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# Pembrolizumab in Peripheral T-Cell Lymphoma and Cutaneous T-Cell Lymphoma

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# Disclosures

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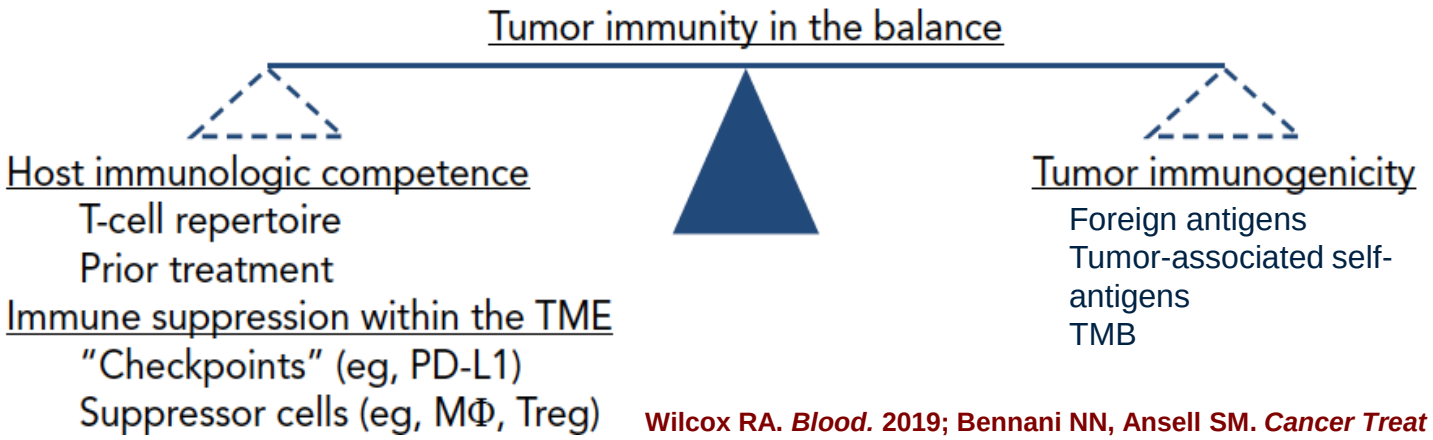
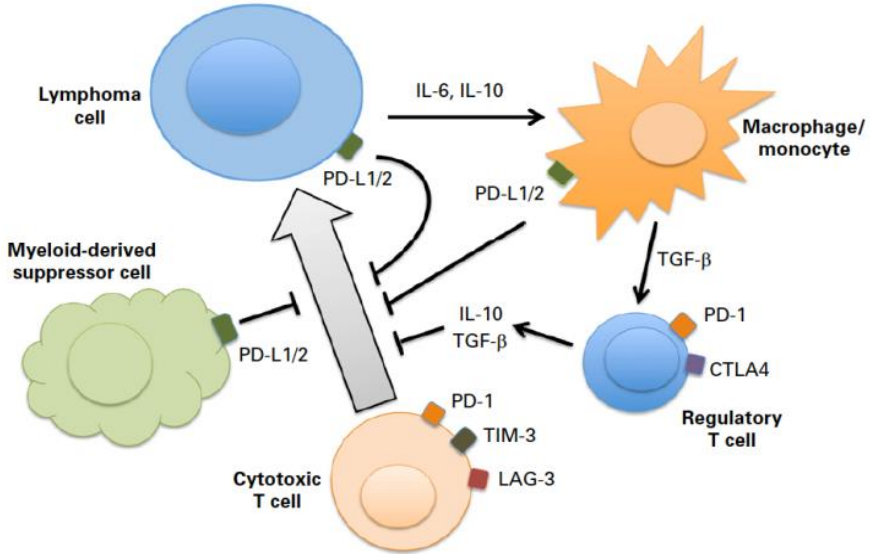
- Honoraria for educational activities: Acrotech, Kyowa Kirin
- Prior research support by Merck

# The Rationale for Checkpoint Blockade in Peripheral and Cutaneous T-cell lymphoma




**How can we activate the antitumor immune response?**




**Wilcox RA. *Blood.* 2019; Bennani NN, Ansell SM. *Cancer Treat Res.* 2019**

- ✓ Immune "graft-versus-lymphoma" effect following allogeneic HCT
- 👎 Suppressive tumor microenvironment:
  - rich infiltrates with monocyte-derived cells &
  - expression of immune checkpoint receptors (PD-1, ICOS, TIGIT and CD27) on both malignant & normal intratumoral T-cells.
- 👎 Increased expression of PD-L1 in a variety of T-cell lymphomas
  - within the tumor microenvironment (73% in CTCL; 39% PTCL-NOS), and by
  - malignant T cells (27% in CTCL;15% in PTCL-NOS).


Wilcox RA, et al. *Blood*. 2009;114:2149–58; Andorsky DJ, et al. *Clin Cancer Res.* 2011;17:4232-44; Goldberg JD, et al. *Leuk Lymphoma.* 2012;53:1124-9; Smith SM, et al. *JCO.* 2013;31:3100-9; Pritchett et al. ASH 2019; Abstract 1517

# Early Evidence for Efficacy of PD-1 Inhibition in T-Cell Lymphoma: Ph 1b Study of Nivolumab in RR NHL & MM

| Baseline Characteristics of T-cell lymphoma pts (n=23) | | |
|---|---|---|
| **Age** | Median (range) | 61 (30-81) |
| **Sex** | Female | 8 (35%) |
| **Race** | White | 17 (74%) |
| | Black | 3 (13%) |
| | Asian | 1 (4%) |
| | Other | 2 (9%) |
| **ECOG** | 0 | 4 (17%) |
| | 1 | 18 (78%) |
| | 2 | 0 |
| | NR | 1 (4%) |
| **Prior therapies** | 2-3 | 6 (26%) |
| | 4-5 | 9 (39%) |
| | ≥6 | 5 (22%) |

| Efficacy in TCL | ORR, No. (%) | CR, No. (%) | PR, No. (%) | SD, No. (%) | mPFS, wks (95% CI) |
|---|---|---|---|---|---|
| **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) |

- ✓ Median FU 42.9 and 44.0 wks for MF and PTCL, respectively.
- ✓ Durable responses: responses ongoing for both patients with MF (response durations 24.3+ & 50.0+ wks) & one pt with PTCL (response durations 10.6 and 78.6+ wks).
- ✓ Median duration of SD 11.0 wks (7.1 to 42.9+ wks) for 10 pts.

Lesokhin AM et al. *Journal of Clinical Oncology* 2016. 34:2698-704

# Pembrolizumab in PTCL

# Pembrolizumab in RR T-cell Lymphoma: Prospective Phase 2 Trial

Multicenter single-arm phase 2 trial of pembrolizumab given at IV 200mg q3wks for up to 2y or until PD/toxicity

**Eligible if:**

- ≥ 18 years or older
- Relapsed or refractory
- mature T-cell lymphoma,
- ≥ 1prior line of therapy
- ECOG 0-1
- Good organ function
- Not immunosuppressed
- No recent, active, or severe autoimmune disease

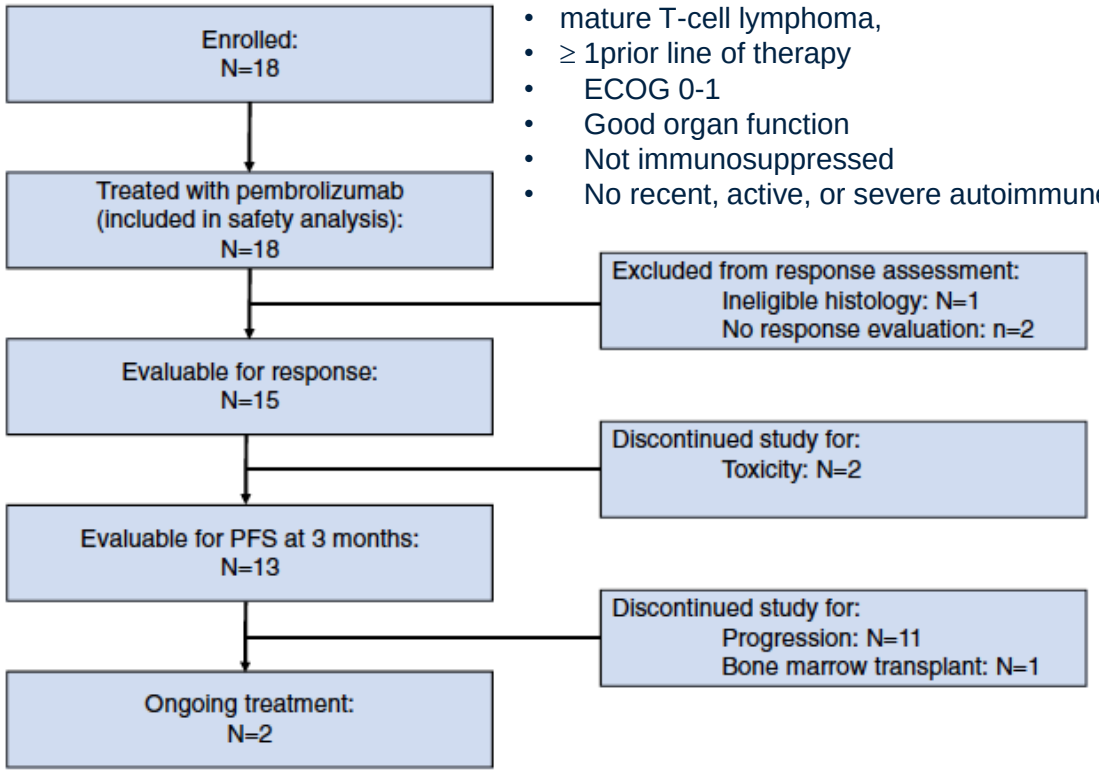



**Table 1 Patient Characteristics (N = 17)[a]**

| Characteristic | n, (%) |
|---|---|
| Media age, y (range) | 71 (18-88) |
| Gender, male | 8 (47) |
| Histology | |
| PTCL-NOS | 7 (41) |
| FTL | 4 (18) |
| tMF | 3 (18) |
| Other[b] | 3 (23) |
| Median number of prior therapies (range) | 2 (1-9) |
| > 2 prior therapies | 6 (35) |
| Refractory to last therapy[c] | 11 (65) |

[b] *MEITL, HSTCL, Alk-ALCL (n =1 each).*

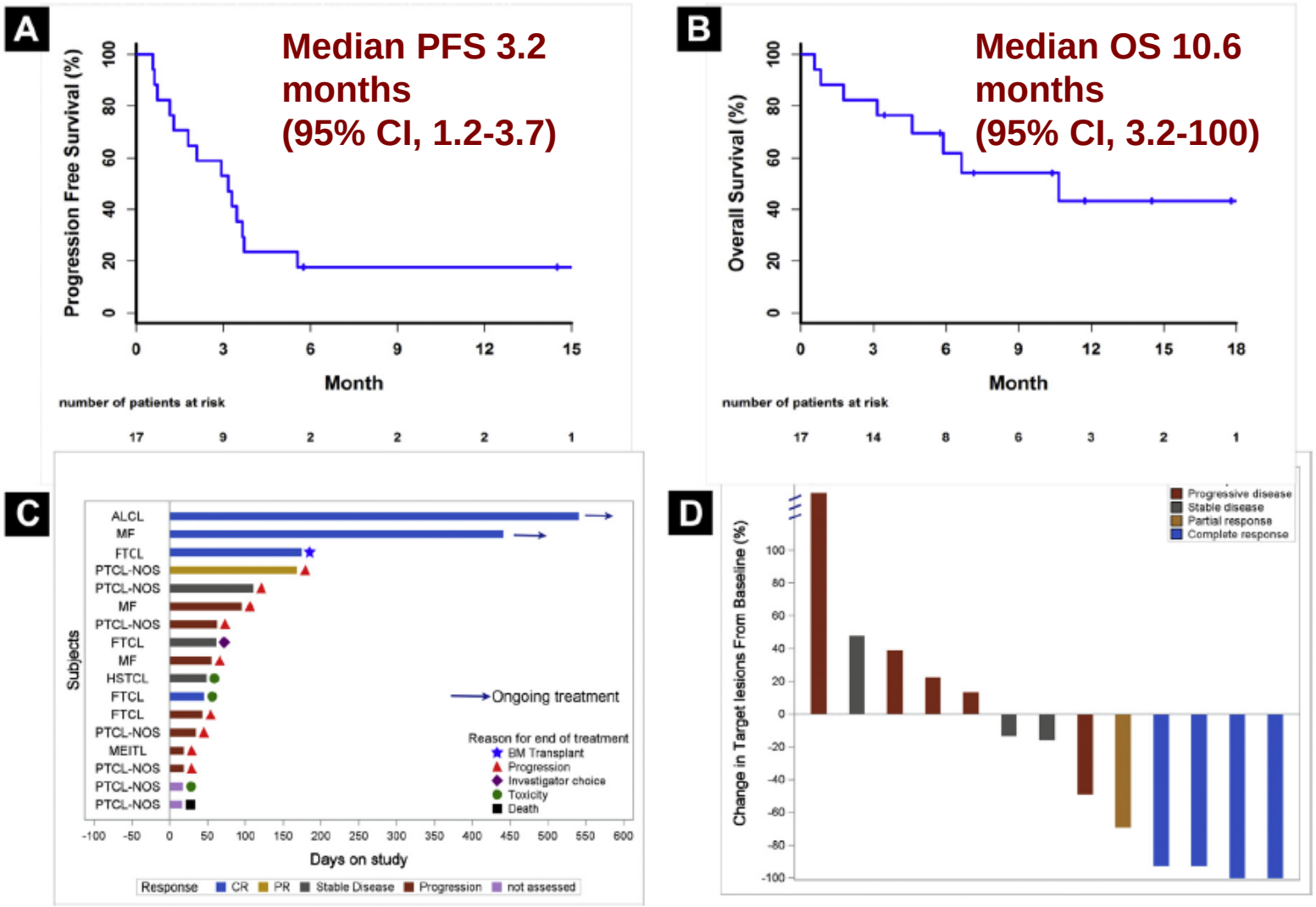
# Efficacy of Pembrolizumab in RR T-cell Lymphoma

**Response rate (in evaluable patients):**
ORR 33%
(5/15; 95%CI, 9%-57%);
CR rate 27%
(4/15; 95% CI, 4%-49%)

Median DOR 2.9 months; (95% CI, 0-10.1), however 2 censored early (toxicity; HCT) and 2 remained in remission > 15 months

Study was stopped early for futility as the primary endpoint (3-months PFS 50%) was not met on a pre-specified early futility assessment.

No clear hyper-progression was observed.



# Safety of Pembrolizumab in RR PTCL

| Grade ≥3 AEs at Least Possibly Related to Pembrolizumab (N=18) | Total N (%) | Grade N (%) | | |
|---|---|---|---|---|
| | | 3 | 4 | 5 |
| Febrile Neutropenia | 1 (6) | 1 (6) | | |
| HLH | 1 (6) | 1 (6) | | |
| Lung Infection | 1 (6) | 1 (6) | | |
| Hyperglycemia | 1 (6) | 1 (6) | | |
| Hyponatremia | 1 (6) | 1 (6) | | |
| Muscle Weakness | 1 (6) | 1 (6) | | |
| PSN | 1 (6) | 1 (6) | | |
| Pleural Effusion | 1 (6) | 1 (6) | | |
| Pneumonitis | 2 (11) | 1 (6) | 1 (6) | |
| Rash | 2 (11) | 1 (6) | 1 (6) | |
| Hypotension | 1 (6) | 1 (6) | | |
| Vasculitis | 1 (6) | 1 (6) | | |

| Immune-related Adverse Events in the Safety Population (N=18) | Total N (%) | Grade N (%) | | | | |
|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 |
| Hypothyroidism | 2 (11) | 1 (6) | 1 (6) | | | |
| Adrenal Insufficiency | 1 (6) | | 1 (6) | | | |
| Diarrhea | 1 (6) | | 1 (6) | | | |
| LFT abnormalities | 1 (6) | 1 (6) | | | | |
| Pneumonitis | 2 (11) | | | 1 (6) | 1 (6) | |
| Rash | 3 (17) | 1 (6) | | 2 (11) | | |
| Vasculitis | 1 (6) | | | 1 (6) | | |
| HLH | 1 (6) | | | 1 (6) | | |

- **Most common AEs:** rash (17%), hypothyroidism, watering eyes, chills, edema, fatigue, fever, injection reactions, dyspnea, pneumonitis (11% each).
- No unexpected toxicities were seen.
- **2 participants discontinued treatment for toxicities** (n=1 for pneumonitis & vasculitis each);
- 1 pt died of likely septic shock 2nd to presumed skin infection.

Barta SK et al. *Clin Lymphoma Myeloma Leuk.* 2019 Jun;19(6):356-64

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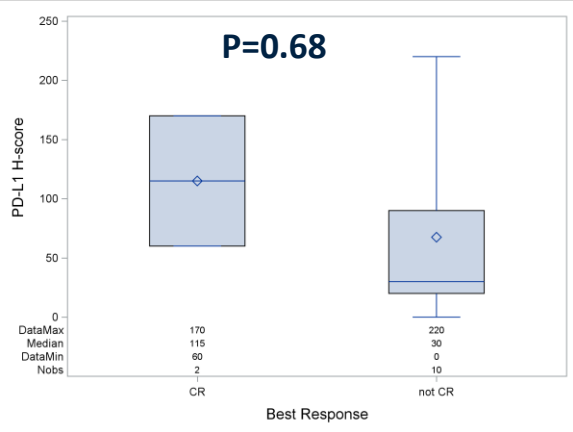
# Correlatives: NK and T-cell function;  PD1, PD-L1 IHC & pAKT expression

**PD-L1 H-scores:**
Median H-score 115 in pts with CR vs 30 in those without CR (p=0.38).

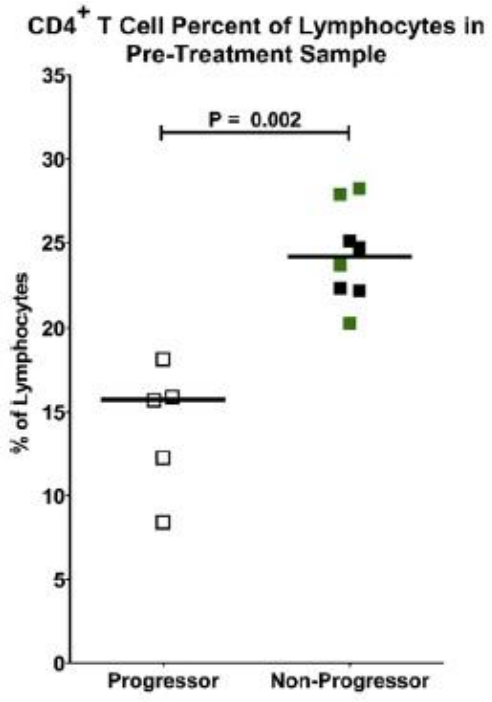


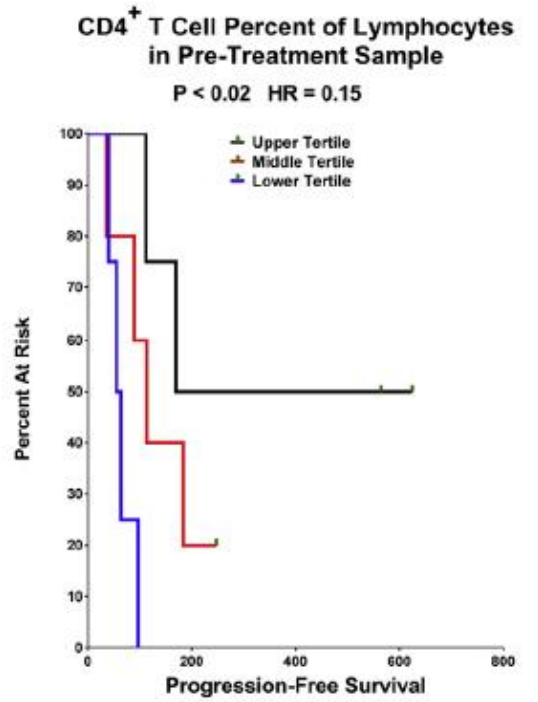

**PD-L1 H-score and CR as Best Response**

**p-AKT-expression:**
Median H-score not significantly higher in responders (30 (responders) vs. 0 (non-responders), p=0.73).

Of note, PD-L1 and p-AKT expression were highly correlated (Pearson correlation coefficient 0.99).

Patients with a higher baseline median percentage of **PB CD4⁺ T cells** within the total lymphocyte population had better outcomes



# Nivolumab in RR TCL – Prospective Phase 2 trial

| | Total N=12 |
|---|---|
| **Age** | |
| Median (Range), years | **65 (35- 75)** |
| **Male Gender**, n (%) | **6 (50)** |
| **ECOG Performance Score**, n (%) | |
| **0** | **7 (58)** |
| **1** | **4 (33)** |
| **2** | **1 (8)** |
| **No of Prior Lines of Therapy Median (Range)** | **2 (1-6)** |
| **Prior ASCT**, n (%) | **6 (50)** |

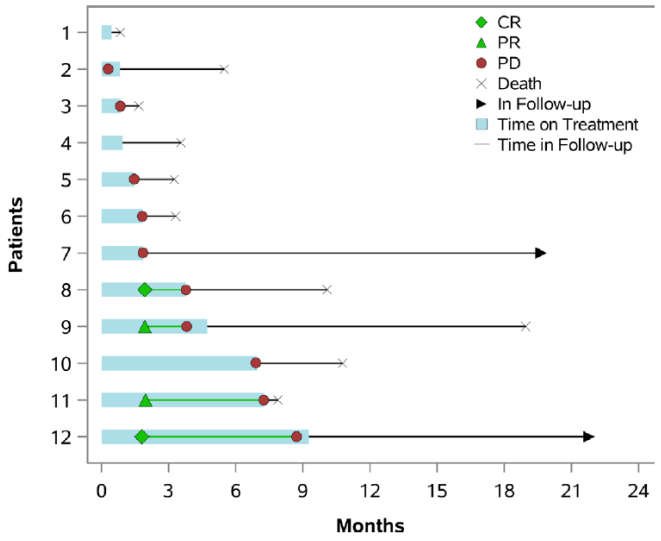
| | Total N=12 |
|---|---|
| **T-cell Lymphoma Subtype**, n (%) | |
| Angioimmunoblastic T-Cell Lymphoma | **6 (50)** |
| Peripheral T-cell Lymphoma, not otherwise specified | **3 (25)** |
| Anaplastic Large Cell Lymphoma, ALK negative | **1 (8)** |
| Enteropathy-associated T-Cell Lymphoma | **1 (8)** |
| Hepatosplenic Gamma Delta T-Cell Lymphoma | **1 (8)** |
| **Ann Arbor Stage**, **III/IV** n (%) | **12 (100)** |
| **Extranodal Involvement**, n (%) | **11 (92)** |

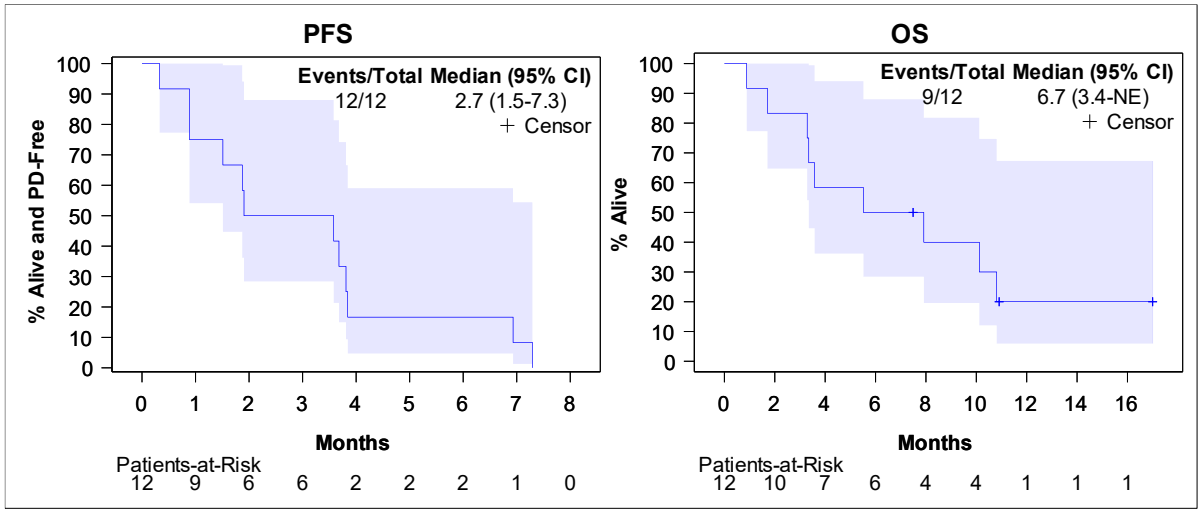
**Modified slide courtesy of Nora Bennani**

Bennani NN et al. American Society of Hematology, December 8,2019, Abstract # 467

# Nivolumab in RR TCL – Outcomes & Correlatives

| | Total N=12 |
|---|---|
| **Overall Response Rate**, n (%) **(95% CI)** | **4 (33) (12.3 - 63.7)** |
| Complete Response : - 1 ALK-ALCL - 1 AITL | **2** |
| Partial Response : - 1 PTCL-NOS - 1 EATL | **2** |




**Correlatives:**
IHC for expression of PD- 1 and PD- L1 and EBV not associated with response.

NGS- based tumor profiling assay of genes implicated in the host cancer- fighting immune response:

- 7 genes were upregulated in responders versus non- responders:
- ADRB2, SLFN11, **KLRF1**, CD163, CD244, **KLRK1, KLRD1**
- 3 **upregulated genes in responders** that are **involved in NK cell function**: Killer cell lectin like receptor K1 (KLRK1), killer cell lectin like receptor F1 (KLRF1), and killer cell lectin like receptor D1 (KLRD1).
- 9 genes were downregulated: GAD1, C4A_C4B, CPE, IFNLR1, RDM1, USP9Y, KIT, CXCL14, FAP

**Modified slide courtesy of Nora Bennani**

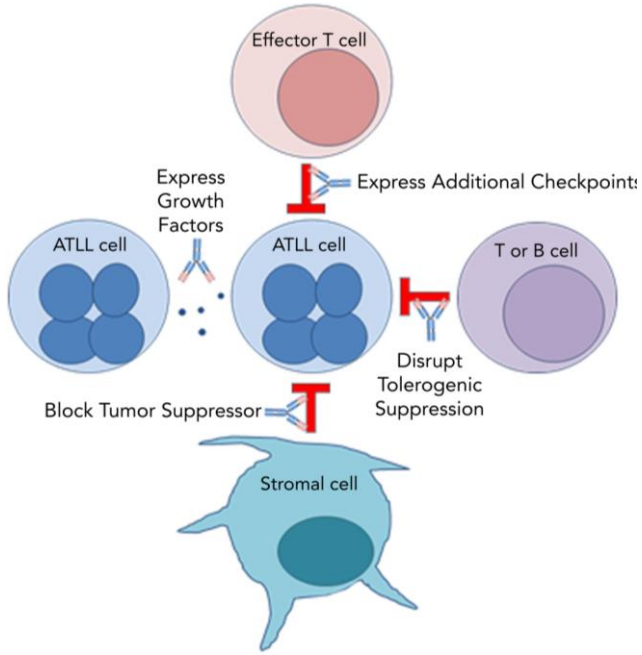

Bennani NN et al. American Society of Hematology, December 8,2019, Abstract # 467
Bennani NN, et al. J Immunother Cancer 2022.

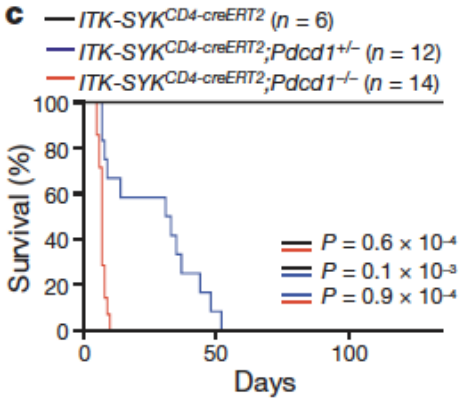
# Concerns for Hyperprogression

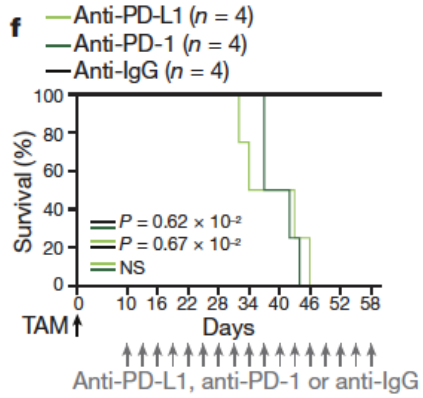
- Unifying mechanism for hyperprogression not available – maybe disease specific or multifactorial?

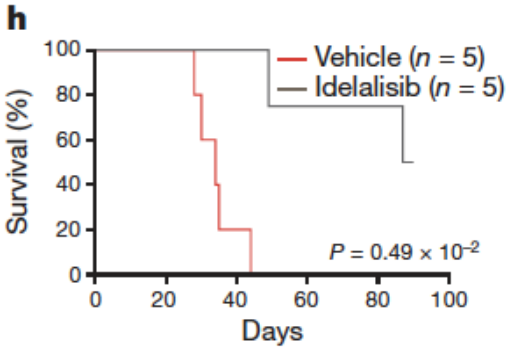
**Possible Mechanisms:**

- ✓ **PD-1** can be a **potent tumor suppressor** in the context of a T-cell malignancy driven by constitutive TCR signaling
- ✓ Stromal PD-L1 acts as a tumor suppressor by binding to PD-1 expressed on lymphoma cells
- ✓ **PD-1 blockade may drive expression of additional checkpoints** that promote the suppressive activity
- ✓ PD-1 blockade alters expression of tumor-promoting growth factors
- ✓ **PD-1 uniquely governs immunity in patients with chronic or smoldering ATLL**




- May reflect an unanticipated loss of tumor suppression rather than a selective advantage for a specific clone

Rauch DA, et al. *Blood.* 2019;134:1406-14; Wartewig, T, et al. *Nature. 2017;*552(7683): 121-5.

# Pembrolizumab plus Romidepsin in RR PTCL

| Demographics | PTCL (n=20) |
|---|---|
| **Age (range in years)** | 51-81 |
| **Gender, n (%)** | Male: 12 (63)<br>Female: 7 (36) |
| **Race, n (%)** | Caucasian: 11 (58)<br>African-American: 3 (16)<br>Hispanic/Latino: 4 (21)<br>Other: 1 (5) |
| **Bone Marrow involvement, n (%)** | 5 (26) |
| **Prior therapies, n (%)** | </=2: 11 (57)<br>>/=3: 8 (42) |
| **Prior Radiation, n (%)** | 5 (26) |
| **Elevated LDH, n (%)** | 13 (68) |
| **ECOG >/=3, n (%)** | 0 (0) |
| **Stage 3 or 4, n (%)** | 16 (84) |
| **Disease status, n (%)** | Relapse: 2 (11)<br>Refractory: 17 (89) |
| **Pathology, n (%)** | PTCL, NOS: 8 (42)<br>MF; transformed: 3 (16)<br>AITL: 3 (16)<br>ALCL: 3 (16)<br>NK/T cell: 2 (10) |

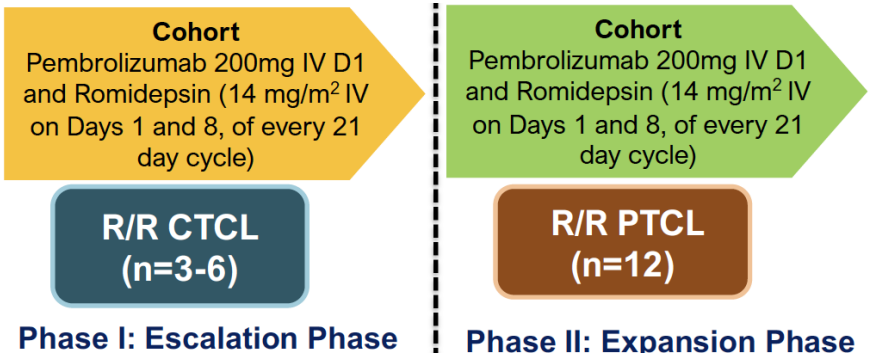
**N=8 achieved a CR,**

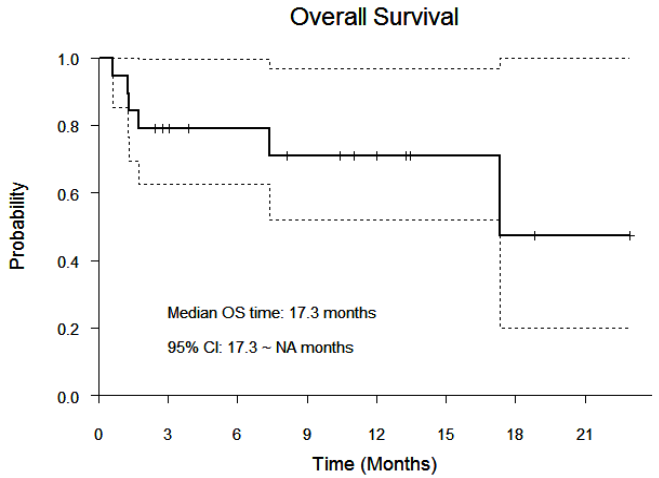
- 4 have been off treatment for >1 year without relapse,
- 2 are still on therapy for >2 years, and
- 1 underwent a haplo-SCT.

**Higher PD-L1 expression a/w CR**

| Results | N=20 (%) |
|---|---|
| **Best response:** | **Complete Response: 8 (43)**<br>**Partial Response: 2 (10)**<br>Stable Disease: 2 (10)<br>Progressive Disease:7 (37)<br>**Overall Response Rate: 10 (53)** |
| **PD-L1 positive:** | Total: 9 (47)<br>PTCL, NOS: 4 (21)<br>MF; transformed: 2 (10)<br>AITL: 2 (10)<br>ALCL: 2 (10)<br>NK/T cell: results pending |
| **COO in PTCL nos:** | Total: 6<br>TBX21: 3<br>GATA3: 2<br>Unclassifiable: 1 |

| Immune Adverse Events (IrAE) | |
|---|---|
| **Hyperprogression** | **2 (11)** |
| Immune colitis | 1 (5) |
| Cytokine storm and HLH | 1 (5) |
| Immune gastritis | 1 (5) |




**Slides (modified) courtesy of S. Iyer.** Iyer SP, et al. *Blood.* 2020; 36 (Suppl 1):40-1

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# Pembrolizumab in CTCL

# Pembrolizumab in MF and SS

**CITN-10:** Multicenter, phase II, single-arm trial of pembrolizumab for up to 24 cycles

**Eligibility criteria**

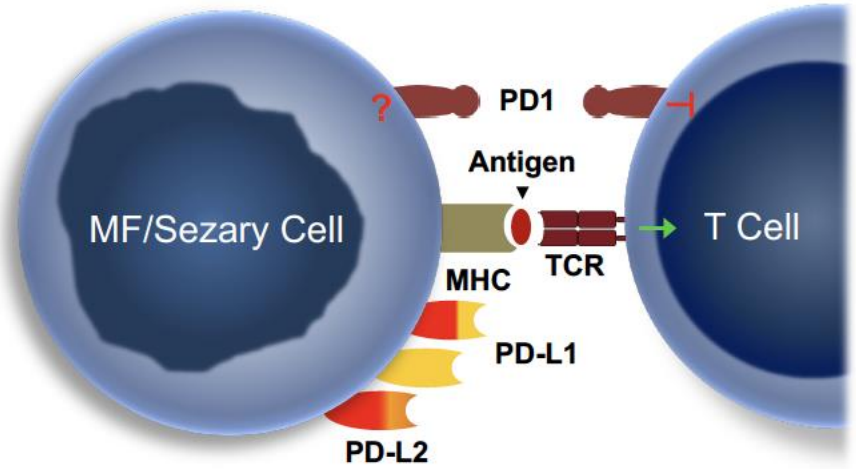
- RR MF or SS (clinical stage IB to IV) after >1 standard systemic therapy.
- Age 18 years or older.
- ECOG 0 or 1.
- Measurable disease on the basis of the mSWAT.
- Adequate organ function as assessed by laboratory testing.

**Excluded if:**

- CNS disease;
- active autoimmune disease that required systemic treatment within the past 3 months;
- treatment with radiation, phototherapy, histone deacetylase inhibitor, retinoids, interferons, therapeutic doses of systemic corticosteroids, or denileukin diftitox within 2 weeks;
- treatment with cytotoxic agents, investigational therapies, or tumor-targeting monoclonal antibodies within 4 weeks;
- treatment with alemutuzumab within 8 weeks;
- treatment with any T-cell stimulatory or checkpoint antibody within 15 weeks; or
- any history of prior anti-PD-1, anti-PD-L1, or anti-PD-L2 therapy.

**The PD1/PDL1 immune checkpoint axis appears central to MF/SS biology**

Figure (modified courtesy of Dr. Youn Kim




- **PD1** – highly expressed
- **PD-L1** – can be expressed
- **PD-L1** – can be translocated
- **PD-L2** – can be translocated

## Pembrolizumab in Relapsed and Refractory Mycosis Fungoides and Sézary Syndrome: A Multicenter Phase II Study

Michael S. Khodadoust, MD, PhD[1]; Alain H. Rook, MD[2]; Pierluigi Porcu, MD[3]; Francine Foss, MD[4]; Alison J. Moskowitz, MD[5]; Andrei Shustov, MD[6]; Satish Shanbhag, MBBS, MPH[7]; Lubomir Sokol, MD, PhD[8]; Steven P. Fling, PhD[9]; Nirasha Ramchurren, PhD[9]; Robert Pierce, MD[9]; Asa Davis, PhD[9]; Richard Shine, PharmD, BCPS[9]; Shufeng Li, MS[1]; Sophia Fong[1]; Jinah Kim, MD, PhD[1]; Yi Yang, MS[9]; Wendy M. Blumenschein[10]; Jennifer H. Yearley, DVM, PhD, DACVP[10]; Biswajit Das, PhD[11]; Rajesh Patidar, MS[11]; Vivekananda Datta, MD, PhD[11]; Erin Cantu[11]; Justine N. McCutcheon[11]; Chris Karlovich, PhD[11]; P. Mickey Williams, PhD[11]; Priyanka B. Subrahmanyam, PhD[1]; Holden T. Maecker, PhD[1]; Steven M. Horwitz, MD[5]; Elad Sharon, MD, MPH[12]; Holbrook E. Kohrt, MD, PhD[1]†; Martin A. Cheever, MD[9]; and Youn H. Kim, MD[1]

Khodadoust MS, et al. *JCO.* 2020; 38(1): 20-8

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# CITN-10: Participants and Responses

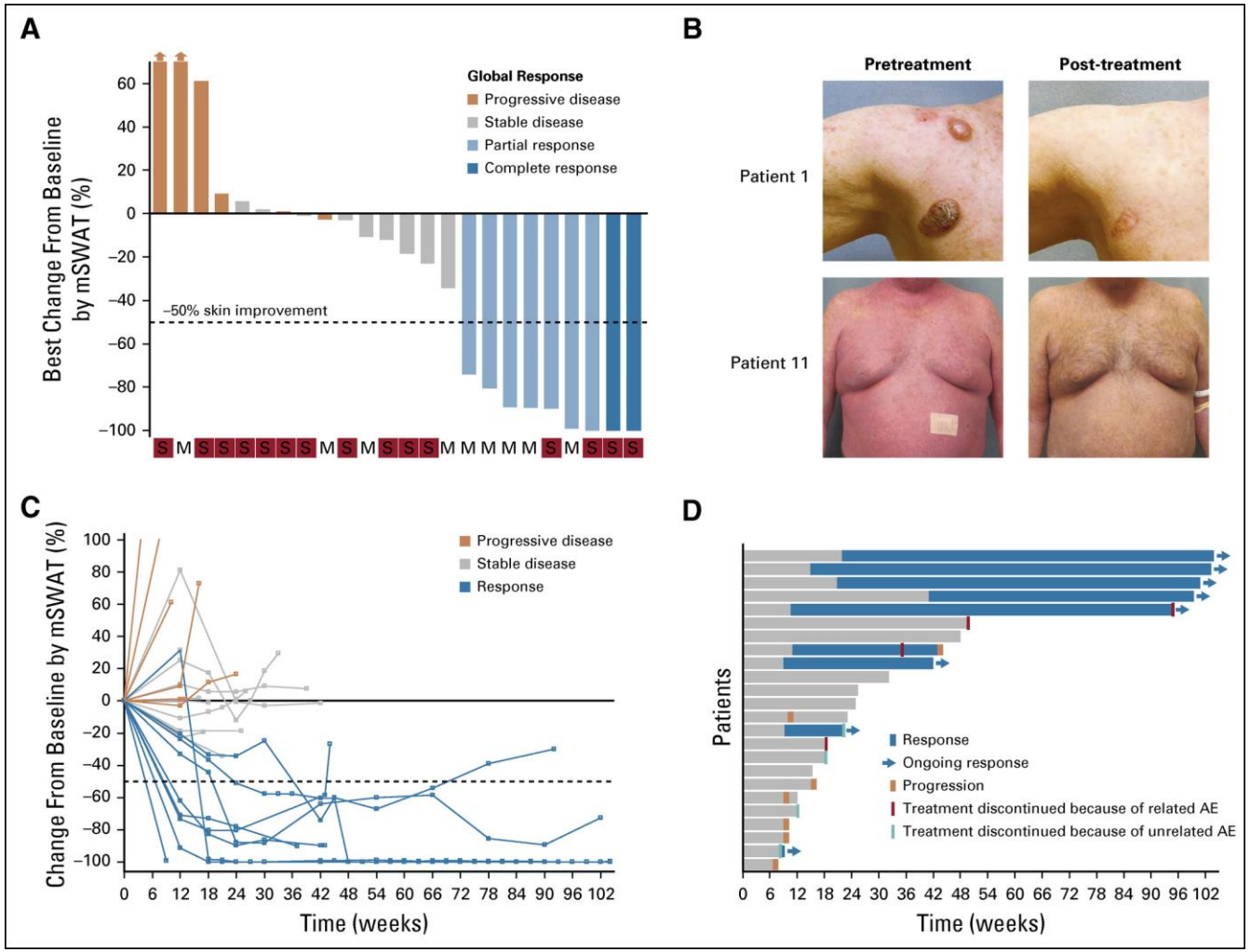
**N=24**
**Overall Response Rate: 38% (9/24)**
**CR Rate 8% (2/24)**

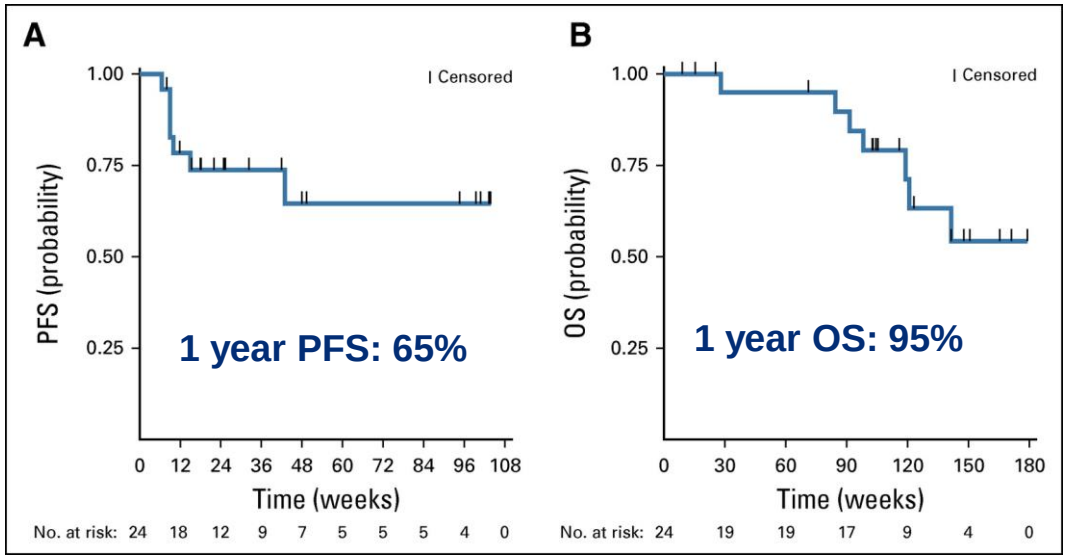
| Characteristics | Total, n=24 | Response | | | | ORR, n (%) |
|---|---|---|---|---|---|---|
| | n(%) | CR | PR | SD | PD | |
| Gender | | | | | | |
| Male | 18 (75) | 0 | 6 | 8 | 4 | 6/18 (33) |
| Female | 6 (25) | 1 | 2 | 1 | 2 | 3/6 (50) |
| Diagnosis | | | | | | |
| MF | 9 (38) | 0 | 5 | 2 | 2 | 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) |

| Characteristics | N (%) | Response Rate N (%) |
|---|---|---|
| Previous lines of therapy | | |
| 1-2 | 5 (21) | 2 of 5 (40) |
| 3 | 4 (17) | 2 of 4 (50) |
| 4 | 5 (21) | 2 of 5 (40) |
| 5-6 | 5 (21) | 2 of 5 (40) |
| 6 | 5 (21) | 1 of 5 (20) |
| Baseline mSWAT score | | |
| 1-50 | 5 (21) | 1 of 5 (20) |
| 51-100 | 10 (42) | 4 of 10 (40) |
| 101-150 | 7 (29) | 2 of 7 (29) |
| 15 | 2 (8) | 2 of 2 (100) |
| Baseline blood Sézary cell count, cells/μL | | |
| 1 | 18 (75) | 8 of 18 (44) |
| ≥ 1,000 | 6 (25) | 1 of 6 (17) |
| PD-L1 expression, percentage | | |
| ≤ 30 | 13 (54) | 4 of 13 (31) |
| 31-60 | 7 (29) | 4 of 7 (57) |
| 6 | 4 (17) | 1 of 4 (25) |
| Skin flare (patients with Sézary syndrome only) | | |
| Present | 8 (53) | 3 of 8 (38) |
| Absent | 7 (47) | 1 of 7 (14) |

Khodadoust MS, et al. *JCO.* 2020; 38(1): 20-8

# CITN-10: Response and Survival



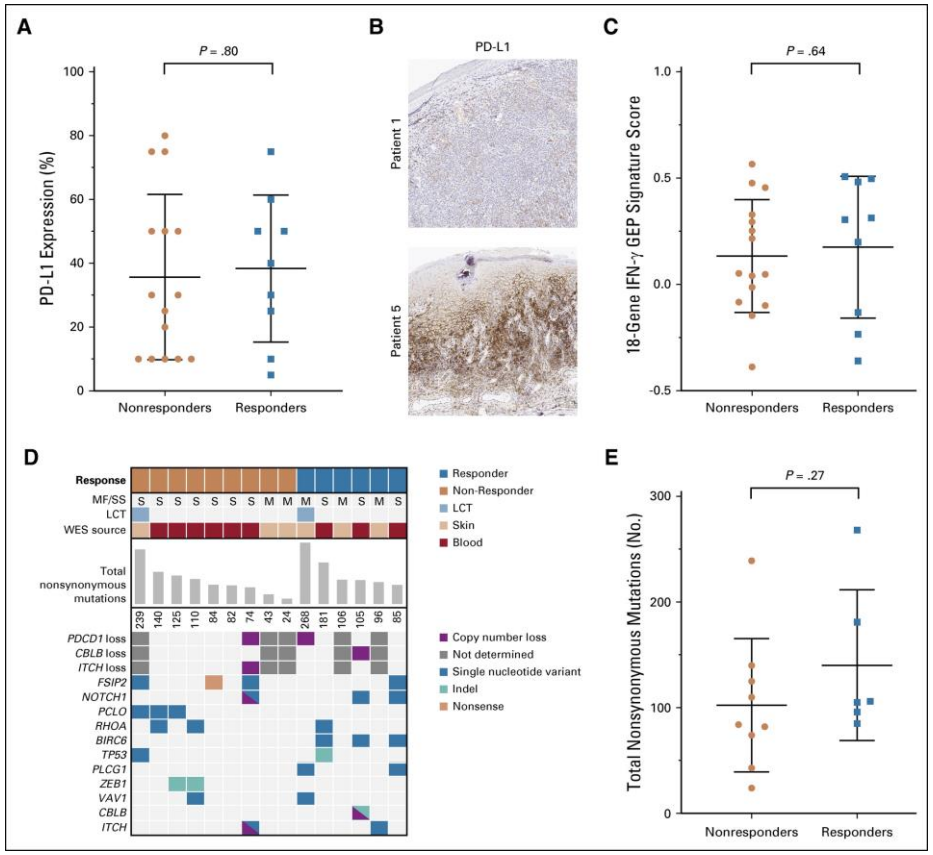




- Median time of response follow-up: 58 weeks.
- Median DOR was not reached
- Only 1 of 8 responding patient subsequently lost response (discontinued treatment b/o pneumonitis 8 weeks before subsequent progression).

Khodadoust MS, et al. *JCO.* 2020; 38(1): 20-8

# CITN-10: Potential Response Biomarkers

## Exploratory biomarkers of response



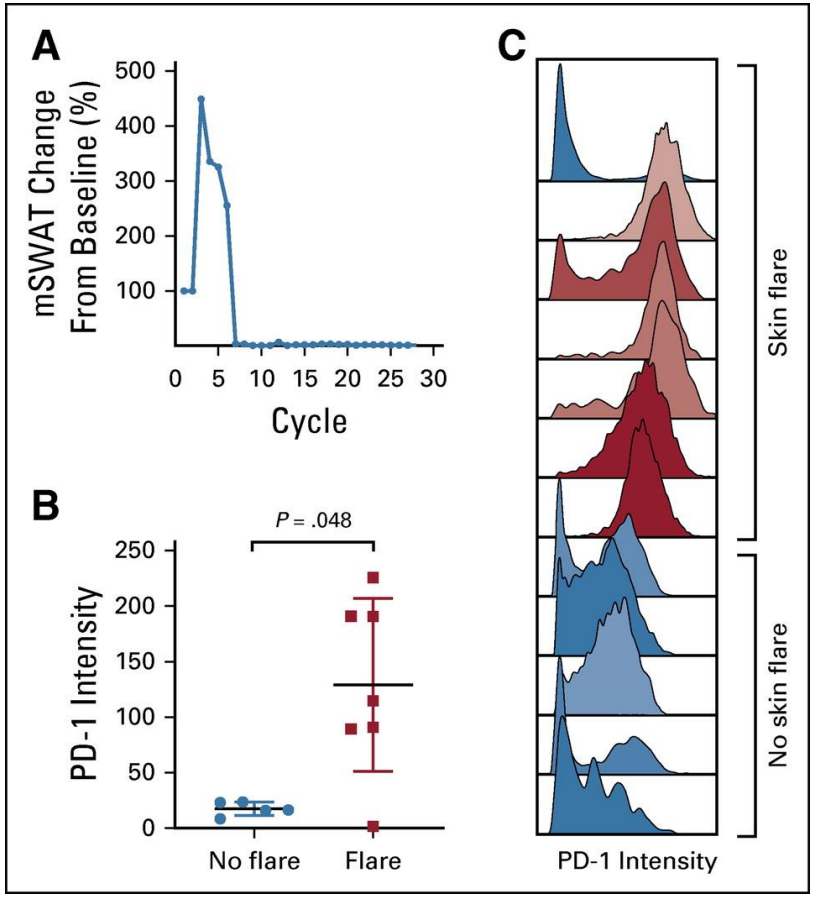

No biomarker (**PD-L1 expression, INF γ–related signature, immune cell population (mass cytometry), mutations (WES), or TMB**) was associated with response.

No participant had translocations of PD-L1 or PD-L2.

One patient with a CBLB deletion (CBLB is required for PD-1-mediated T-cell inhibition) achieved an ongoing CR.

**Skin flare reaction** a/w high expression of PD-1 on circulating Sézary cells pre-Rx therapy (7-fold higher).

## Mass cytometry profiling of PBMCs




Khodadoust MS, et al. *JCO.* 2020; 38(1): 20-8

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# PD-L1 SV May Predict Response to anti-PD1 Therapy

Genetic disruptions of the PD1/PD-L1 pathway exists in CTCL.

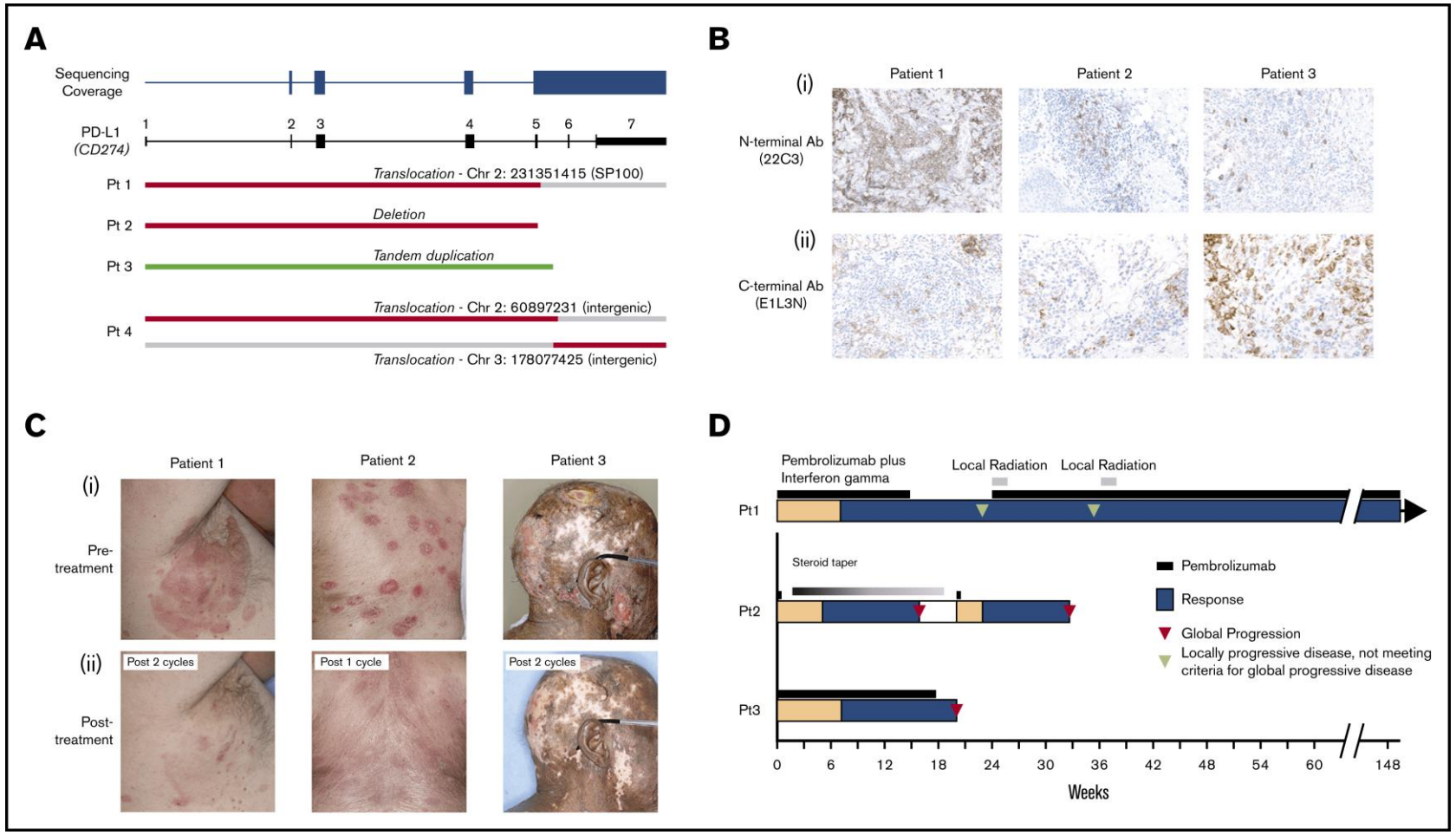
Among these events are **structural variants (SVs)** involving ***CD274*** encoding PD-L1, incl. **recurrent alterations causing disruption of the 3′ untranslated region (UTR) of PD ligands**, which interferes with the binding site for downregulatory microRNAs and consequently **enhances PD-L1 protein expression.**

**Targeted NGS** panel to identify PD-L1 SVs **in n=69** patients with MF/SS **identified 4 patients with PD-L1 SV.**

**Response to pembrolizumab-based therapy:**

- N=3 with CTCL and PD-L1 SVs treated with pembrolizumab (n=1 not treated with pembro-based Rx).
- All 3 patients treated with pembrolizumab experienced rapid clinical responses.
- All patients had a h/o LCT.

PD-L1 SVs may identify CTCL patients susceptible to anti–PD-1–based immunotherapy




Beygi S, et al. *Blood Advances.* 2021; 5(3): 771-4

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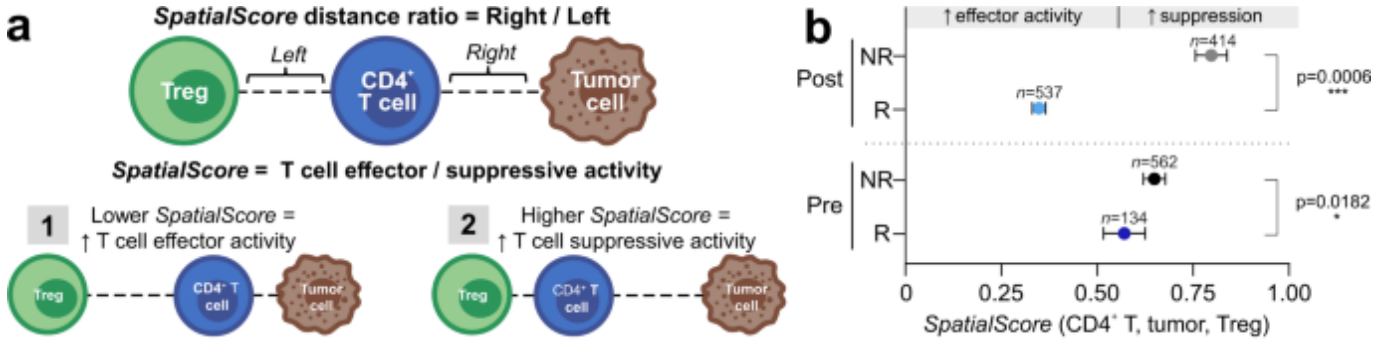
# Immune Cell Topography predicts response to PD-L1i in CTCL

CO-Detection by indEXing (**CODEX**) multiplexed tissue imaging with transcriptomic analysis using RNA-seq reveals topographical differences in effector PD-1⁺CD4⁺ T cells, tumor cells, and immunosuppressive Tregs.

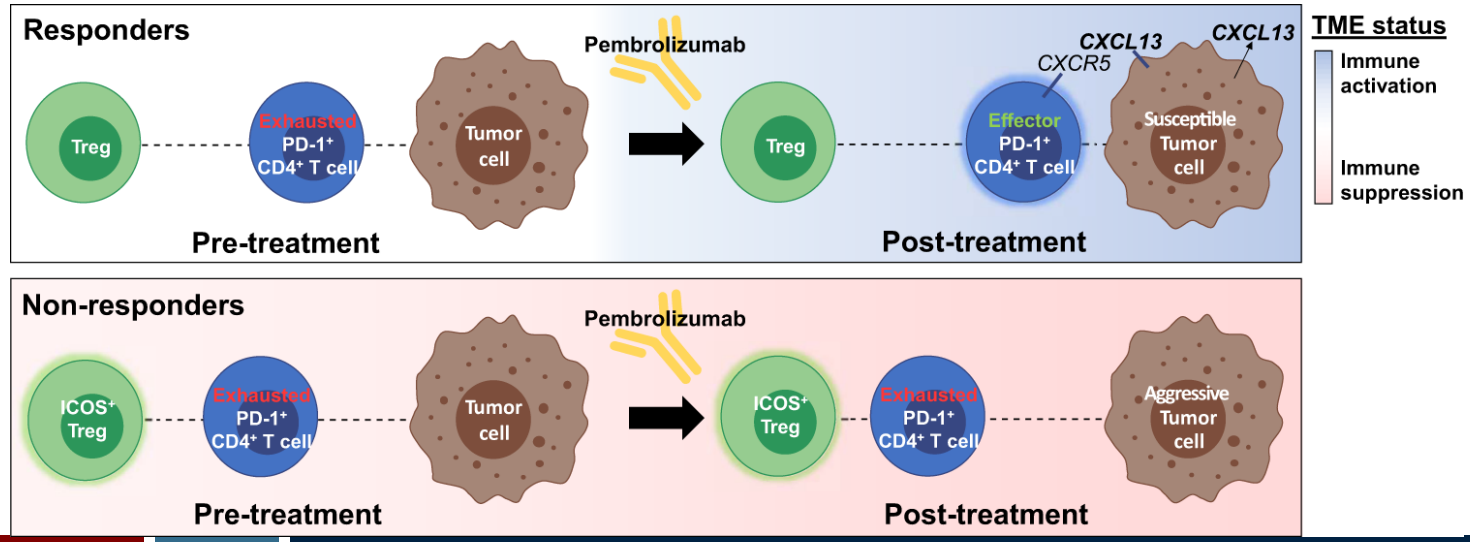
***SpatialScore***:
Ratio of the physical distance between each CD4⁺ T cell & its nearest tumor cell relative to its nearest Treg .

Spatial biomarker that correlates strongly with pembrolizumab response Can be recapitulated using a clinically accessible multiplexed IHC (mIHC) platform.

**The SpatialScore**




**PD-1 blockade, T cell effector activity is restored in responders.**
**Nonresponders have a continually exhausted T cell phenotype.**



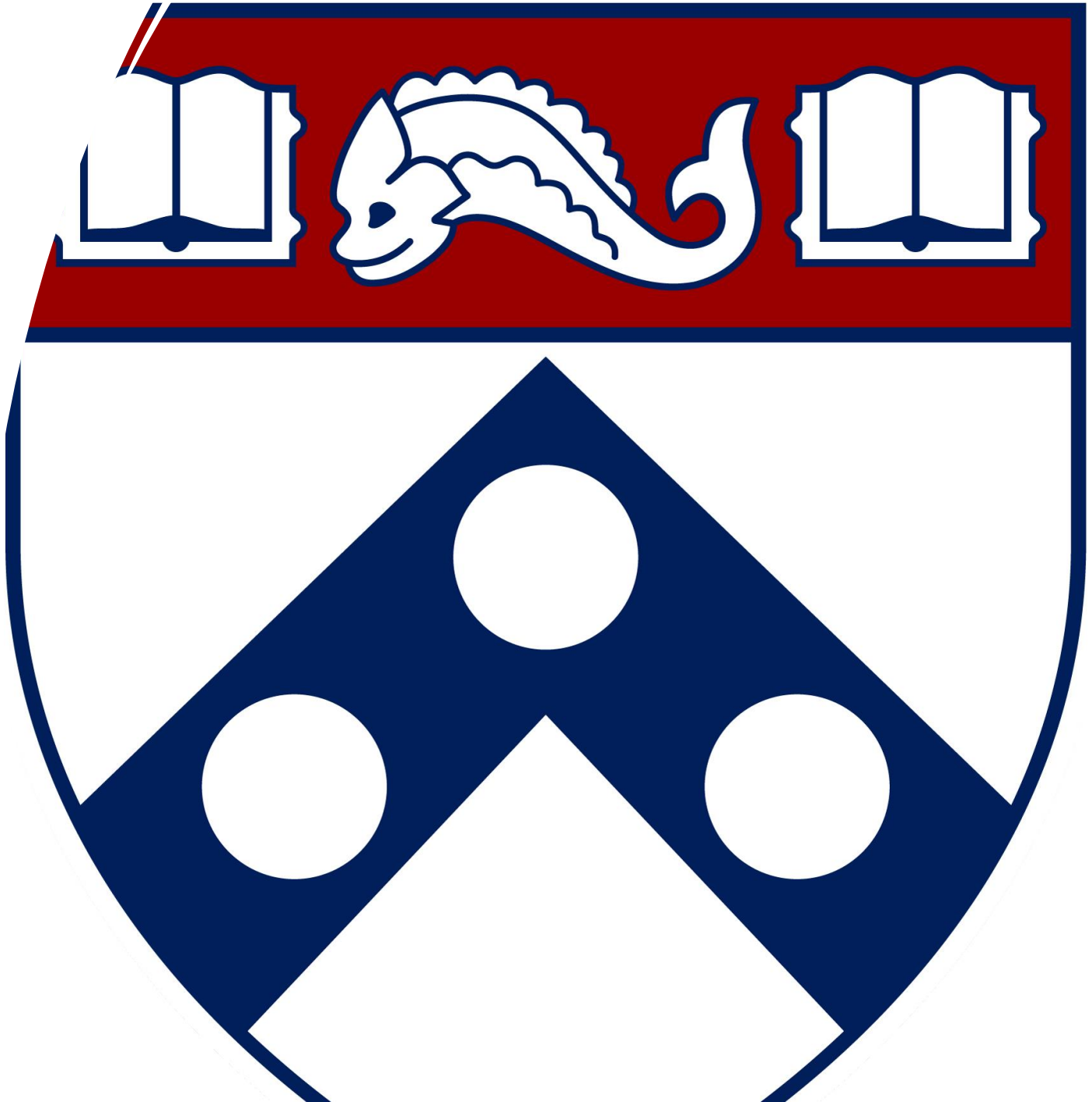

⇧ **CXCL13** expression **is predictive of a lower SpatialScore** & improved clinical outcomes seen in CTCL.

**CXCL13** may help **localize effector PD-1⁺ CD4⁺ T cells** within the TME by **attracting CXCR5⁺ CD4⁺ T cells** to the tumor site.

Phillips D, et al. *Nature Communications* 2021; 12(1):6726

# Summary and Conclusions

- Pembrolizumab has moderate single agent activity in PTCL and CTCL.
- Concerns for hyperprogression, particularly in PTCL.
- No universal definitive biomarkers for response or hyperprogression (unclear mechanism) have been identified. However, PD-L1 structural variants and *TME topography (i.e. SpatialScore)* may predict response.
- Acquired resistance mechanism remain unknown.
- While in CTCL responses can be durable, combinatorial therapies (e.g. HDACi, PI3Ki, radiation) particularly in PTCL may prolong responses and abate hyperprogression.

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