Pembrolizumab in CTCL

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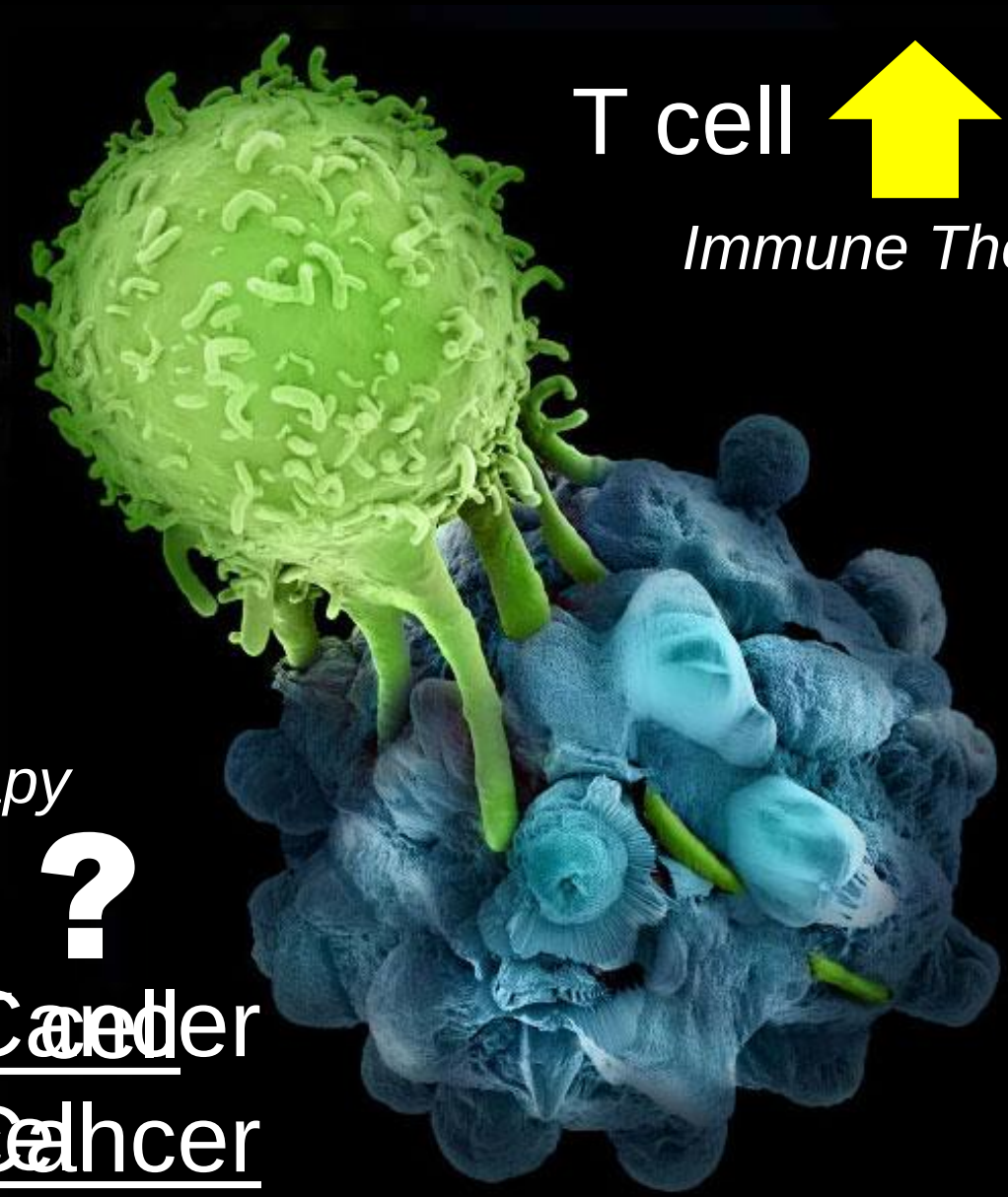
Cancer Immunotherapy



T cell

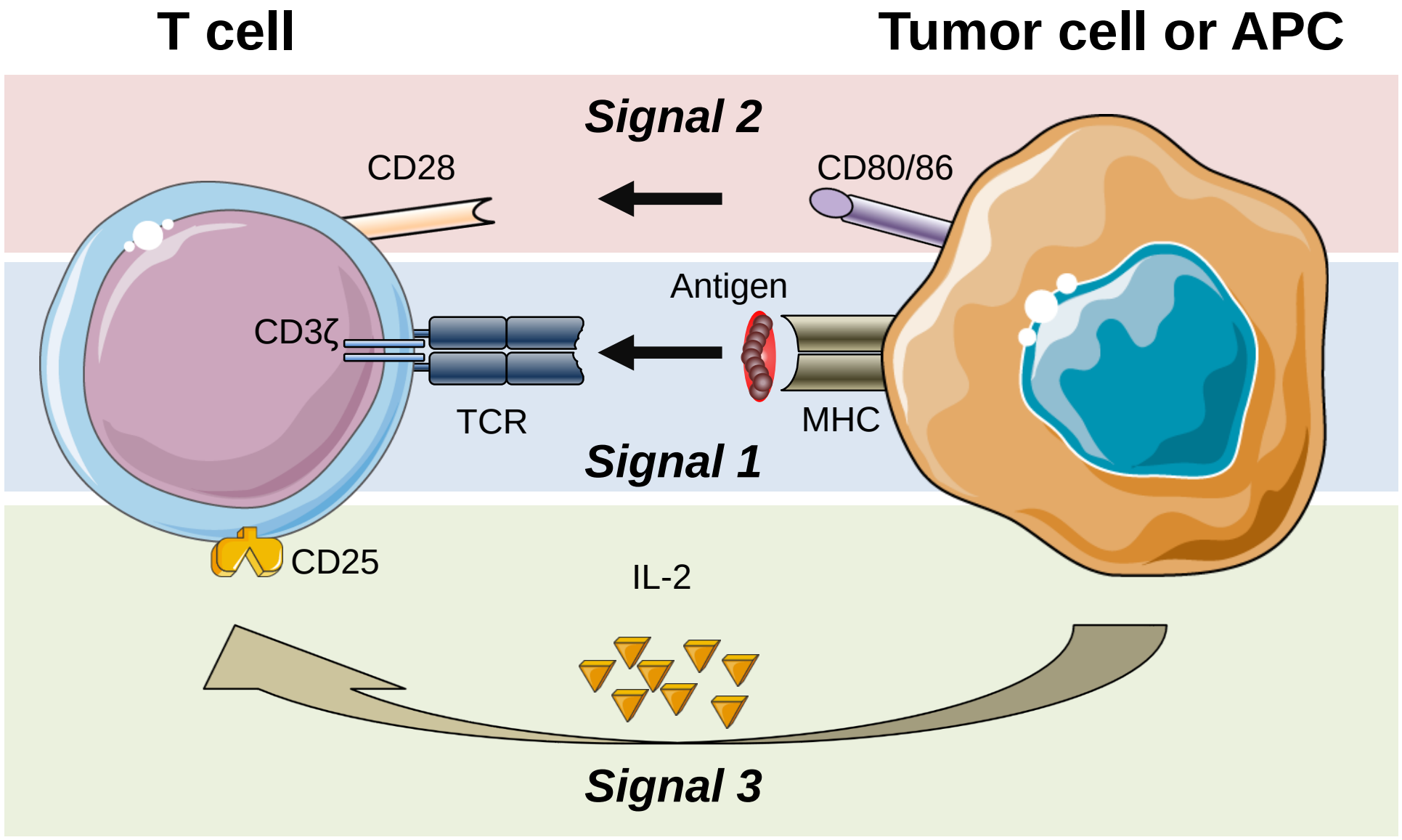
Immune Therapy

Immune Therapy

?

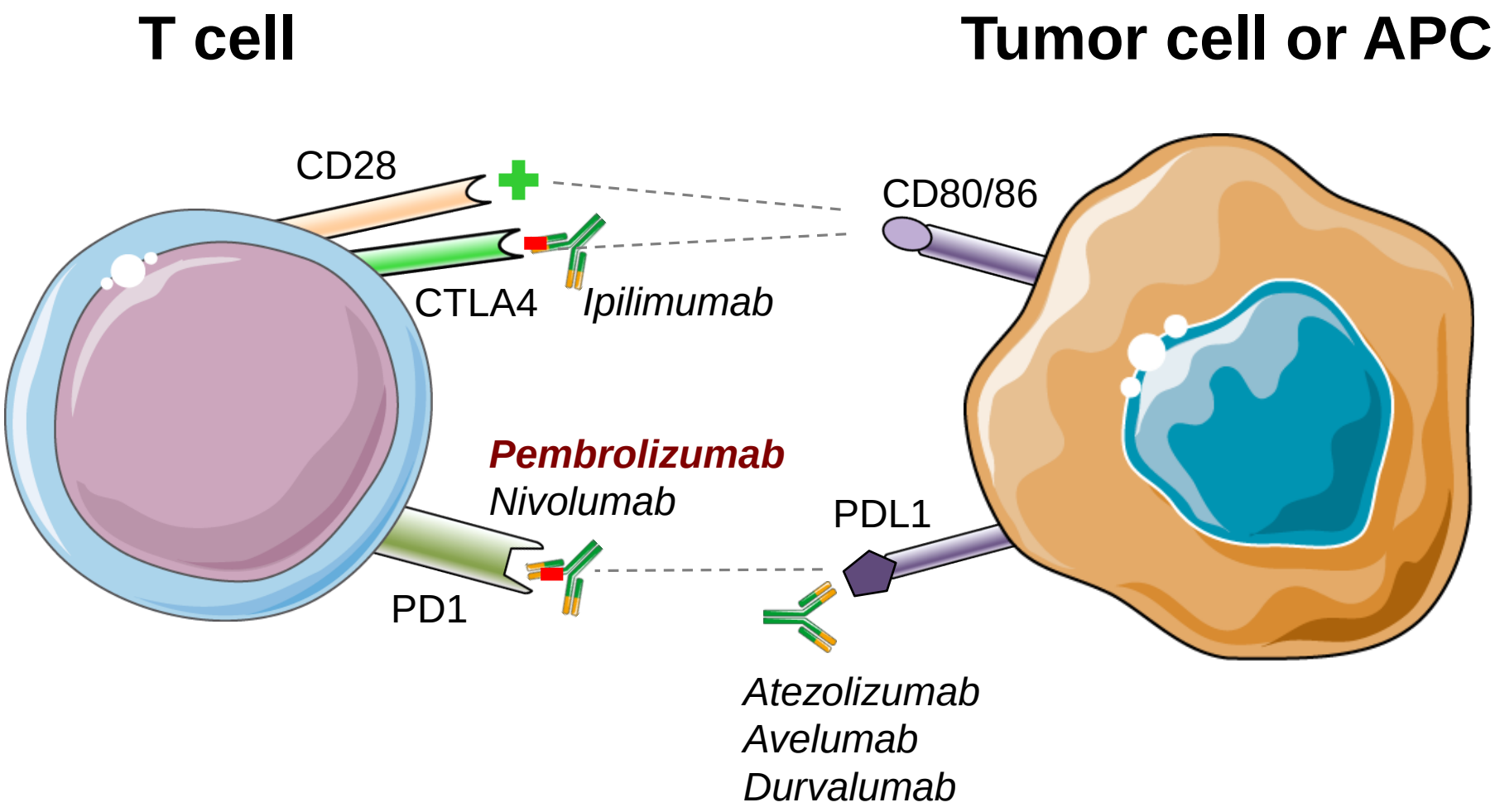
Cancer cell

Normal T cell biology - activation



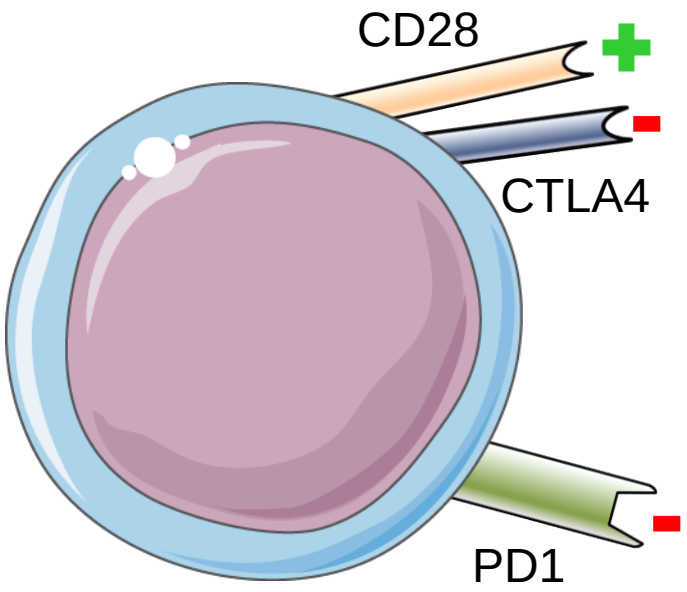
Courtesy of M Khodadoust

Normal T cell biology - inhibition

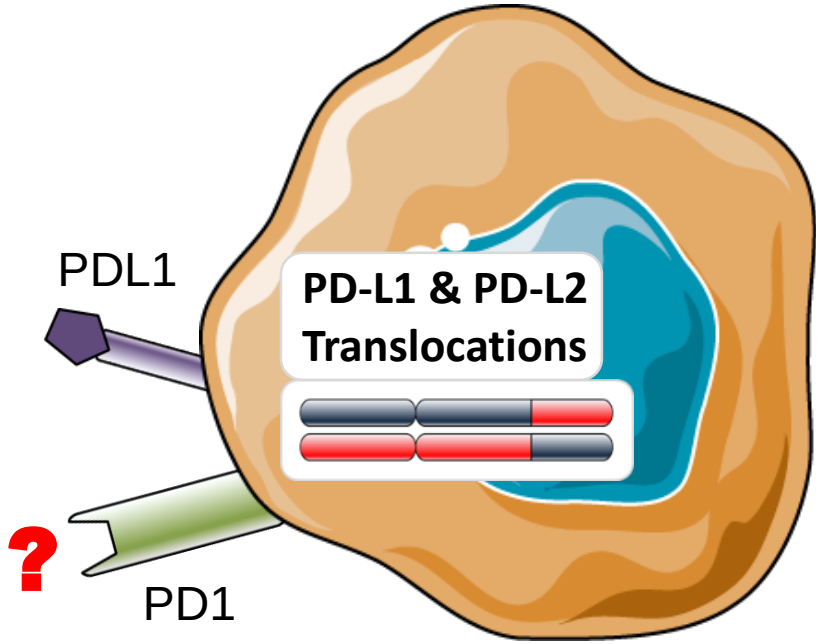


Cutaneous T cell lymphomas – PD1 / PD-L1

T cell

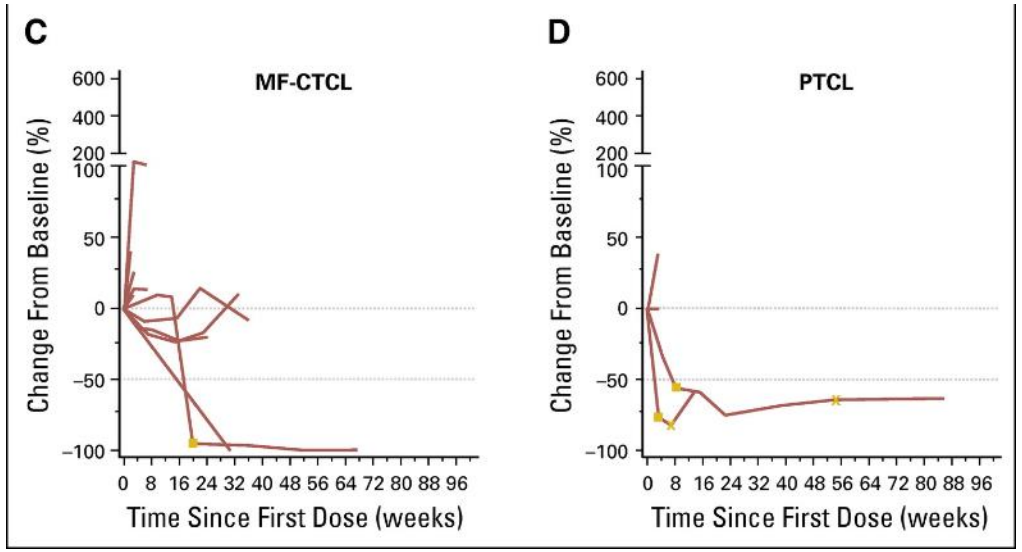


CTCL:
MF or Sézary cell



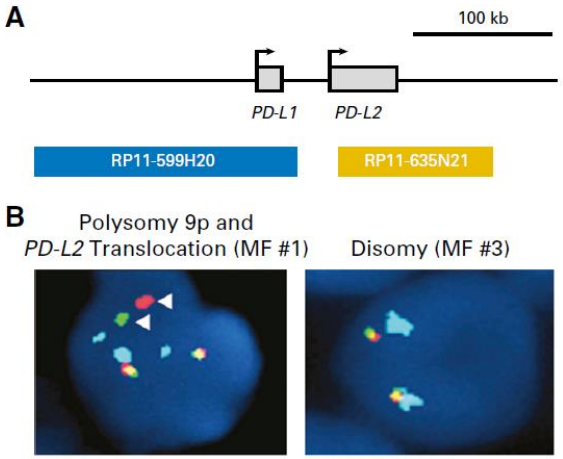
Activity of PD-1 inhibitors in CTCL?

Nivolumab for T cell lymphoma



Lesokhin et al. J Clin Oncol 2016.

Tumor	OR, No. (%)	CR, No. (%)	PR, No. (%)	SD, No. (%)	Median PFS, Weeks (95% CI)
B-cell lymphoma (n = 31)	8 (26)	3 (10)	5 (16)	16 (52)	23 (7 to 44)
DLBCL (n = 11)	4 (36)	2 (18)	2 (18)	3 (27)	7 (6 to 29)
FL (n = 10)	4 (40)	1 (10)	3 (30)	6 (60)	NR (7 to NR)
Other B-cell lymphoma (n = 10)	0	0	0	7 (70)	11 (3 to 39)
T-cell lymphoma (n = 23)	4 (17)	0	4 (17)	10 (43)	10 (7 to 33)
MF (n = 13)	2 (15)	0	2 (15)	9 (69)	10 (7 to 35)
PTCL (n = 5)	2 (40)	0	2 (40)	0	14 (3 to NR)
Other CTCL (n = 3)	0	0	0	0	7 (6 to NR)
Other non-CTCL (n = 2)	0	0	0	1 (50)	10 (2 to 18)
Multiple myeloma (n = 27)	1 (4)	1 (4)*	0	17 (63)	10 (5 to 15)



- Low activity in “CTCL” with nivolumab (2 of 13 “MF” with PR), trial had multiple cohorts, lack of specifics in CTCL cohort, unclear if MF/SS-specific assessment tools and response criteria were utilized
- 2 pts with PR had relevant genomic alterations

cancer immunotherapy trials network

ASH 12/2016

Cancer Immunotherapy Trials Network Protocol # CITN-10

A Phase 2 Study of Pembrolizumab for the Treatment of Relapsed/Refractory Mycosis Fungoides and Sézary Syndrome

Principal Investigator: Y Kim, H Kohrt (Co-PI)

Lead Sub-I/Correlative Lead: **M Khodadoust**

Z Rahbar, J Kim (pathology), S Li (biostatistician)

Stanford University SOM

Coordinating Center (CITN): M Cheever

R Shine (project manager); Steven Fling (laboratory lead)

CITN, Fred Hutchinson Cancer Research Center

Investigative sites/site PI:

A Rook (U Penn), F Foss (Yale), PG Porcu (OSU), A Shustov (SCCA),

A Moskowitz/S Horwitz (MSKCC), L Sokol (Moffitt), S Shanbhag (Johns Hopkins)

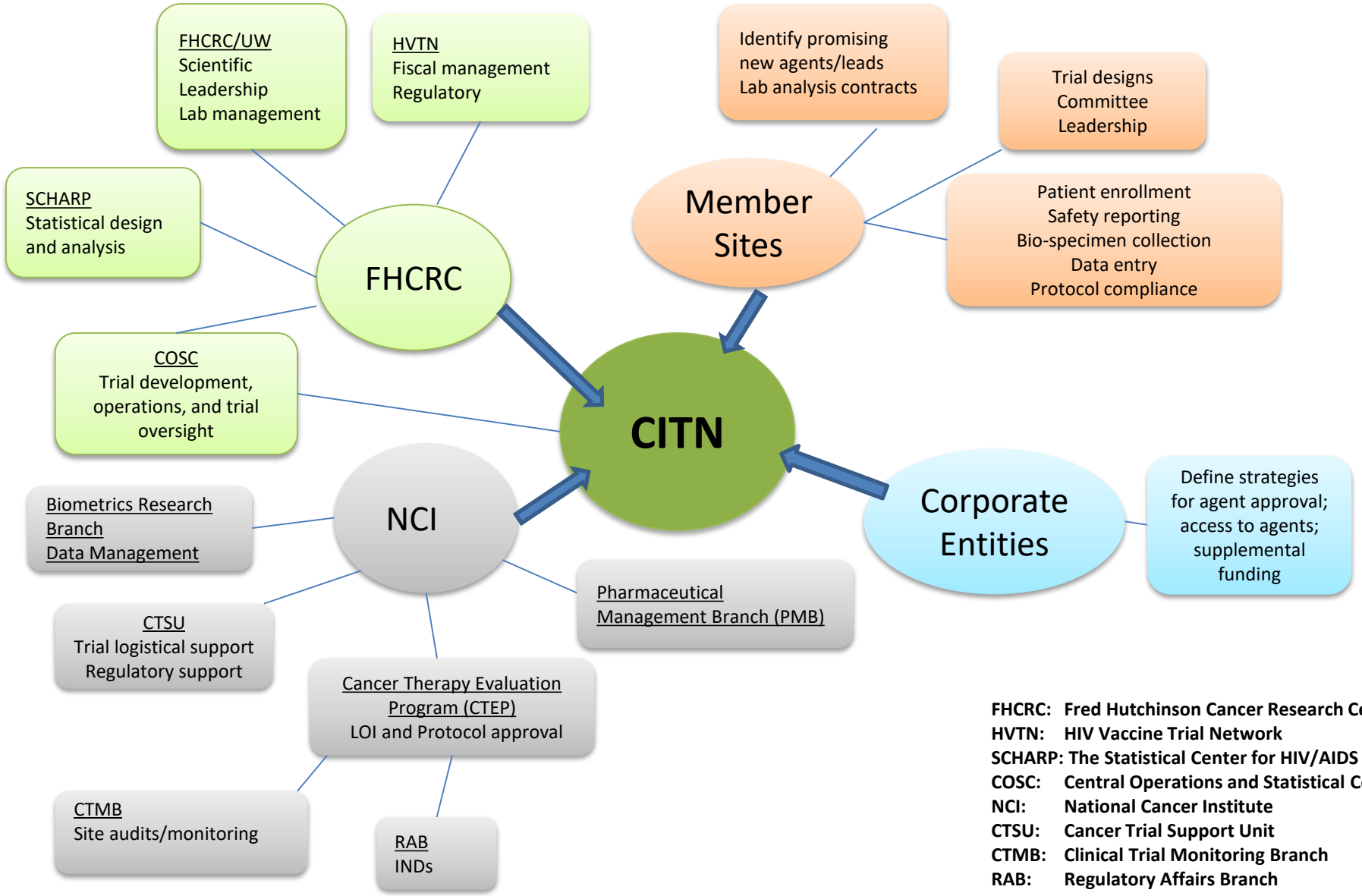
Correlative Studies: S Fling, Y Yang, J Yearley, P Balsubrahmanyam, H Maecker

NCI Collaboration: E Sharon

Funding Support: National Cancer Institute

Merck

Cancer Immunotherapy Trials Network (CITN)



FHCRC: Fred Hutchinson Cancer Research Center
HVTN: HIV Vaccine Trial Network
SCHARP: The Statistical Center for HIV/AIDS Research & Prevention
COSC: Central Operations and Statistical Center
NCI: National Cancer Institute
CTSU: Cancer Trial Support Unit
CTMB: Clinical Trial Monitoring Branch
RAB: Regulatory Affairs Branch
PMB Pharmaceutical Management Branch

cancer immunotherapy trials network

Phase II trial design

Design

- Multicenter, single-arm trial, coordinated centrally by CITN including biorepository
- 24 patients with previously treated MF or SS (Simon stage

Eligibility

- Stage IB-IVB MF or SS
- Failed at least 1 systemic therapy

Schedule

- Pembrolizumab at 2 mg/kg every 3 weeks for up to 2 years
- mSWAT with each cycle; global assessment q 12 wks (4 cycles)

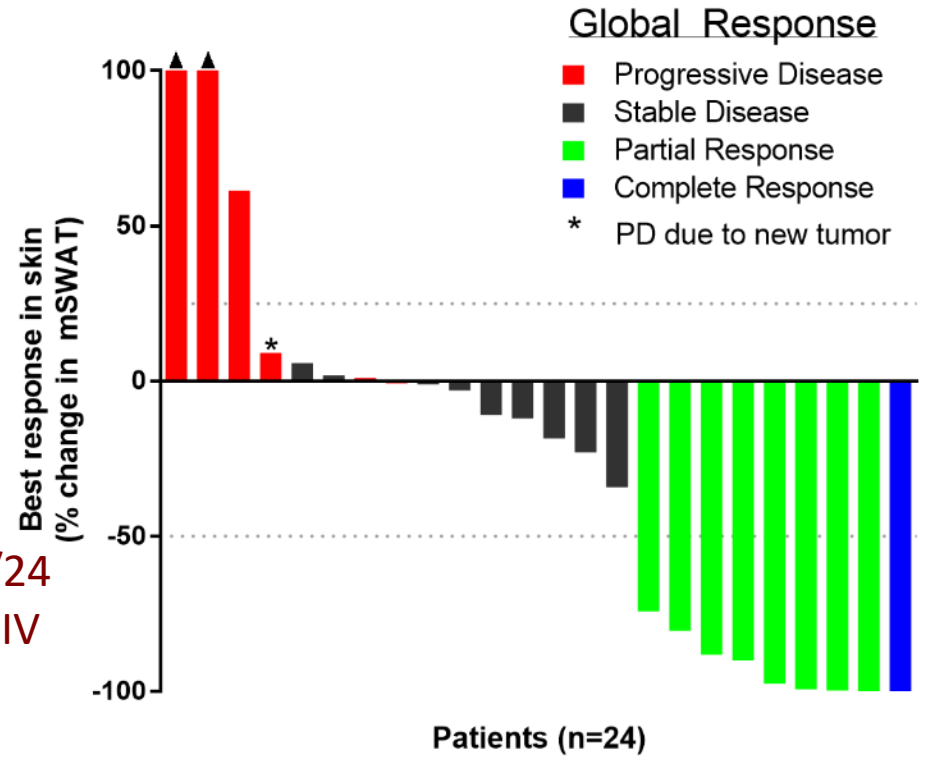
Objectives

- **Primary endpoint – Overall Response Rate** (by global consensus criteria)
- Secondary endpoints – Safety, TTR, DOR, PFS
- Extensive translational correlative studies planned

Clinical response

Characteristics	Total, n=24	Response				ORR, n (%)
	n(%)	CR	PR	SD	PD	
Gender						
Male	18 (75)	0	6	8	4	6/18 (33)
Female	6 (25)	1	2	1	2	3/6 (50)
Diagnosis						
MF	9 (38)	0	5	2	2	5/9 (56)
SS	15 (63)	1	3	7	4	4/15(27)
Stage						
IB	1 (4)	0	0	0	1	0/1 (0)
IIB	2 (8)	0	2	0	0	2/2 (100)
IIIA	3 (12)	0	2	1	0	2/3 (67)
IIIB	3 (12)	0	1	0	2	1/3 (33)
IVA	15 (63)	1	3	8	3	4/15 (27)
Number of prior systemic therapies						
<4	9 (38)	0	4	3	2	4/9 (44)
≥4	15 (63)	1	4	6	4	5/15 (33)

23/24 IIB-IV

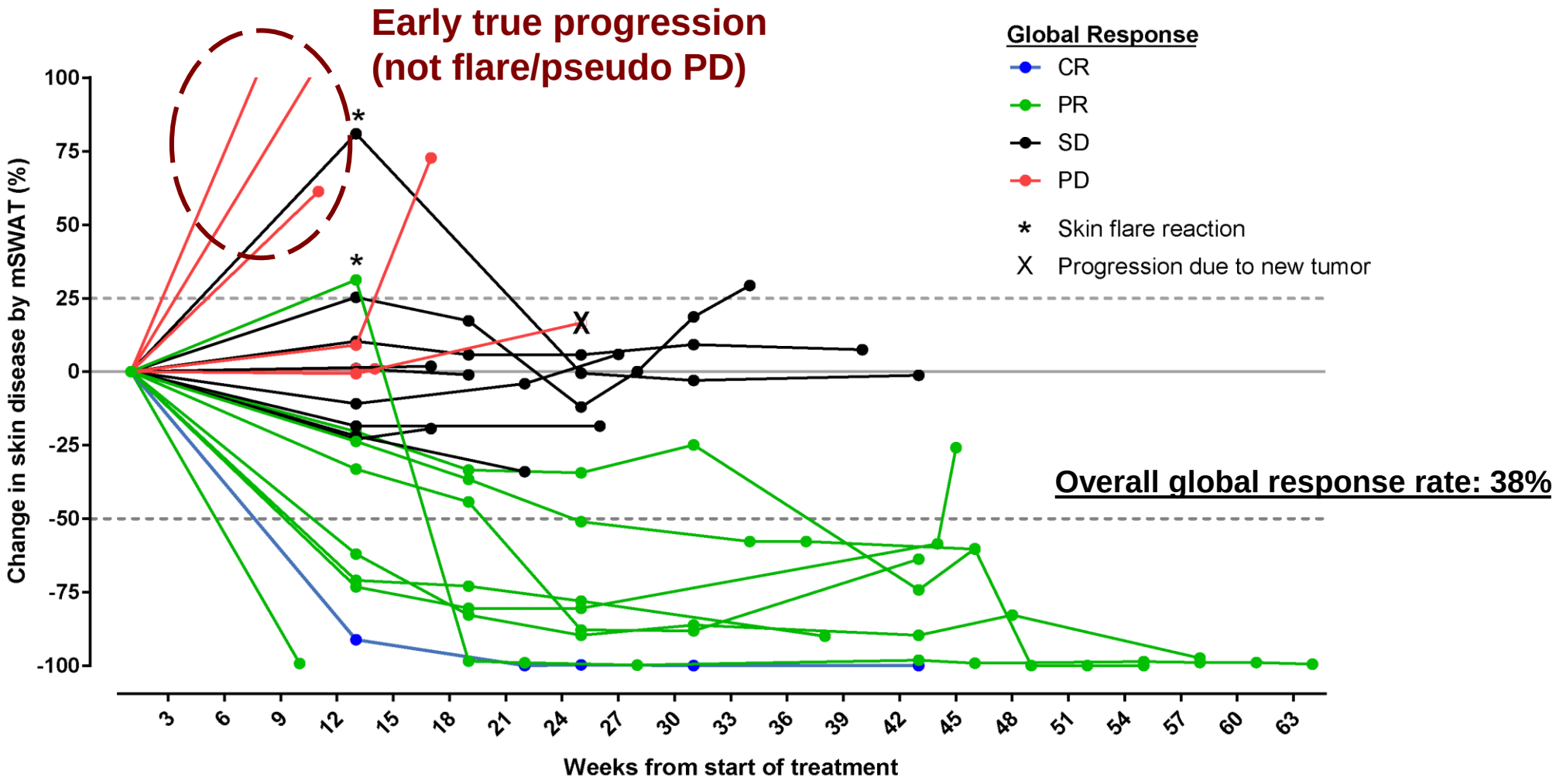


Follow up time (wks) - median(range): 40(9 - 60)
TTR (wks): 11(8-41) DOR: Median not reached; 89% ongoing
PFS: Median not reached 1-year PFS: 69%

Overall Response Rate: 38% (9 patients)

Overall response rate: 38%

Deep and durable responses with pembrolizumab



Overall global response rate: 38%

Longer follow-up at ASH 2018
With complete translational studies

44 yo AA F with Sézary syndrome, stage IVA2, global PR

(h/o phototherapy, romidepsin)

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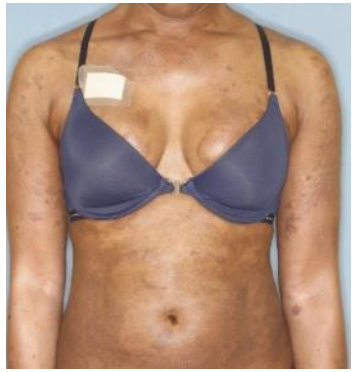
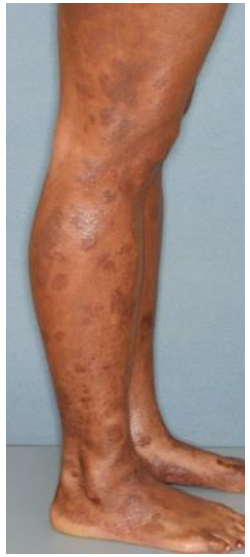
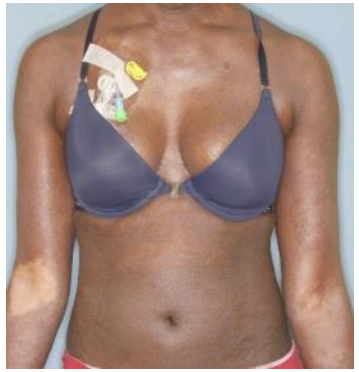
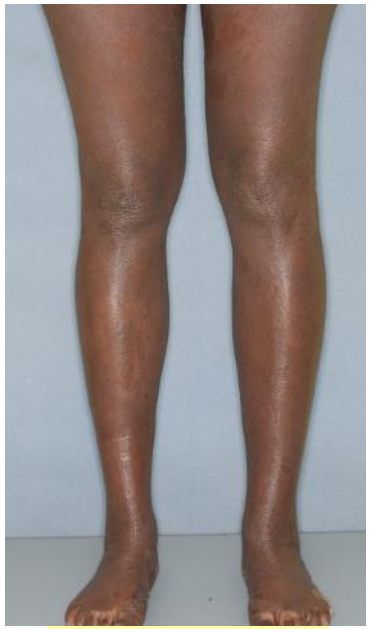


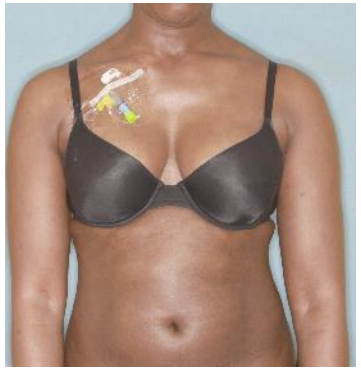


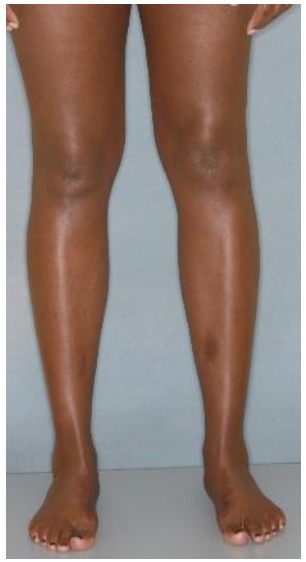
Baseline





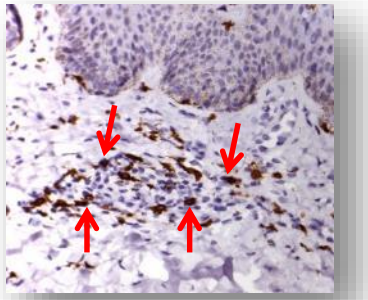
Immune mediated flare Gr 2 erythroderma



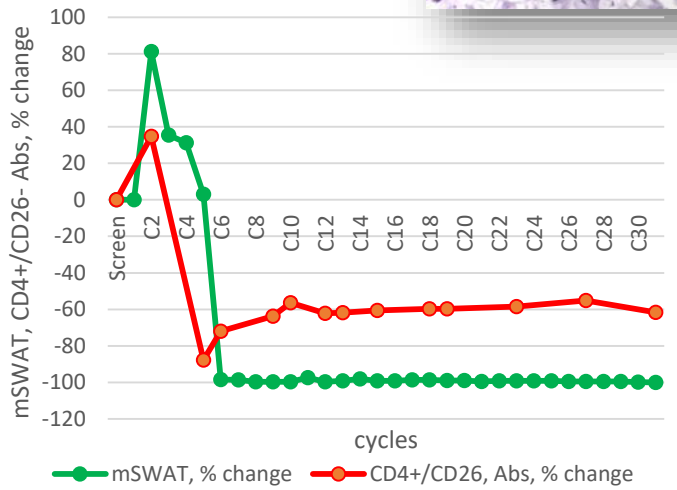


C13D1

CD8+ T cells



C2D1, Grade 2 Erythroderma Immune mediated



Global PR C6 => CR

(Skin/PR C6D1, Blood/CR C5D1, LN/CR C12D1)

C2D1: skin/blood worsened with immune mediated flare

63M with MF, stage IIB, LCT+, global PR

(h/o PUVA, bexarotene, RT, ECP, IFN, vorinostat, romidepsin, gemcitabine, pralatrexate)

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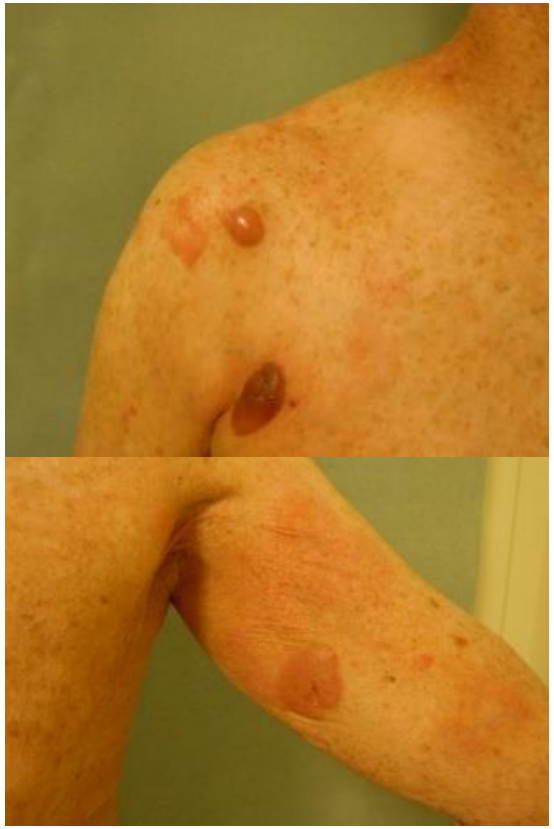
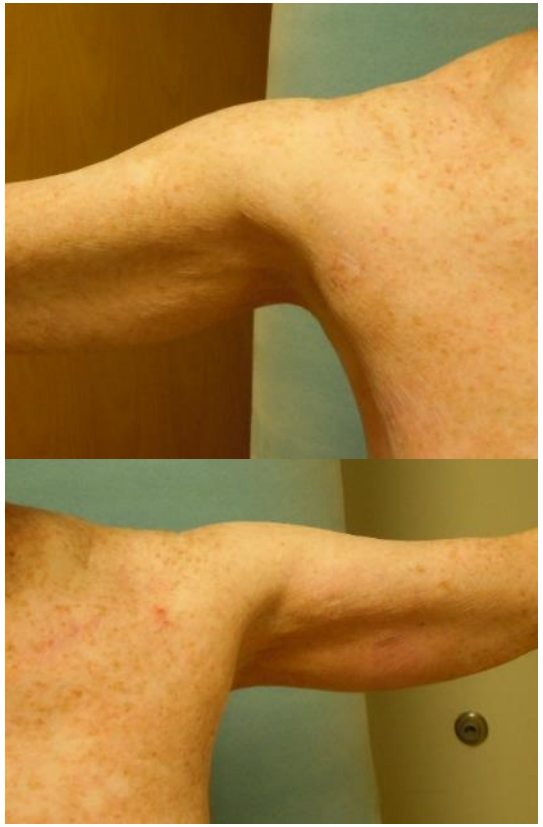
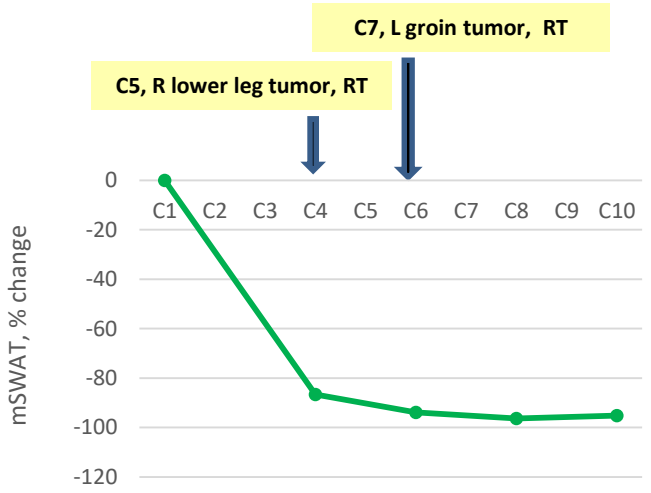




Baseline **C14**



Global PR

(Skin/PR C4D1, Blood/ Non-measurable at baseline, LN/ Non-measurable at baseline)

C5D4-C6D6: R lower leg tumor, RT: 12 Gy

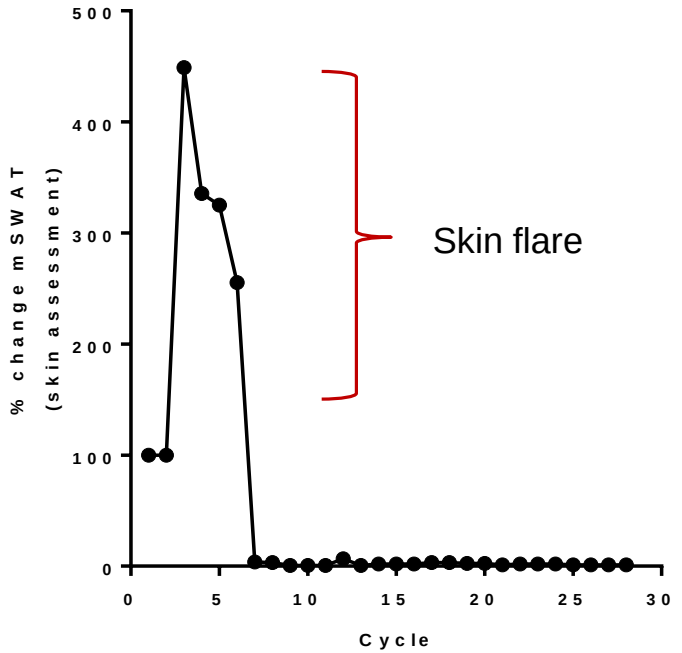
C6D19-C7D17: left groin tumor, RT: 12 Gy

Toxicity/tolerability

Recurrent or Gr 3/4 related adverse events (excluding skin)

	Grade 1/2		Grade 3/4	
Events	**Patients**	**%**	**Patients**	**%**
Anemia	1	4%	2	8%
Diarrhea	2	8%	1	4%
Infusion-related reaction	2	8%	0	0
Leukopenia	2	8%	0	0
Transaminitis	1	4%	1	4%
Duodenitis	0	0	1	4%
Hyperuricemia	0	0	1	4%

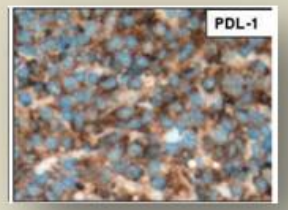
- Safety overall was excellent with expected toxicities
- Two related SAEs
  - Duodenitis (steroid-refractory)
  - Pneumonitis (steroid-responsive)



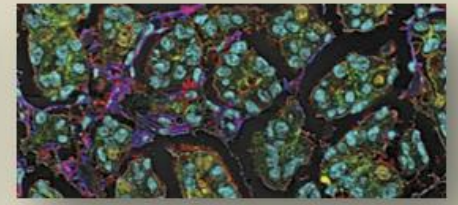
- 8 patients experienced a **skin-flare reaction**
  - All eight had **Sézary Syndrome**.
  - Did not result in discontinuation
  - Did not correlate with either response/progression

Correlative Studies – Extensive Biomarker Analysis

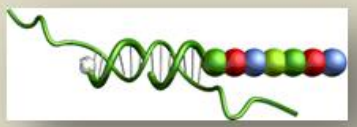
Microenvironment profiling



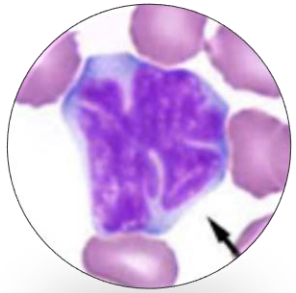
IHC



Multiplexed Ion Beam Imaging

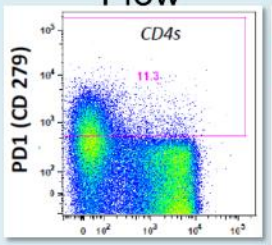


Nanostring GEP

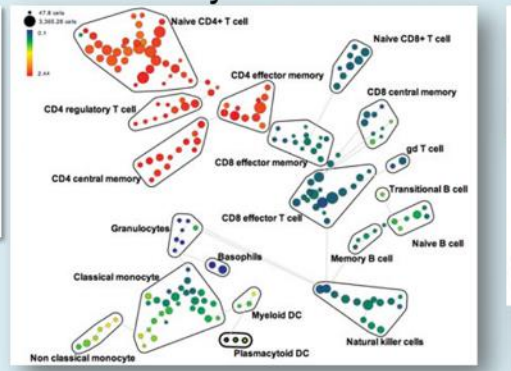


Systemic Immune Profiling

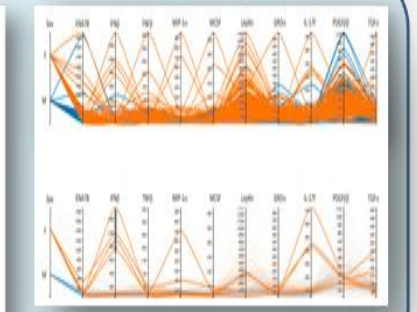
Flow



CyTOF

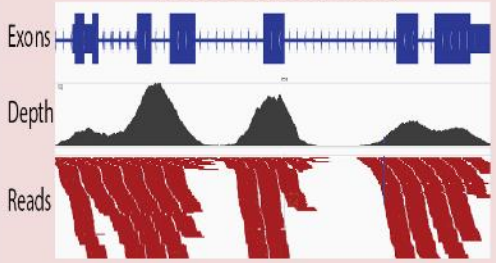


Luminex

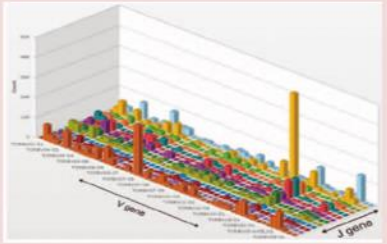


Molecular Profiling

Whole exome seq

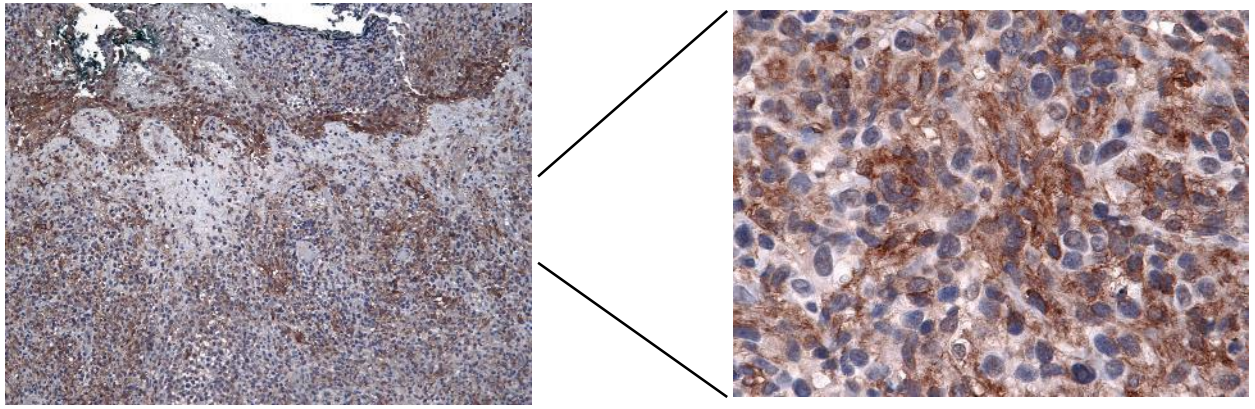


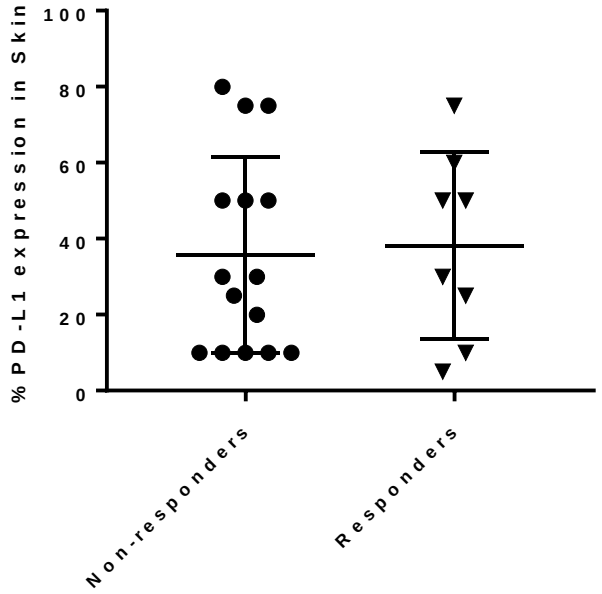
TCR –high throughput seq



Immunohistochemistry

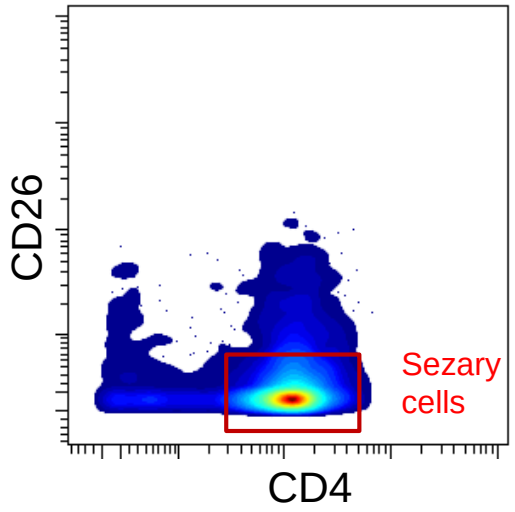
- PD-1/PD-L1 expression is a key biomarker candidate
- Expression of PD-L1 did not correlate with response to pembrolizumab
- Additional markers were also assessed, no correlation with clinical response
  - ✓ CD4
  - ✓ CD8
  - ✓ Foxp3
  - ✓ CD163
  - ✓ PD1
  - ✓ PDL2





High dimensional analysis - CyTOF

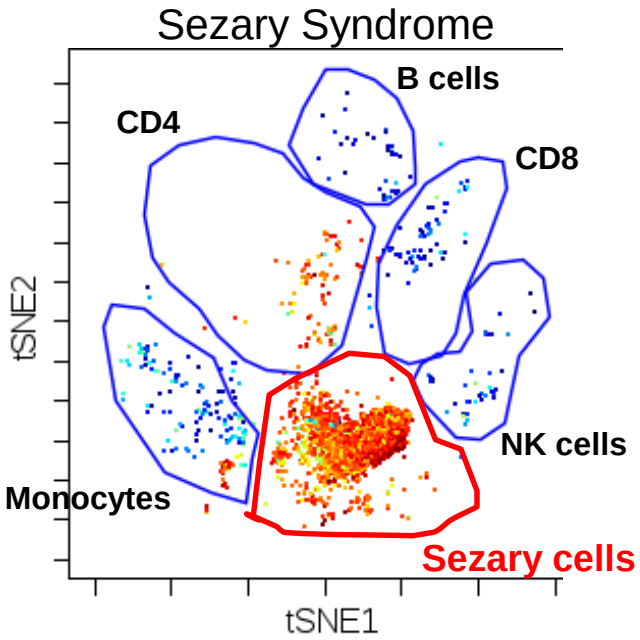
Immunophenotypic discrimination of normal CD4 cells and Sezary cells can be challenging (CD4+/CD26-) esp in low-intermediate SC burden

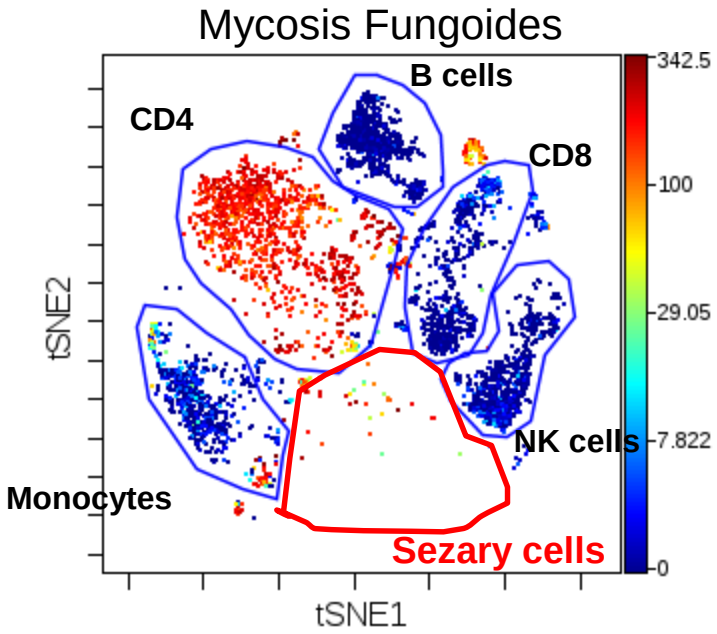


CyTOF – simultaneous staining of 33 abs

Discriminates normal and malignant T cells - even without CD7 or CD26

More precise characterization of malignant cells

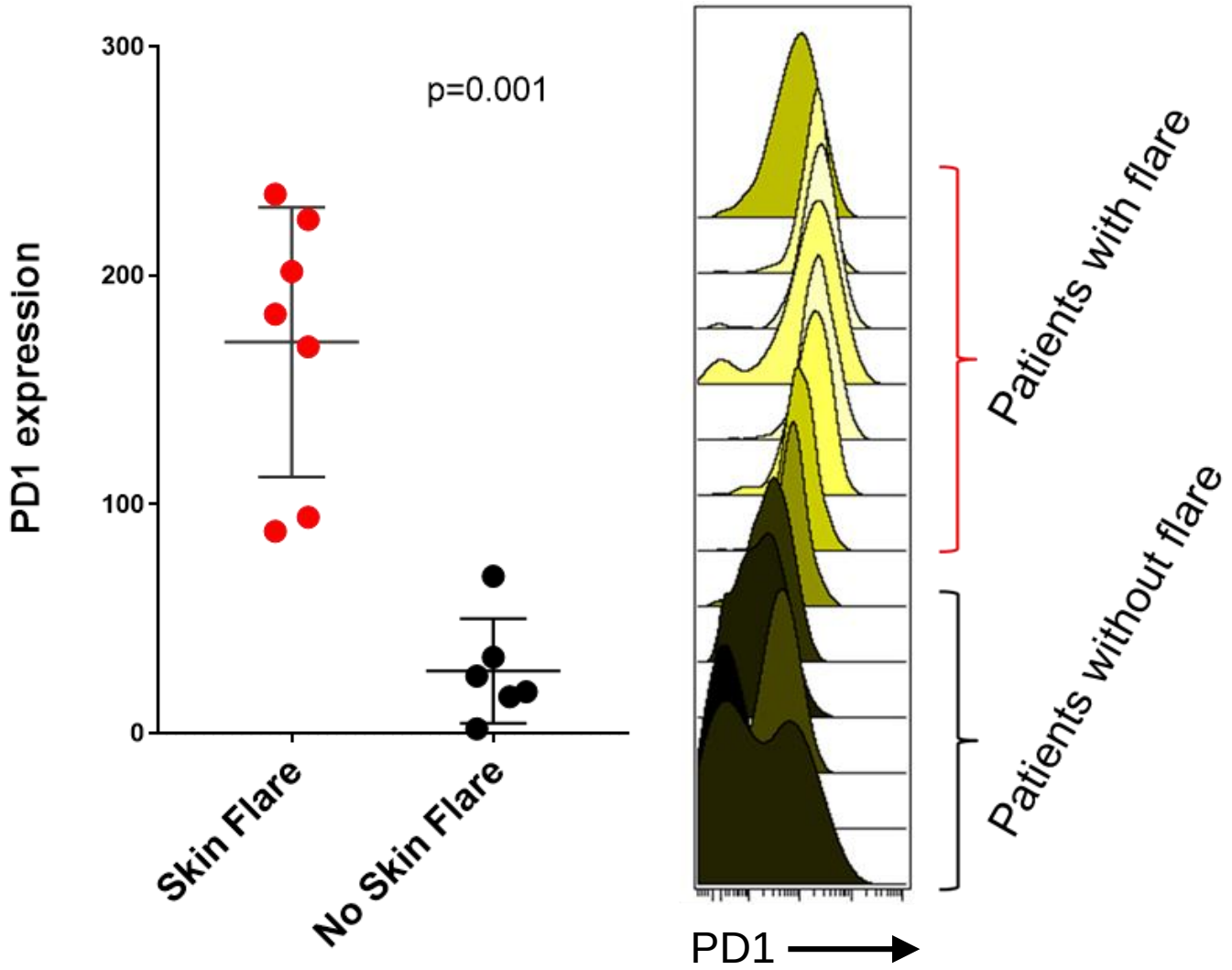




Pretreatment PD1 expression predicts skin flare

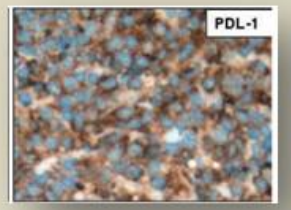
CyTOF identified high PD1 expression on Sezary cells as predictor for skin flare reaction

Luminex cytokine profiling associated skin flares with post-treatment increase in IL-12 levels, suggesting Th1 driven reaction

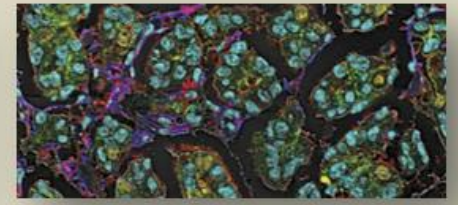


Extensive Biomarker Analysis, *near complete*

Microenvironment profiling



IHC



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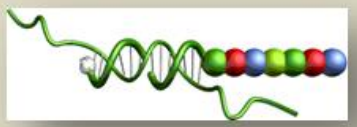

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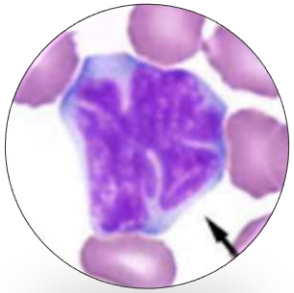

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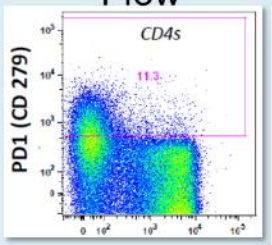
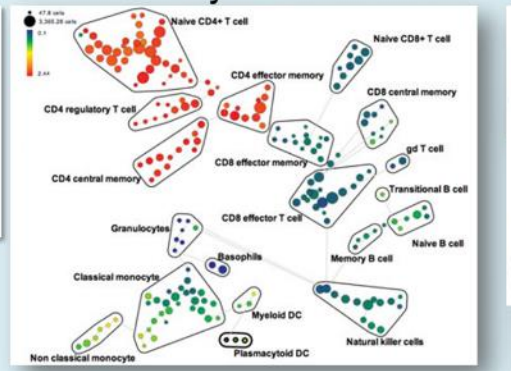
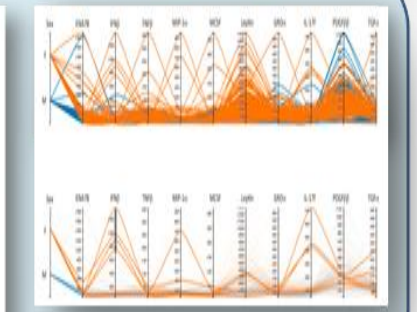


CyTOF

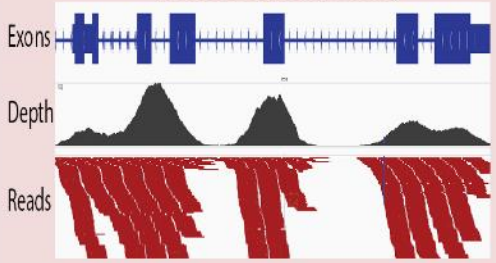


Luminex

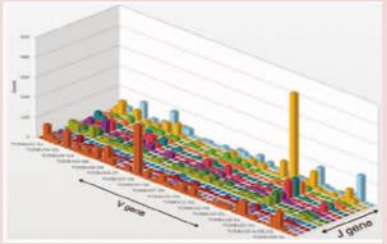


Molecular Profiling

Whole exome seq



TCR –high throughput seq



Anti-PD-1 mab, pembrolizumab, in MF/SS
Summary

- Objective clinical responses are observed in 9/24 (38% ORR)
  - Observed in both MF (IIB) and SS (IVA)
  - Responses in heavily treated pts (5 of 9 responders ≥4 prior systemic therapies)
  - Responses appear to be **durable**
    - 8 of 9 responses ongoing
- Well-tolerated, anticipated and toxicity was manageable
  - **Skin flare** seen in Sezary patients with high PD1 expression
- Biomarker/translational data pending, help in predicting response and tumor/immune escape mechanisms, and esp to understand who have early progression
- Follow up trial: CITN-13 **pembrolizumab with interferon-gamma**

NCI Protocol: CITN-13

A Phase II Trial of MK-3475 (pembrolizumab) and Interferon Gamma 1-b Combination Immunotherapy in Patients with Previously Treated MF/SS

Principal Investigator: M Khodadoust, Y Kim
Stanford University SOM

Coordinating Center (CITN): M Cheever
A Davis (project manager); Steven Fling (laboratory lead)
CITN, Fred Hutchinson Cancer Research Center

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A Moskowitz/S Horwitz (MSKCC), D Fisher (DFCI), N Mehta-Shah (Wash U)

Correlative Studies: S Fling

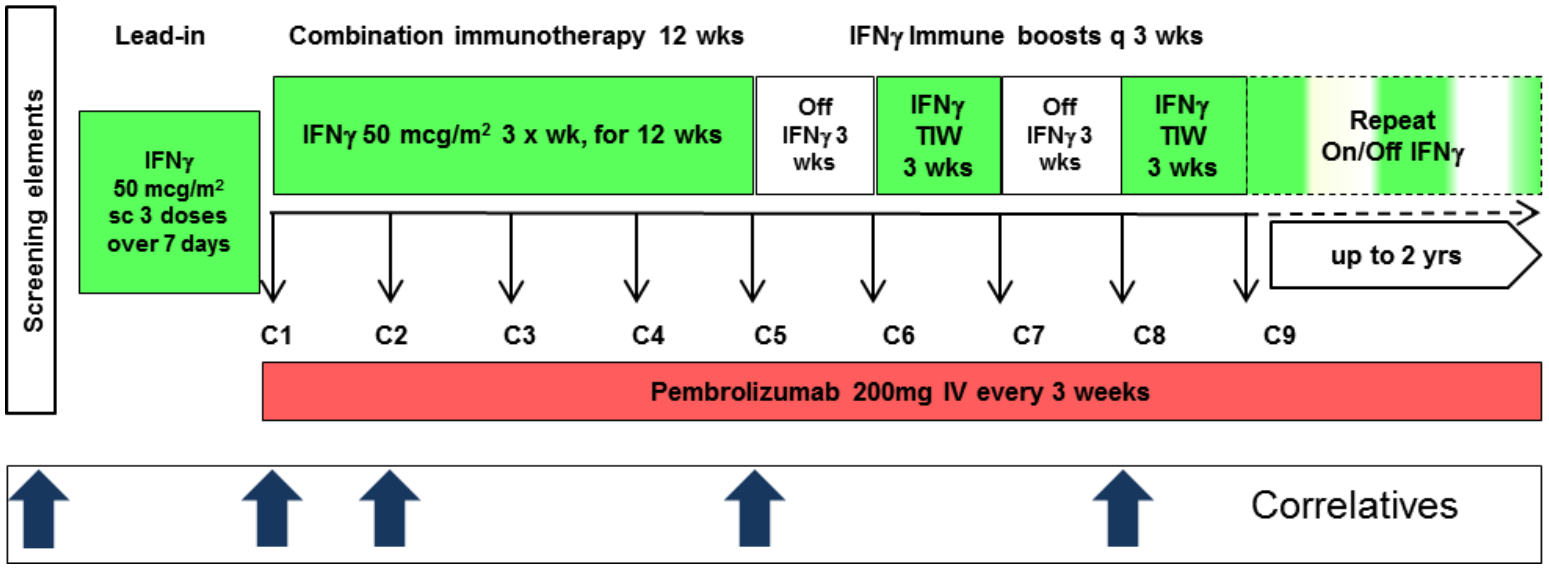
NCI Collaboration: E Sharon

Funding Support: National Cancer Institute
Merck, Horizon

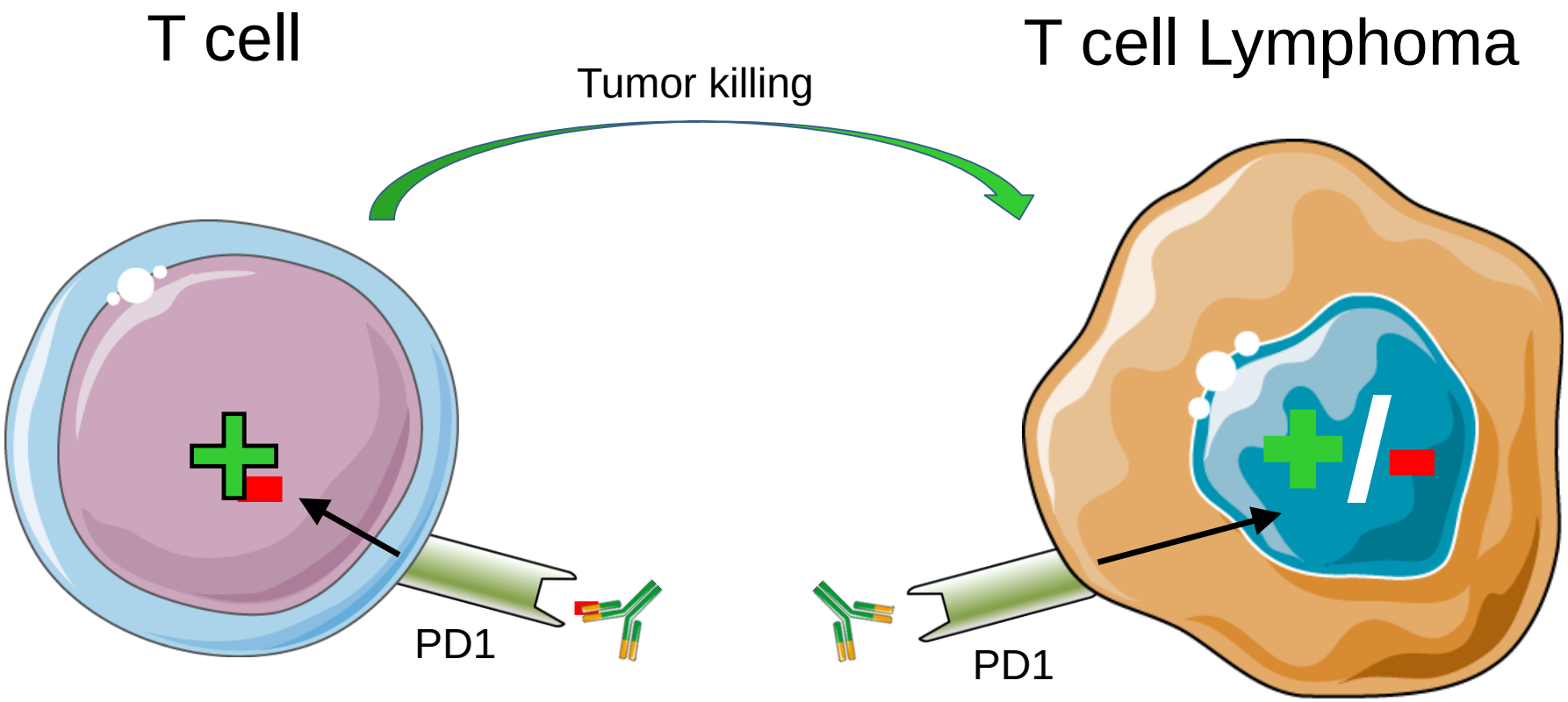
CITN13 – Treatment Schema

Interferon-gamma: 50 mcg/m2 3x per week; with 1 week lead-in
Dose escalation to 75 mcg/m2 and 100 mcg/m2 permitted at boost periods if not in CR

Pembrolizumab: 200 mg flat dose every 3 weeks



Role of PD-1 signaling in T cell lymphomas



LETTER

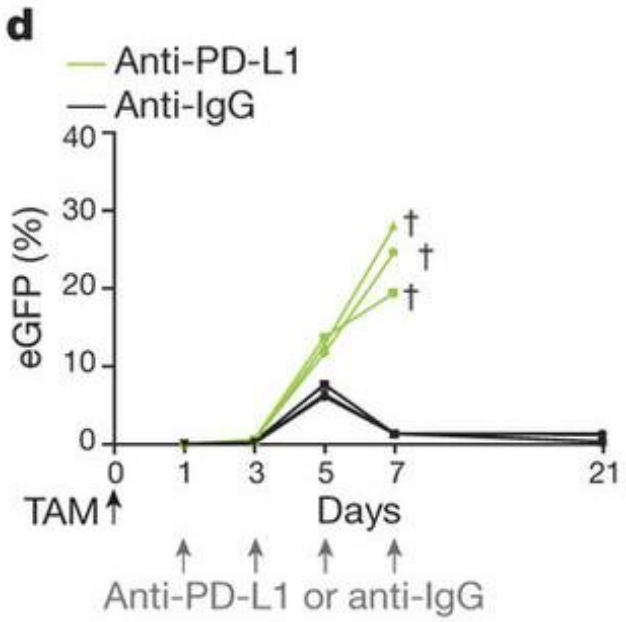
Wartewig Nature 2017

doi:10.1038/nature24649

PD-1 blockade may have potential to activate T cell lymphomas

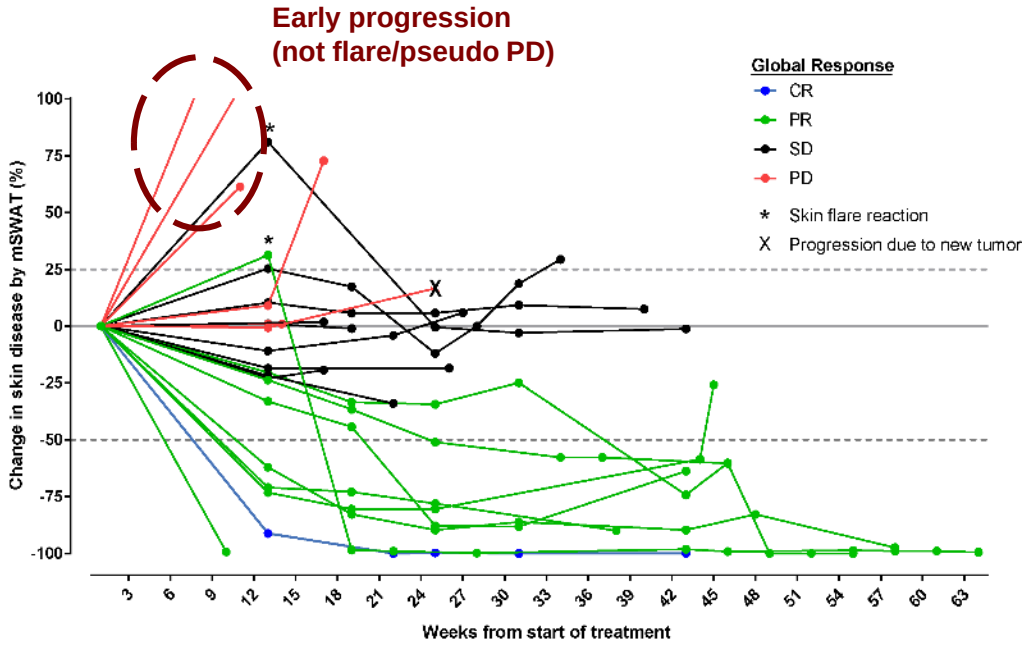
PD-1 is a haploinsufficient suppressor of T cell lymphomagenesis

Tim Wartewig[1,2], Zsuzsanna Kurgyis[1,2], Selina Keppler[1,2], Konstanze Pechloff[1,2,3], Erik Hameister[1,2], Rupert Öllinger[2,4], Roman Maresch[2,4], Thorsten Buch[5], Katja Steiger[6], Christof Winter[1,2,3], Roland Rad[2,3,4] & Jürgen Ruland[1,2,3,7]



PD-1 enhances levels of tumor suppressor PTEN and attenuates signaling by AKT and PKC.

Reportedly PD-1 copy number loss is frequent in T cell lymphoma and may predispose to T cell lymphomagenesis



PD-1 inhibitor possibly promoting CTCL

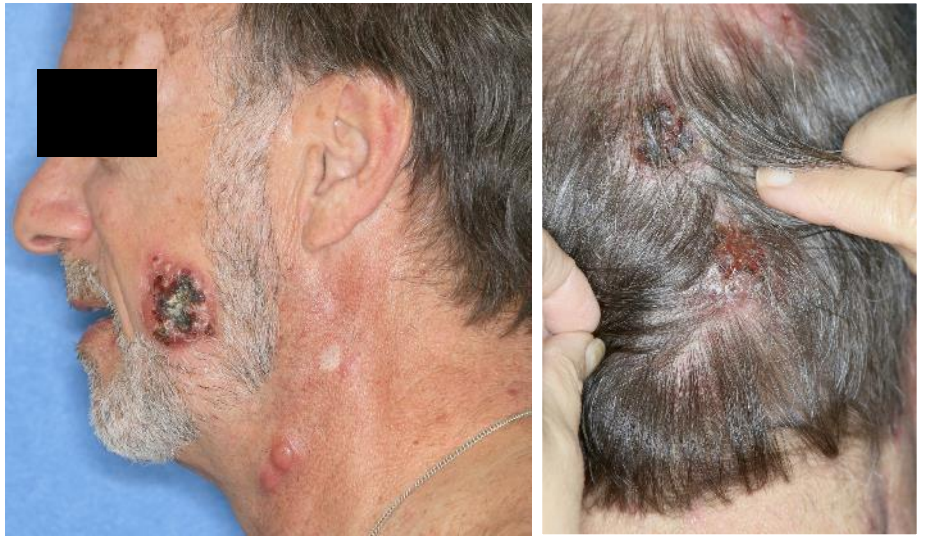
- 62 yo man with **metastatic melanoma** to lung and brain
- Receives ipilimumab x 4: progressive disease of melanoma
- Receives pembrolizumab: near complete response of melanoma

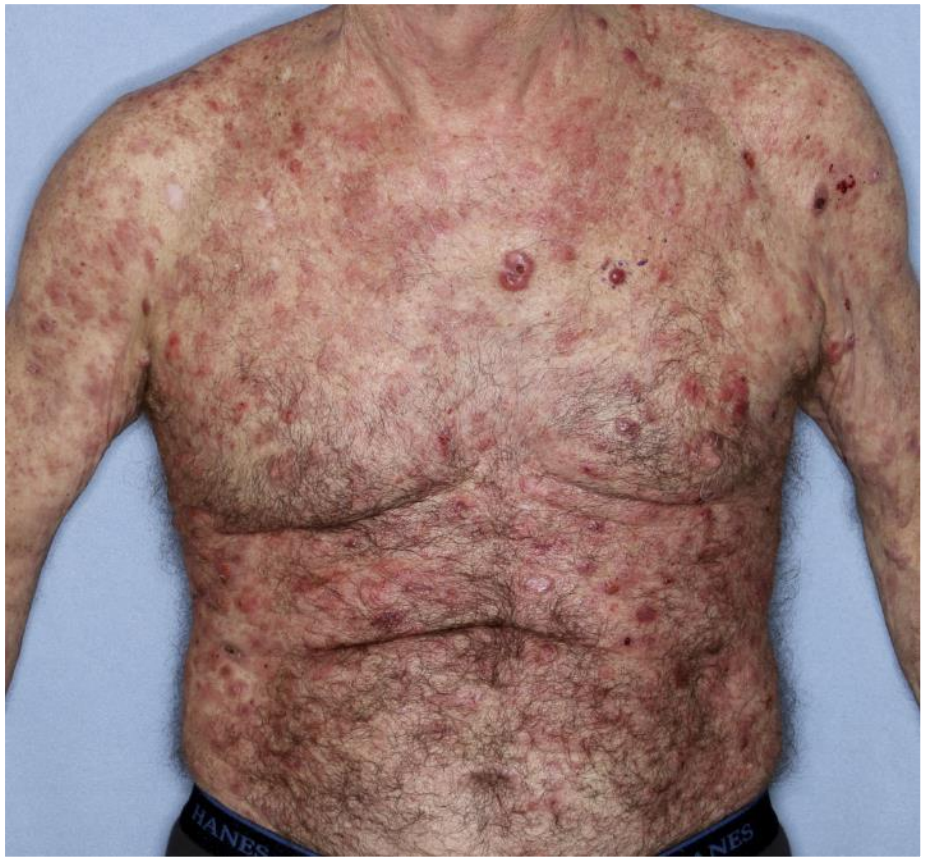
But ~ 11 months after starting pembrolizumab for met melanoma, begins to develop skin lesions

Biopsy shows a CD8+/TCRβ+ epidermotropic cytotoxic T cell lymphoma

Did anti-PD-1 therapy induce T cell lymphoma?

More to learn about PD-1/PD-L1 inhibition in TCL





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Patients and their families