

# The mTORC1 Inhibitor Everolimus Produces Tumor Responses in Patients with Relapsed T-cell Non-Hodgkin Lymphoma

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## OBJECTIVES

- To investigate mTOR pathway activation in T cell lymphoma (TCL) cell lines.
- Assess clinical anti-tumor activity in patients with relapsed/refractory TCL in a Phase II trial (MC048G) of the mTORC1 inhibitor everolimus as a single-agent

**Clinical Trial:** Patients were eligible if relapsed T-cell lymphoma (TCL). No limit on # of prior Rx. Patients were required to be ≥18 years old, have measurable disease by CT or MRI with at least one lesion that has a single diameter of >2 cm or tumor cells in the peripheral blood >5 x10<sup>9</sup>/L.

- Treatment was everolimus 10 mg daily
- Patients were restaged after 2 and 6 cycles and every 3 cycles thereafter.

## METHODS

**In Vitro Studies:** Six human PTCL cell lines were utilized: ALCL PTCL cell lines SUDHL1 (DSMZ Germany), SR786 (DSMZ) and Karpas 299 (ATCC, US). The CTCL cell lines SeAx (Sezary syndrome) and MyLa (mycosis fungoides) were generous gifts from Dr. Robert Gniadecki (University of Copenhagen); and, HuT 78 (Sezary Syndrome, ATCC). Cell lines were grown in RPMI 1640 supplemented with 10% fetal bovine serum (FBS). CD3 cells were sorted from peripheral blood from normal controls.

**Plasma cytokine analysis in paired patient samples:** Plasma was collected and cryopreserved from patients before starting everolimus treatment and after 2 cycles of therapy for analysis of changes in plasma cytokine levels. These were analyzed as previously reported. We focused on changes in 7 cytokines – EGF, IL-6, IL-12, IP-10, sIL-2R $\alpha$ , MIG, and IL-1RA.

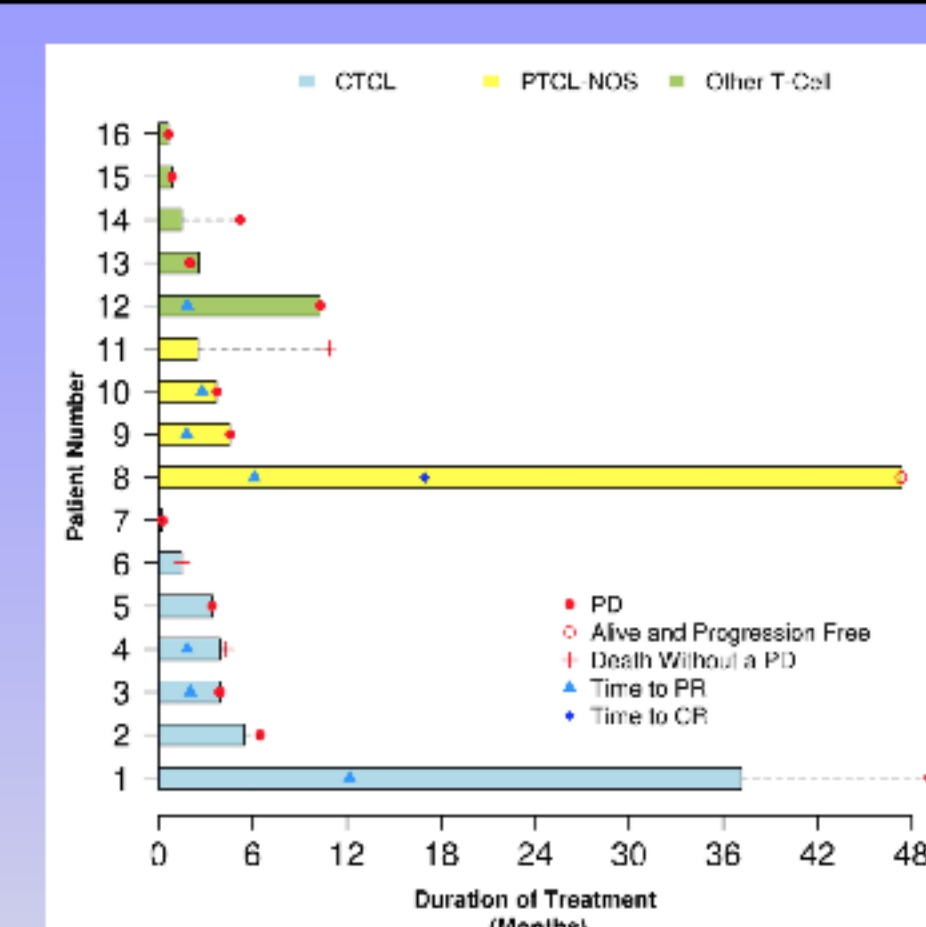
## RESULTS

Characteristic	Total (N=16) Number (%)
Age – Median, Range	60 years (35-81)
Gender, Male	13 (81%)
Years from diagnosis to registration	
Median, range	3.5 (1.0 – 20.4)
Ann Arbor stage for PTCL patients	
2	1 (11%)
4	8 (89%)
ISLCEORTC Stage for CTCL patients	
IIB	6 (66%)
III	1 (14%)
Performance Score	
0	4 (25%)
1	11 (69%)
2	1 (6%)
Number of Previous Treatments	
Median, range	3 (1 -11)
Prior Stem Cell Transplant	5 (31%)
Type of T-cell Lymphoma	
CTCL - Mycosis fungoides	7 (44%)
Peripheral T-cell lymphoma, unspecified	4 (25%)
Anaplastic large cell lymphoma - systemic type	2 (13%)
Angioimmunoblastic T-cell lymphoma	1 (6%)
Extranodal NK/TCL, nasal type	1 (6%)
Precursor T lymphoblastic leukemia/lymphoma	1 (6%)

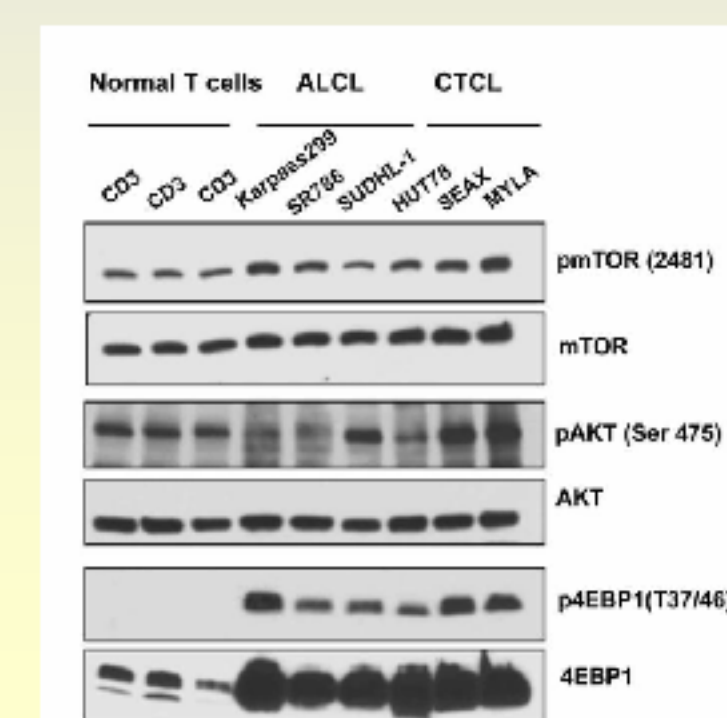
Abbreviations: PTCL, peripheral T-cell lymphoma; CTCL, cutaneous T-cell lymphoma; ISLCEORTC, International Society for Cutaneous Lymphomas/European Organization of Research and Treatment of Cancer

- Patients received a median of 3.1 months of treatment (range, 0.2-47.3 months)
- ORR all patients - 44% (7/16; 95% CI: 20-70)
  - 1 CR (PTCL-NOS)
  - 6 PR (3 MF; 2 PTCL-NOS; 1 ALCL)
- ORR 43% (3/7) in CTCL;
- ORR 75% (3/4) in PTCL NOS
- ORR 20% (1/5) in other TCL.

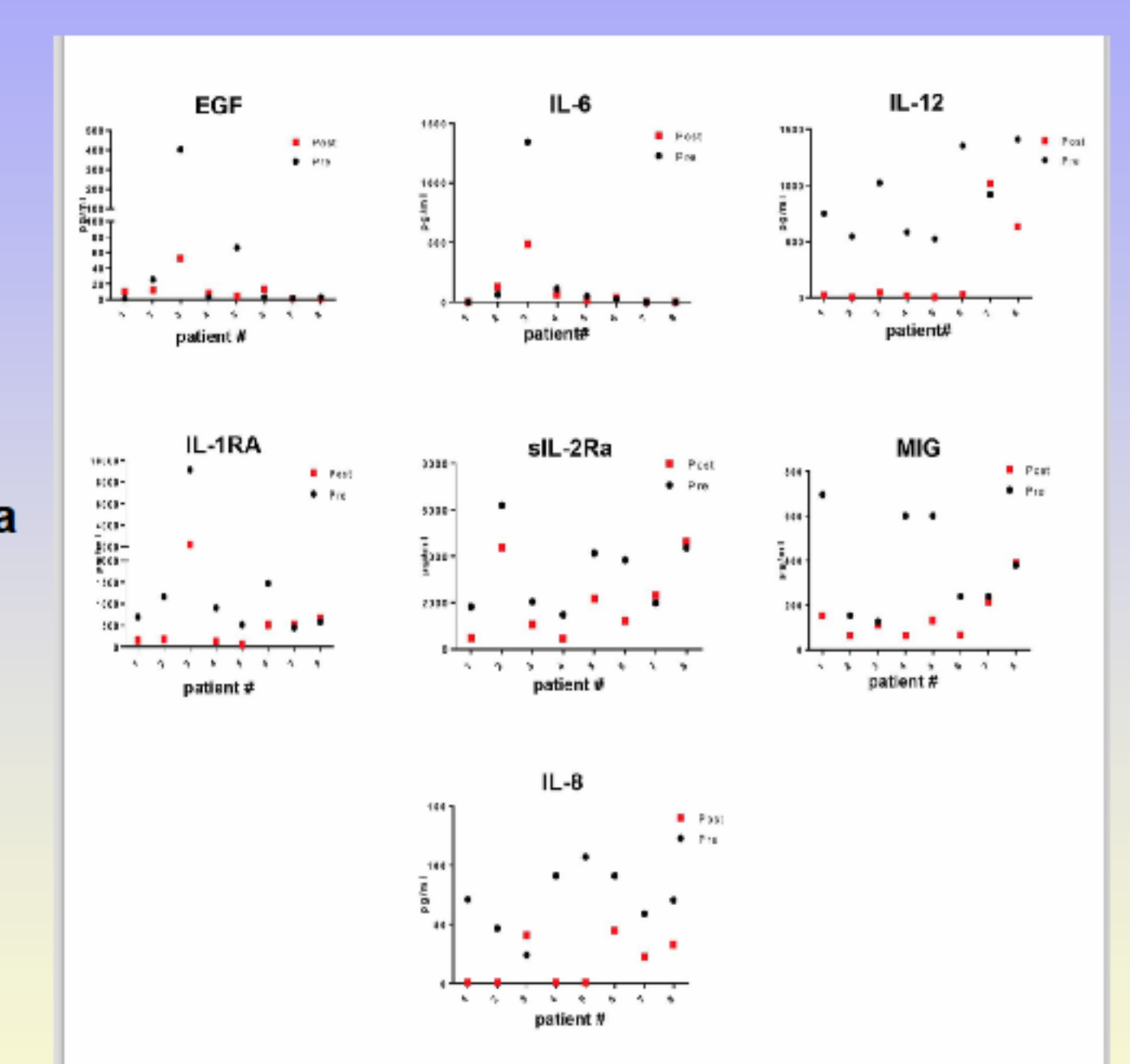
**Fig 1: Duration of Response**



**Figure 2: Activation of mTOR signaling in T-cell lymphoma cell lines (n=6) and normal T-cells (n=3).** Western blotting was performed on six TCL cell lines of ALCL (Karpas 299, SUDHL1 and SR786) and CTCL (HuT 78, SeAx and MyLa) subtypes along with CD3+ T cells using phosphorylation site-specific antibodies for mTOR, AKT and 4EBP1.



**Figure 3: Change in plasma cytokine levels in 8 patients after 2 cycles of everolimus therapy.** The best response to everolimus for these 8 patients was CR in patient 4; PR in patients 1, 2, 6 and 7; and stable disease in patients 3, 5 and 8.



## CONCLUSIONS

- The mTOR pathway is constitutively activated in the T cell lymphoma (TCL) cells and is responsible for TCL proliferation.
- This is first trial to demonstrate that mTORC1 inhibitors (everolimus) have substantial anti-tumor activity (44% ORR) in patients with relapsed TCL.
- Future trials of mTORC inhibitors in TCL are warranted as single agents or in combination.

## References

- Witzig TE et al Blood. 2015 Apr 28 ePub