Cutaneous toxicities to oncologic therapies and Interpretation of PD-L1 Immunohistochemistry

Michael T. Tetzlaff MD, PhD
Associate Professor
Departments of Pathology, Section of Dermatopathology and Translational and Molecular Pathology
The University of Texas MD Anderson Cancer Center
Executive Officer
Translational Research Program
The Alliance for Clinical Trials

Commonly encountered cutaneous reactions to targeted therapy and immune checkpoint blockade

Michael T. Tetzlaff MD, PhD
Associate Professor
Departments of Pathology, Section of Dermatopathology and Translational and Molecular Pathology
The University of Texas MD Anderson Cancer Center
Executive Officer
Translational Research Program
The Alliance for Clinical Trials

Significance of cutaneous toxicities to oncologic therapies

- Skin often exhibits toxicity early in the course of therapy and is accessible.
- Indicator of response to therapy
  - Response to EGFR inhibitor therapy correlates with development and severity of skin rash
  - Response to immune checkpoint blockade correlates with pigmented alteration
- Mimicker of disease recurrence
  - Panniculitis can mimic disease recurrence
  - May require alteration of therapy
    - Bullous pemphigoid in immune checkpoint blockade
  - May require further procedure
    - SCC in the context of RAF inhibitors

Common specific cutaneous toxicities to oncologic therapies

- Anti-EGFR inhibitors
  - Papulopustular eruption

- RAF inhibitor therapy
  - Squamous neoplasia
  - Panniculitis

- Immune checkpoint blockade (α-CTLA4 and α-PD-1/α-PD-L1)
  - Lichenoid dermatitis
  - Bullous pemphigoid reaction
  - Granulomatous infiltrates
Cutaneous toxicity to EGFR-inhibitor

- EGFR is a transmembrane protein that transmits mitogenic signals via intracellular tyrosine kinase domain

- Anti-EGFR inhibitors
  - Monoclonal antibodies to EGFR: cetuximab, panitumumab
  - Small molecular inhibitor: erlotinib, gefitinib
  - Dual kinase inhibitors: lapatinib, neratinib, afatinib

- EGFR expressed in skin and skin adnexal structures

- Most common reactions to EGFR inhibitors
  - Papulopustular eruption
  - Xerosis
  - Changes in hair and nails
  - Mucositis

Papulopustular eruption to EGFR-inhibitor

- Reported in up to 90% of patients on EGFRi
  - Most develop within 1-2 weeks of initiating therapy
  - Dose dependent
  - More severe with monoclonal antibodies than small molecular inhibitors
  - Severity of rash correlated with response to therapy
    - Marker of therapeutic efficacy

- Follicular papules/pustules on T-zone of face or seborrheic areas, scalp, and upper trunk

Image courtesy of Dr. Jon Curry MD
Cutaneous reaction to EGFR-inhibitor therapy
A marker of therapeutic efficacy

Determinants of Tumor Response and Survival With Erlotinib in Patients With Non–Small-Cell Lung Cancer

Table 6: Univariate and multivariate analysis of tumor response to erlotinib.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;70</td>
<td>0.48</td>
<td>0.46</td>
</tr>
<tr>
<td>ECOG performance status 3, 4</td>
<td>0.69</td>
<td>0.68</td>
</tr>
<tr>
<td>No. of positive lymph nodes</td>
<td>0.26</td>
<td>0.26</td>
</tr>
<tr>
<td>No. of poor chemotherapy agents, 1 or 2</td>
<td>0.27</td>
<td>0.27</td>
</tr>
<tr>
<td>Time since initial diagnosis, &lt; vs vs ≥1 year</td>
<td>0.64</td>
<td>0.64</td>
</tr>
</tbody>
</table>

Other changes due to EGFR-inhibitor

- **Paronychia**
  - 20% of treated patients
  - Involvement of thumbs and big toes, predominant
  - Develops after 4-8 weeks of treatment
- **Alopecia**
  - Seen in 5% of treated patients
  - Late toxicity, occurs months after EGFRi therapy
  - Non-scarring or scarring alopecia
- **Hand and foot skin reaction (HFSR)**
  - Common with class II EGFRi therapy and with multi-kinase inhibitors (e.g. sorafenib)
  - Skin fissures
  - Trichomegaly
  - Xerosis

Cutaneous epithelial proliferations with BRAFi

- Activating somatic mutations in **BRAF** occur in ~50-60% of primary cutaneous melanoma
- BRAF activation triggers MAPK signaling via phosphorylation of downstream targets
- **BRAF inhibitors (BRAFi)** target activated **BRAF**
  - First generation: TKIs (e.g. sorafenib)
  - Second generation: vemurafenib, dabrafenib
- Most common toxicity of BRAFi monotherapy is a cutaneous epithelial proliferation
  - Approximately 50-75% of patients develop.
  - Develop within few to several months after therapy
  - Range: 4-14 months (mean=8.6 months)

Image courtesy of Dr. Jon Curry MD
Cutaneous epithelial proliferations with BRAFi

- Keratosis pilaris
- Seborrheic keratosis
- Actinic keratosis
- Verruca vulgaris (verrucous keratosis)
- Keratoacanthoma
- Squamous cell carcinoma

Mechanism of cutaneous epithelial proliferation in BRAFi

- Sequenced 33 cancer associated genes from 237 KA/SCCs
  - 19 BRAFi
  - 53 Immunosuppressed
  - 165 ‘spontaneous’

- Mutations in 38/237 cases

- BRAFi-associated tumors were enriched for activating mutations in HRAS
- Paradoxical activation of wild type BRAF by BRAFi thought to ‘unmask’ pre-existing RAS-primed oncogenic keratinocytes

55 yo woman with BRAFV600E mutant melanoma treated with surgery, radiation and interleukin-2 was enrolled on a BRAFi (dabrafenib) trial.

After 2 months of therapy, she developed multiple indurated tender subcutaneous nodules on the anterior thighs and arms.
BRAFi associated panniculitis

- Rare but important complication of BRAFi
- Median age: 43.5 years
- 32F:10M
- Median days on BRAFi= 36 (range: 3 days - 16 months)
- Included vemurafenib and dabrafenib (+/- trametinib)

BRAFi associated panniculitis

Panniculitis With Arthralgia in Patients With Melanoma Treated With Selective BRAF Inhibitors and Its Management

Vemurafenib-induced neutrophilic panniculitis
- Rare but important complication of BRAFi
- 40+ patients reported in the literature since 2012
- Median age: 43.5 years
- 32F:10M
- Median days on BRAFi= 36 (range: 3 days - 16 months)
- Included vemurafenib and dabrafenib (+/- trametinib)

Immune checkpoint blockade in cutaneous malignancy

Puts a brake... on a natural brake

Immune checkpoints are natural brakes on the immune system:
- CTLA4 binds B7
- PD-L1 binds PD-1

Engagement of PD-L1 with its ligand PD-1:
- Inhibitory signals
- Reduced T-cell proliferation
- Reduced T-cell activity

Immune checkpoint antibody blockade relieves inhibitory signals, allowing continued propagation of the immune system against tumor antigens.
Immune checkpoint blockade in cutaneous oncology

- **Ipilimumab (α-CTLA-4)**
  - Approved by FDA in 2011
- **Nivolumab and Pembrolizumab (α-PD-1)**
  - Approved by FDA in 2014
- **Avelumab (α-PD-L1)**

Cutaneous toxicity to immune checkpoint blockade

- Skin toxicity of any type and any grade
  - ~ 50-70% in patients receiving anti-CTLA-4
  - ~ 20-30% in patients receiving anti-PD-1/PD-L1
- Specific types of skin toxicity are being recognized with these antibody therapies
  - Inflammatory, immunobullous, panniculitis and regressing nevi
- Important to recognize these occur as they can potentially mimic disease recurrence or cause interruption in therapy

Cutaneous toxicity in immune checkpoint blockade: eczema, lichenoid, vitiligo

Cutaneous adverse events (AEs) of anti-programmed cell death (PD-1) therapy in patients with metastatic melanoma: A single-institutional cohort

<table>
<thead>
<tr>
<th>Lichenoid</th>
<th>Eczema</th>
<th>Vitiligo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occurrence</td>
<td>% of patients</td>
<td></td>
</tr>
<tr>
<td>Acne, comedones</td>
<td>25 (11.6%)</td>
<td></td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>2 (0.9%)</td>
<td></td>
</tr>
<tr>
<td>Eczema</td>
<td>14 (6.5%)</td>
<td></td>
</tr>
<tr>
<td>Seborrheic dermatitis</td>
<td>3 (1.4%)</td>
<td></td>
</tr>
<tr>
<td>Panniculitis</td>
<td>8 (3.7%)</td>
<td></td>
</tr>
<tr>
<td>Immunobullous</td>
<td>16 (7.4%)</td>
<td></td>
</tr>
<tr>
<td>Erythematous rash</td>
<td>5 (2.3%)</td>
<td></td>
</tr>
<tr>
<td>Pityriasis</td>
<td>3 (1.4%)</td>
<td></td>
</tr>
<tr>
<td>Urticaria</td>
<td>2 (0.9%)</td>
<td></td>
</tr>
<tr>
<td>Seborrheic keratosis</td>
<td>7 (3.2%)</td>
<td></td>
</tr>
<tr>
<td>Erythematous plaques</td>
<td>3 (1.4%)</td>
<td></td>
</tr>
<tr>
<td>Nodules</td>
<td>42 (19.2%)</td>
<td></td>
</tr>
<tr>
<td>Acneiform</td>
<td>2 (0.9%)</td>
<td></td>
</tr>
<tr>
<td>Seborrheic keratosis</td>
<td>2 (0.9%)</td>
<td></td>
</tr>
<tr>
<td>Pityriasis</td>
<td>3 (1.4%)</td>
<td></td>
</tr>
<tr>
<td>Urticaria</td>
<td>2 (0.9%)</td>
<td></td>
</tr>
<tr>
<td>Seborrheic keratosis</td>
<td>7 (3.2%)</td>
<td></td>
</tr>
<tr>
<td>Erythematous plaques</td>
<td>3 (1.4%)</td>
<td></td>
</tr>
<tr>
<td>Nodules</td>
<td>42 (19.2%)</td>
<td></td>
</tr>
</tbody>
</table>

Cutaneous toxicities to PD-1 blockade more commonly biopsied

- Lichenoid
- Immunobullous (bullous pemphigoid)
- Panniculitis
65-year-old man with stage IV BRAF G466E melanoma
Discontinued ipilimumab (3 mg/kg) after 3 cycles due to therapy related neuropathy
Began pembrolizumab (2 mg/kg)
After one week, he developed erythematous papules which coalesced into plaques involving hands and legs and rapidly progressed to the trunk and bilateral extremities, without oral lesions.

Image courtesy of Susan Chon, MD.
55 yo woman with chemotherapy resistant ovarian serous carcinoma receiving Nivolumab.

After 3 cycles, she developed a widespread erythematous scaly and pruritic plaques on upper back, chest and neck.

Image courtesy of Auris Huen MD, PharmD.
63 yo man with recurrent metastatic SCC of the tongue receiving Nivolumab.

After 8 weeks, he presented with erythematous scaly plaques of the neck and chin with overlying tense vesicles rapidly progressing to involve the bilateral forearms shins and mid back.

Nivolumab was withheld and topical steroids were applied with lesional improvement.

After one missed dose, therapy was re-started.

New cutaneous bullae and oral erosions developed forcing cessation of Nivolumab and oral prednisone for complete resolution of lesions.
Immunobullous disease with PD-1 blockade

A total of 13 patients described:
- 9 Men: 4 Women
- Median age: 73 years (Range: 42-85y)
- Melanoma (n=8), Lung Adeno (n=2), SCC (n=2), Urothelial ca (n=1)
- Pembrolizumab (n=6), Nivolumab (n=6), Dirvalumab (n=1)
- Median time to diagnosis: 18 weeks (range: 6-84 weeks)
- Discontinuation of therapy: YES (n=5)

Direct Immunofluorescence (DIF) studies

Biopsy from patient’s peri-lesional skin
Add fluorescently labelled antibodies for α-complement (C3), α-IgG, α-IgA


Turcan I and Jonkman M.F. Cell Tissue Res. 2015. 360:545-569.

Immunobullous disease with PD-1 blockade

Bullous pemphigoid, an autoantibody-mediated disease, is a novel immune-related adverse event in patients treated with anti-programmed cell death 1 antibodies


Autoimmune Bullous Skin Disorders with Immune Checkpoint inhibitors targeting PD-1 and PD-L1

Arrows point to IgG, IgA, IgM, C3, and C4 in the tissue sections.
39 year old Caucasian woman with history of stage III melanoma metastatic to the right axillary lymph node with a \textit{BRAFV600E} mutation.

Enrolled in a clinical trial to receive ipilimumab and nivolumab in the neoadjuvant setting followed by surgical excision and single agent nivolumab.

Five months after surgery while on single agent nivolumab, she developed numerous painful subcutaneous nodules on her bilateral lower extremities, which progressively enlarged and were markedly $^{18}$F-FDG PET/CT avid.
Special stains (Gram/FITE/GMS) negative for bacterial (including acid-fast) and fungal organisms; cultures also negative.

Immunohistochemical studies with an anti-melanocytic cocktail (HMB45, anti-MART1 and anti-tyrosinase) and antibodies for S100 and Sox-10 negative for metastatic melanoma.

No immunohistochemical evidence to support a subcutaneous T-cell or NK cell lymphoma.

Further review of her chart:
- No recent history of or clinical evidence to suggest recent/ongoing infection.
- No history of (additional) recent changes in medication.
- No evidence of pulmonary symptoms or hilar lymphadenopathy.
- ACE levels within normal limits.
Granulomatous inflammatory infiltrate in skin/subcutis during immune checkpoint blockade: A rare but important mimicker of disease recurrence

- Various morphologic types of skin toxicity may occur to immune checkpoint therapy
- Early recognition skin toxicity will be critical for appropriate patient management
  - Mimickers of disease recurrence
  - Indicators of therapeutic response
  - Possible further intervention or alteration of regimen
PD-L1 in Dermatopathology

**Immune checkpoint blockade in dermatopathology and the relevance of PD-L1 immunohistochemical studies in daily practice**

Michael T. Tetzlaff MD, PhD

Associate Professor
Departments of Pathology, Section of Dermatopathology and Translational and Molecular Pathology
The University of Texas MD Anderson Cancer Center

Executive Officer
Translational Research Program
The Alliance for Clinical Trials

---

**PD-L1 Immunohistochemical studies in dermatopathology**

- Immune checkpoint blockade in cutaneous malignancy
  - Ipilimumab (CTLA-4 blockade) in melanoma
  - Nivolumab and Pembrolizumab (PD-1 blockade) in melanoma
  - Pembrolizumab (PD-1 blockade) and Avelumab (PD-L1 blockade) in Merkel cell carcinoma

- Mechanisms of PD-L1 expression in melanoma—understanding the patterns
  - Induced versus intrinsic

- Correlating PD-L1 expression with clinical response: WHAT TO REPORT?
  - In melanoma, it depends on the regimen to be used
    - In general, PD-L1 positivity correlates with response to single agent Nivolumab or Pembrolizumab, BUT LESS IMPORTANT FOR PD-1 MONOTHERAPY.
  - Lack of PD-L1 expression may indicate need for combination therapies

- How do we detect PD-L1 in practice? What are the challenges?
  - Different FDA-approved companion antibodies depending on the drug.
  - Are they comparable? Does it matter?

---

**PD-L1 Immunohistochemical studies: Case example**

- Dr. Pigment, local medical oncologist, phones you in the office.
  - “You signed out patient John Smith’s needle core biopsy specimen as melanoma to a lymph node.
  - I want to start him on immune checkpoint blockade therapy.
  - Can you run PD-L1 immunohistochemistry?”

- Things to consider:
  - How does PD-L1 stain in melanoma?
    - Is it membranous? Cytoplasmic? Are other cells positive?
  - Which PD-L1 antibody clone (22C3 vs 28-8) should you use?
    - Does it matter? Do the different clones stain tumors similarly?
  - What determines “PD-L1 positivity”? Are there cut-offs?
  - What are the pitfalls of interpretation?

---

**Nivolumab improves survival in patients with metastatic melanoma**

*Nivolumab in Previously Untreated Melanoma without BRAF Mutation*

- n=418 patients with metastatic melanoma
  - Previously untreated
  - No BRAF mutation

- Nivolumab 3 mg/kg/2 weeks
- Dacarbazine 3 weeks

---
Pembrolizumab improves survival in patients with metastatic melanoma

**Pembrolizumab versus Investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial**

- Pembrolizumab
- pembrolizumab
- Investigator choice
- chemotherapy

Determinants of response to PD-L1 blockade

**PD-L1 expression by tumor cells and density of tumor associated T-cell inflammatory infiltrate**

- Predictors of response to PD-1 monotherapy blockade (Pembro):
  - Higher tumor associated CD8+ T-cell infiltrate before and during therapy
  - Higher PD-L1 expression by tumor cells, although low PD-L1 does not exclude

How is PD-L1 expressed in melanoma?

**Tumor associated inflammatory cells drive expression**

How does the associated immune infiltrate drive PD-L1 expression in melanoma

- Tumors with more inflammation express higher levels of PD-L1
- Tumors expressing higher levels of PD-L1 also expressed more IFN-$\gamma$
Four patterns of PD-L1 expression in melanoma reflect distinct mechanisms of expression.

**Inducible** expression:
- IFNγ from T-cells
- Macrophage release of PD-L1

Regional expression + TILS:
- PD-L1 expression in melanoma cell

No expression + TILS:
- “Immune tolerance”

No expression – TILS:
- “Immune ignorance”
Drivers of PD-L1 expression in melanoma

Colocalization of Inflammatory Response with B7-H1 Expression in Human Melanocytic Lesions Supports an Adaptive Resistance Mechanism of Immune Escape

Drivers of PD-L1 expression in melanoma

Summary of patterns of PD-L1 expression

Inducible or endogenous expression on the membrane of tumor cells

Drivers of PD-L1 expression in melanoma

Four patterns of PD-L1 expression in melanoma reflect distinct mechanisms of expression

Regional expression

Absent expression

Diffuse expression

What are the pitfalls of PD-L1 IHC interpretation in melanoma?

Pitfalls of PD-L1 immunohistochemical studies in melanoma

Associated stromal/inflammatory cells also express PD-L1, particularly HISTIOCYTES
Melanin pigment can obscure or mimic PD-L1 positivity. Giemsa counterstain helps to distinguish melanin from DAB.

**Pitfalls of PD-L1 immunohistochemical studies in melanoma**

<table>
<thead>
<tr>
<th>Antibody clone</th>
<th>Target</th>
<th>Domain</th>
<th>Developer</th>
<th>Cutoff</th>
<th>Drug related</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>5H11</td>
<td>Intracellular</td>
<td>Lieping Chen's lab</td>
<td>≥5% membranous staining of tumor cells</td>
<td>ND (1,2)</td>
<td>Pembrolizumab</td>
<td>(39)</td>
</tr>
<tr>
<td>E1L3N</td>
<td>Intracellular</td>
<td>Cell Signaling Technology</td>
<td>≥5% membranous staining of tumor cells</td>
<td>ND (50)</td>
<td>Nivolumab</td>
<td>(1)</td>
</tr>
<tr>
<td>E1J2J</td>
<td>Extracellular</td>
<td>Cell Signaling Technology</td>
<td>ND</td>
<td>ND</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>3B3</td>
<td>Extracellular</td>
<td>Dako</td>
<td>≥25% membranous staining of tumor cells or immune cells that are either denser or closer to the tumor interface</td>
<td>Pembrolizumab</td>
<td>--</td>
<td>(7)</td>
</tr>
<tr>
<td>22C3</td>
<td>Extracellular</td>
<td>Dako</td>
<td>≥5% membranous staining of tumor cells or immune cells that are either denser or closer to the tumor interface</td>
<td>Pembrolizumab</td>
<td>--</td>
<td>(39)</td>
</tr>
<tr>
<td>SP142</td>
<td>Intracellular</td>
<td>Ventana</td>
<td>Sub-section assigned a score based on both tumor and immune cell PD-L1</td>
<td>Nivolumab</td>
<td>(95)</td>
<td></td>
</tr>
<tr>
<td>28-8</td>
<td>Extracellular</td>
<td>Ventana</td>
<td>≥5% membranous staining of tumor cells (minimum 100 cells evaluated)</td>
<td>Nivolumab</td>
<td>(39)</td>
<td></td>
</tr>
<tr>
<td>SP260</td>
<td>Extracellular</td>
<td>Ventana</td>
<td>≥2% Nonspecific staining of tumor cells</td>
<td>Durvalumab</td>
<td>(43)</td>
<td></td>
</tr>
</tbody>
</table>

*Table courtesy of Dr. Jaime Rodriguez*

**Another challenge: Different PD-L1 antibody clones validated in different trials with different α-PD-1 drugs**

Anti-PD-L1 occasionally highlights tumor nuclei. Unclear etiology. NOT POSITIVE.
Different PD-L1 clones validated in different trials with different α-PD-1 drugs with different cut-offs for 'positivity'.

NIVO: 28-8
>5% tumor cell cut-off

Pembro: 22C3
>1% tumor cell cut-off

Do the different PD-L1 clones have different operating characteristics?

Different PD-L1 clones: Do they make a difference?

90 cases of NSCLC with IHC performed for PD-L1 using four clones: 22C3, 28-8, SP142, and E1L3N scored by 13 pathologists to interrogate concordance among (1) assays and (2) pathologists.

Good assay concordance, but some important differences exist—particularly for SP142 clone.

High inter-pathologist concordance for tumor cell PD-L1, not stromal cell.

Different PD-L1 clones: Do they make a difference in melanoma?

N=34 melanomas assessed by IHC for PD-L1 using 5 different antibodies.

• Differences in relative % PD-L1+ tumor cells due to:
  • Heterogeneous PD-L1 display in
  • Geographically distinct regions of the tumor that varied even between nearby sections
  • Not due to differences among the antibodies in melanoma samples.

Overall high concordance among the different clones ($R^2=0.812-0.961$).
Different PD-L1 clones: Intensity or percentage of tumor cells positive?

- Most studies assess “% PD-L1 positive tumor cells”, but do not include a measurement of tumor cell intensity.
- Using an H-score (staining intensity) demonstrate a strong association between H-score and % PD-L1 positive tumor cells.
- Therefore, to the extent that H-score and % are not independent variables, there is not a strong rationale to measure both.

Does the source of the tissue make a difference? Primary versus metastasis and age of the specimen...

- 68 pre-treatment specimens from 41 patients with melanoma, NSCLC, RCC, CRC with IHC performed for PD-L1
  - PD-L1 expression by tumor cells correlated with clinical response
    - PD-L1 expression by TILS did NOT correlate with response
  - Detection of PD-L1 in tumor cells did not vary with specimen age or specimen size (needle core versus excisional biopsy)
  - Correlation between PD-L1 expression and clinical outcome not related to timing of the tissue acquisition.
  - For patients with multiple samples, ‘PD-L1 positivity’ in “any specimen” determined correlation with outcome.
  - There was significant inter- and intra-tumoral heterogeneity.

When PD-L1 expression levels really count

IPI-NIVO therapy has high toxicity.... but PD-L1 negative patients benefit most

- n=954 patients previously untreated patients with unresectable stage III or IV metastatic melanoma
- PD-L1 positive MM fare the same with single agent Nivo or comb Ipi/Nivo
- PD-L1 negative MM respond better to comb Ipi/Nivo versus single agent Nivo
- Grade 3 and 4 toxicities occurred: 44% Nivo, 56% Ipi, but in 69% Combination Ipi/Nivo
- Interpretation of PD-L1 IHC has important implications for combination Ipi/Nivo
  - Patients with “PD-L1 positive” melanomas respond similarly to Nivo as to Ipi/Nivo
When is PD-L1 'negative'? We struggle the most with designation of greater than or less than 1%.

Things to avoid:
1. The tumor is 'positive' or the tumor is 'negative'—GIVE % TUMOR CELLS
2. Not necessary to comment on % Stromal/Inflammatory cells positive.

PD-L1 Immunohistochemical studies: Case example

• Dr. Pigment, local medical oncologist, phones you in the office.
  • "You signed out patient John Smith's needle core biopsy specimen as melanoma to a lymph node.
  • I want to start him on immune checkpoint blockade therapy.
  • Can you run PD-L1 immunohistochemistry to determine if he qualifies?"

An immunohistochemical study performed at the request of the treating clinician with antibodies for PD-L1 (28-8 clone) highlights 15% of the tumor cells with membranous pattern.

PD-L1 Immunohistochemical studies: Case example

72 yo man with a history of invasive melanoma of the left scalp presents with an expanding left neck mass. Needle core biopsy shown. Requesting "PD-L1 immunohistochemistry."
An immunohistochemical study performed at the request of the treating clinician with antibodies for PD-L1 (28-8 clone) highlights >90% of the tumor cells with membranous pattern.

55 yo man with a history of invasive melanoma of the right calf presents with an expanding right inguinal lymph node mass. Needle core biopsy shown. Requesting "PD-L1 immunohistochemistry".
An immunohistochemical study performed at the request of the treating clinician with antibodies for PD-L1 (28-8 clone). Antibodies for PD-L1 do not highlight the tumor cells (<1%).

83 yo woman with melanoma of unknown primary with metastasis to the lung. Excisional biopsy shown. Requesting “PD-L1 immunohistochemistry”.

Case courtesy of Dr. Carlos A Torres-Cabala
An immunohistochemical study performed at the request of the treating clinician with antibodies for PD-L1 (28-8 clone). Antibodies for PD-L1 do not highlight the tumor cells (<1%).
Most common cutaneous toxicities to oncologic therapies

Differential diagnosis: Sub-epidermal bullous disease

- Porphyria Cutanea Tarda
- Acute graft versus host disease
- Burn related bulla
- Suction blister
- Erythema multiforme
- Lichen sclerosus
- Bullous drug eruption
- Bullous insect bite eruption

- Bullous Pemphigoid (BP)
- Cicatricial Pemphigoid
- Epidermolysis Bullosa Acquisita (EBA)
- Bullous Lupus Erythematosus
- Anti p200 pemphigoid
- Dermatitis Herpetiformis (DH)
- Linear IgA disease
Differential diagnosis: Sub-epidermal bullous disease

- Bullous Pemphigoid (BP)
- Cicatricial Pemphigoid
- Epidermolysis Bullosa Acquisita (EBA)
- Bullous Lupus Erythematosus
- Anti p200 pemphigoid
- Dermatitis Herpetiformis (DH)

Indirect Immunofluorescence studies: “SALT SPLIT” skin

1.0 M NaCl
Add patient serum
Add fluorescent α- IgG
Indirect Immunofluorescence studies: “SALT SPLIT” skin

1.0 M NaCl
Add patient serum
Add fluorescent α-IgG

BASAL
Keratinocytes
Hemidesmosomes
Lamina Lucida
Lamina Densa
Anchoring Filaments

BPAs1, Plicin
BPAG2, Alpha 6, Beta 4 Integrin
Salt-split Zone
Laminins 1-5, 6
Entactin/Nidogen
Collagen IV, Perlecain

An immunohistochemical study performed at the request of the treating clinician with antibodies for PD-L1 (22C3 clone) highlights 15% of the tumor cells with membranous pattern.

Immune checkpoint blockade in Merkel cell carcinoma

56% objective response rate to PD-1 inhibitor among stage IIIb or IV MCC patients who had not received prior systemic therapy—-independent of MCPyV status or relative expression of PD-L1 (Clone 22C3).

Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial

32% (28/88) patients with stage IV MCC who failed at least one prior systemic therapy achieved rapid and sustained response to PD-L1 inhibitor— independent of MCPyV status or relative expression of PD-L1 (Clone 73-10).