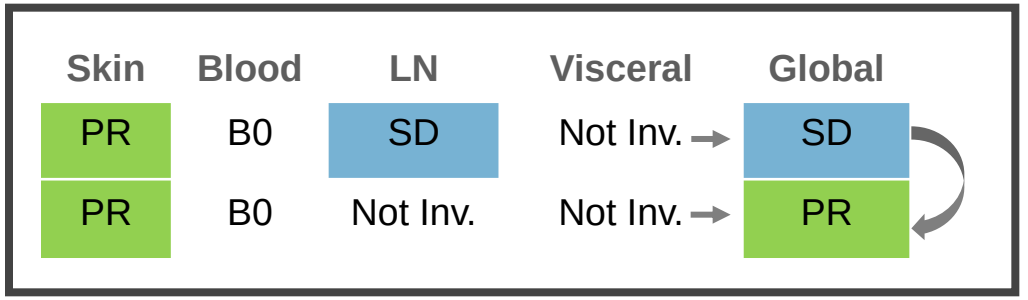
Back up slides

TELLOMAK
LN Assessment by Updated Response Criteria (Olsen 2022)

- Global Response requires assessment of all compartments (Olsen 2011)
- LN response assessment challenging if:
  - LN clinically abnormal but not biopsy-proven (Nx)
  - LN is enlarged due to inflammation (N1, N2)
- According to updated Olsen 2022 criteria LN involvement with lymphoma requires N3 pathology classification

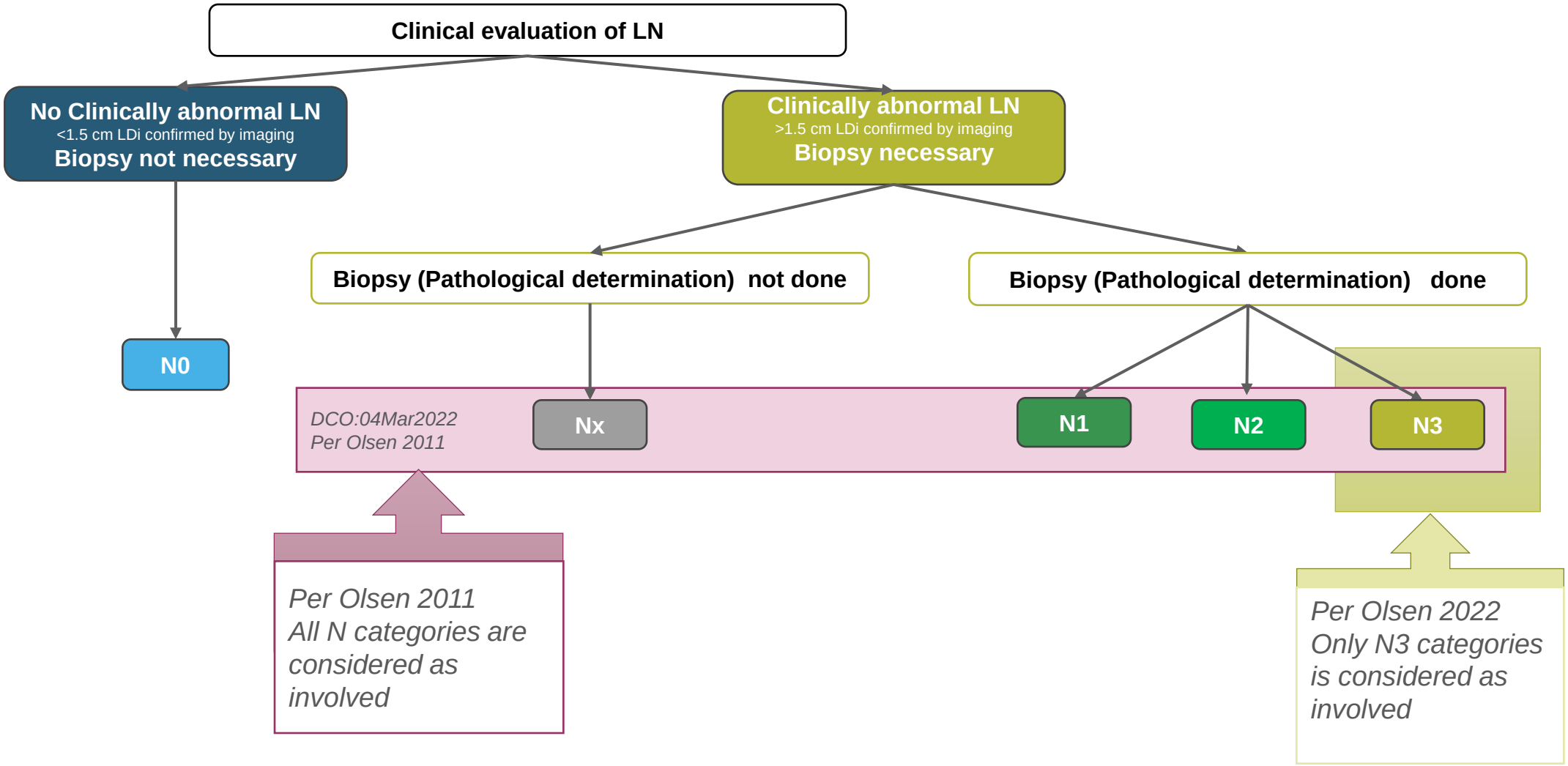




Olsen et al. Blood 2022, 140 (5):419-437

TELLOMAK

LN Assessment by Updated Response Criteria (Olsen 2022)



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