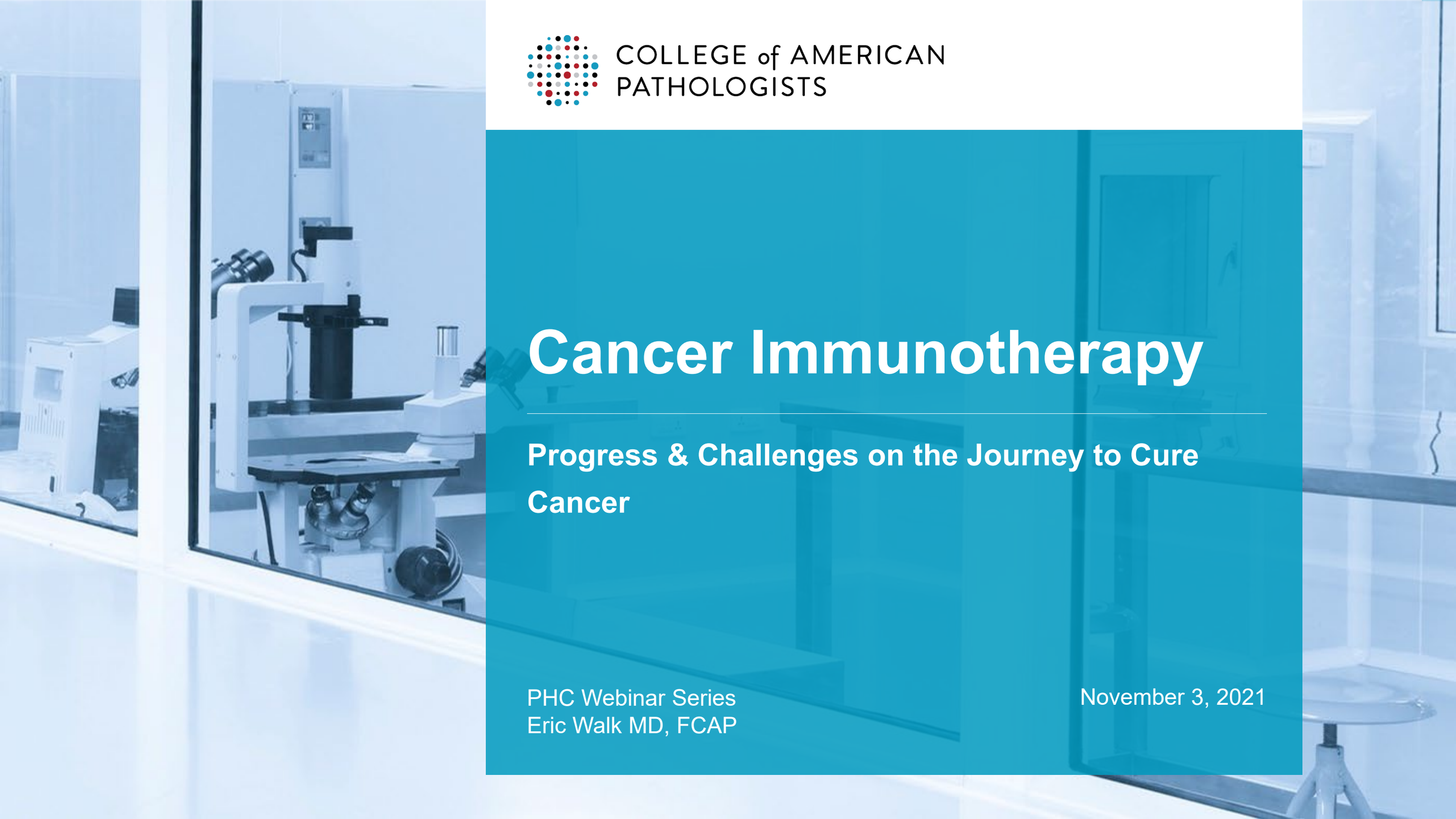

COLLEGE of AMERICAN PATHOLOGISTS

# Cancer Immunotherapy

## Progress & Challenges on the Journey to Cure Cancer

PHC Webinar Series
Eric Walk MD, FCAP

November 3, 2021

# Webinar Host

- This series is sponsored by the Personalized Healthcare Committee (PHC)
- Today's webinar host is Jinjuan Yao, MD, PhD, FCAP

# Housekeeping

- This presentation will be recorded. The recording and PDF will go out to all registrants in one week
- All lines are muted during the presentation
- Please send in your questions as you think of them via the “Question Box” in your control panel

# Eric Walk MD, FCAP

- Graduate of Johns Hopkins University and holds a MD degree from the University of Virginia School of Medicine.
- Board certified in Anatomic and Clinical Pathology and is a Fellow of the College of American Pathologists (CAP). He currently is a member of the CAP Personalized Healthcare Committee.
- Chief Medical Officer at PathAI in Boston, MA and head of the medical group, overseeing Medical Affairs, Regulatory Affairs, and Clinical Affairs. He has over 20 years of experience in precision medicine, oncology drug development and IVD companion diagnostics development.

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# Disclosures

- I am a full-time employee and equity owner of PathAI
- I am a shareholder of Roche

# Learning Objectives

1. Awareness of the latest cancer immunotherapy clinical data including FDA approvals/changes and combination therapy data.

2. Familiarity with current cancer immunotherapy biomarkers such as PD-L1, MMR/MSI and TMB, as well as emerging biomarkers and technologies such as the microbiome and machine learning.

3. Awareness of future cancer immunotherapy targets/compounds such as anti-TIGIT and anti-LAG3 including the latest clinical data and the predictive biomarkers being explored.

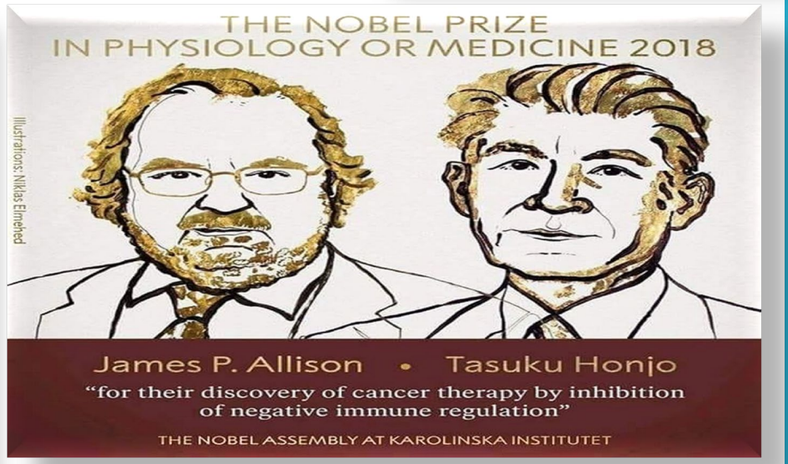
# Cancer Immunotherapy

## *A revolution in-progress*



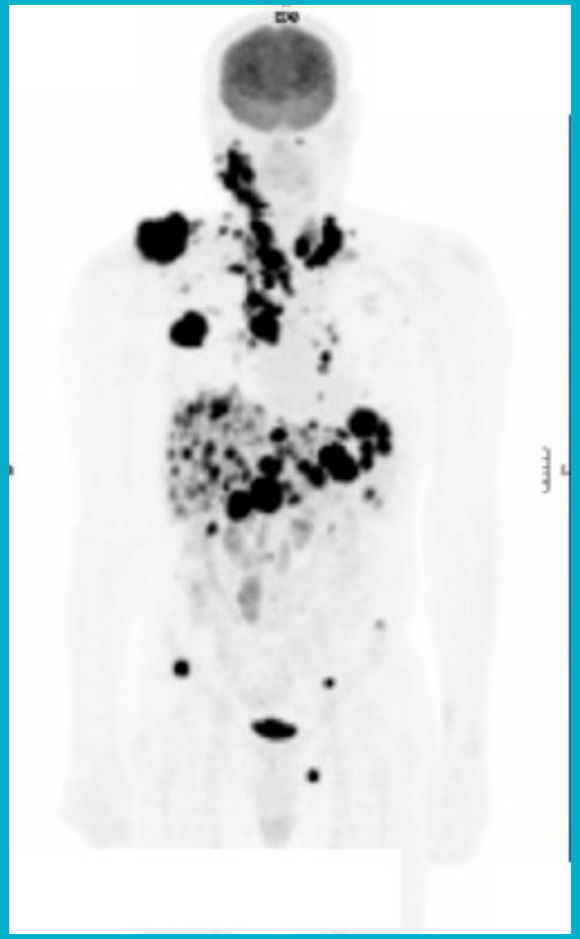


"[After immunotherapy] ... they didn't find any cancer at all."

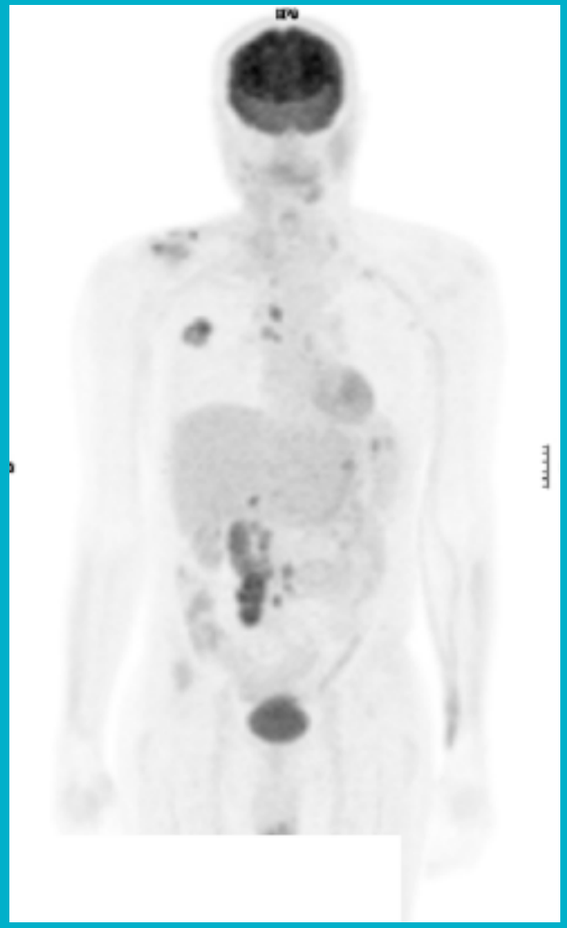


# Metastatic Melanoma Response to Ipilimumab

Before Ipilimumab
04/22/11



After Ipilimumab
08/05/11



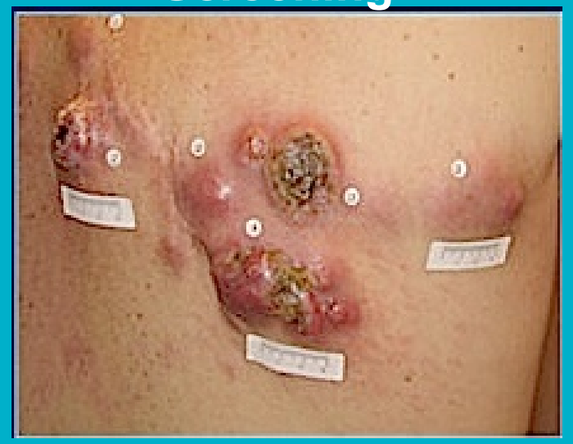
http://www.slideshare.net/roblyngold/community-oncology-clinical-debates-advanced-melanoma



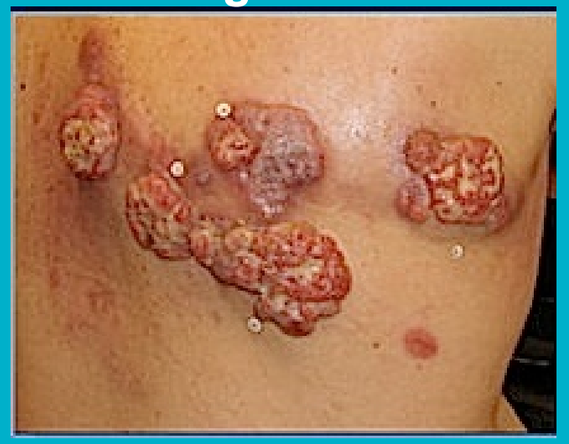
Case by Antoni Ribas, MD, PhD.

# Unique Kinetics of Response in Patients Treated With Ipilimumab

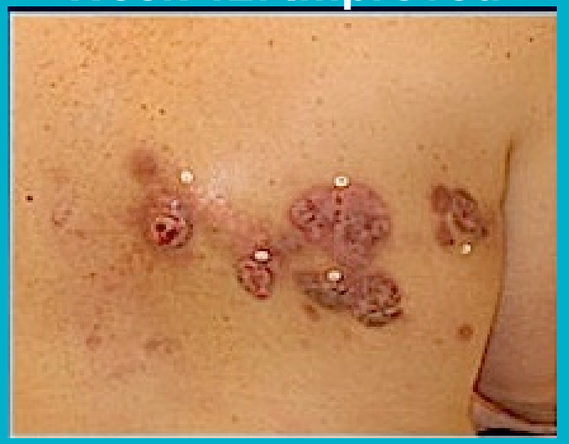
**Screening**



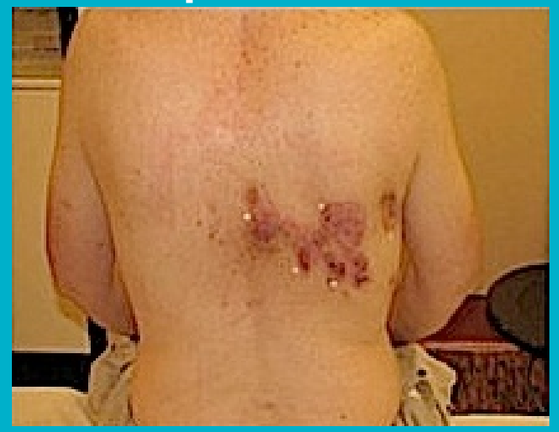
**Week 12: Swelling and Progression**



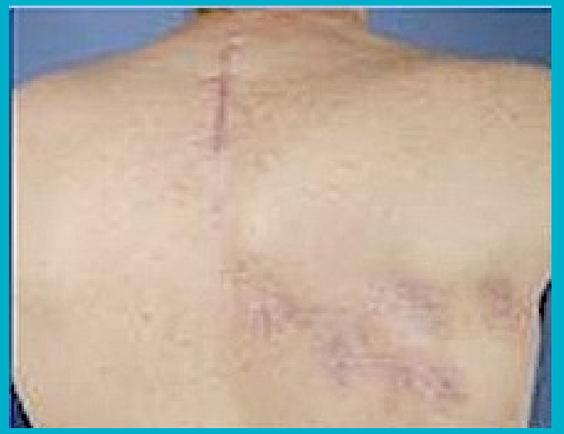
**Week 12: Improved**



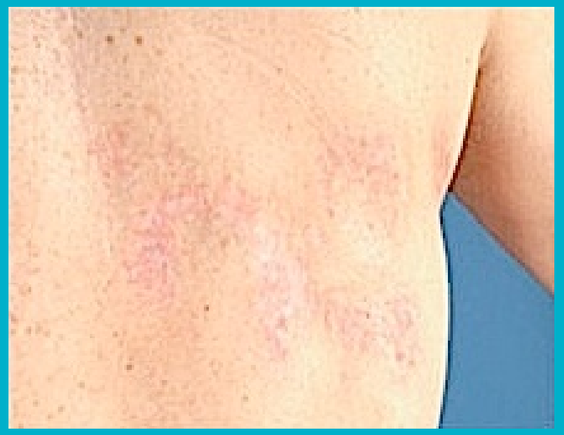
**Week 16: Continued Improvement**



**Week 72: Complete Remission**



**Week 108: Complete Remission**





Images courtesy of Jedd D. Wolchok, MD.

http://www.slideshare.net/roblyngold/community-oncology-clinical-debates-advanced-melanoma

# Cancer Immunotherapy Patient: Jeff and His Wife Linda

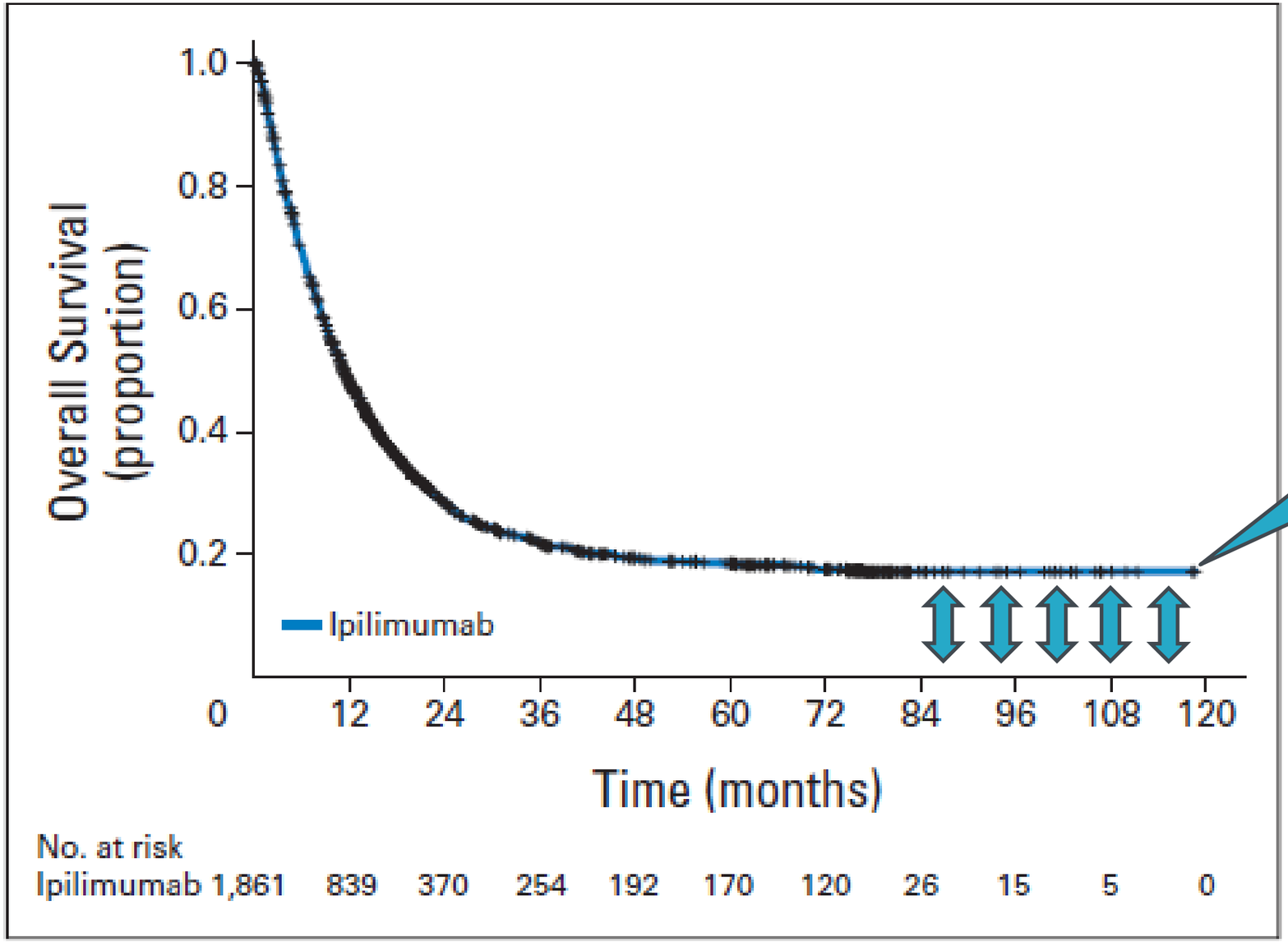
*Diffuse large B-cell lymphoma treated with CAR-T therapy*

**Jeff's Journey**

- 2012: dx w/ stage 4 DLBCL
- Tx: R-CHOP
- 2018: recurrence
- Tx: Kymriah CAR-T
- Complete metabolic response (FDG PET) in 5 days
- No detectable CD19 cells

# Ipilimumab Long-term Outcome Data in Metastatic Melanoma

*Durable overall survival benefit @ 10 years is unprecedented*






Schadendorf et al. JCO 2015

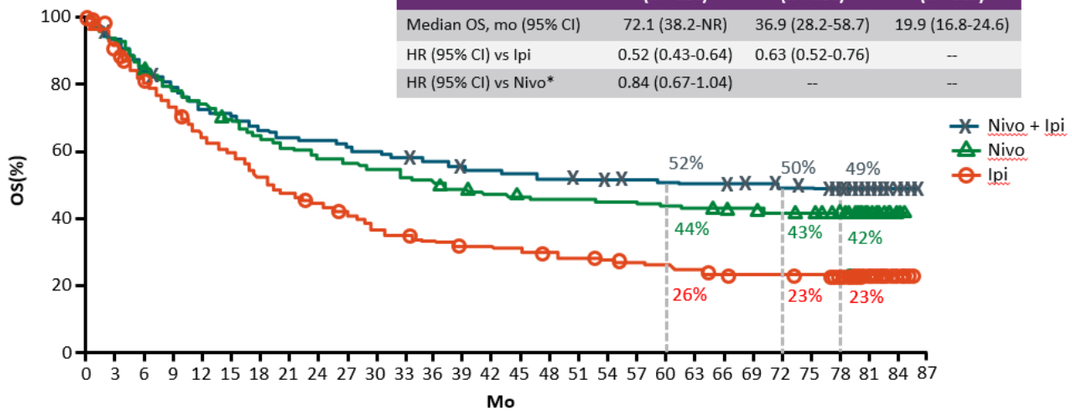
# Cancer Immunotherapy Long-term Outcome Data

*Nivolumab + Ipilimumab 6.5-year outcome data in 1L advanced melanoma*

*Pembrolizumab vs chemo 5-year outcome data in 1L NSCLC*

## CheckMate 067 6.5-Yr Follow-up: OS

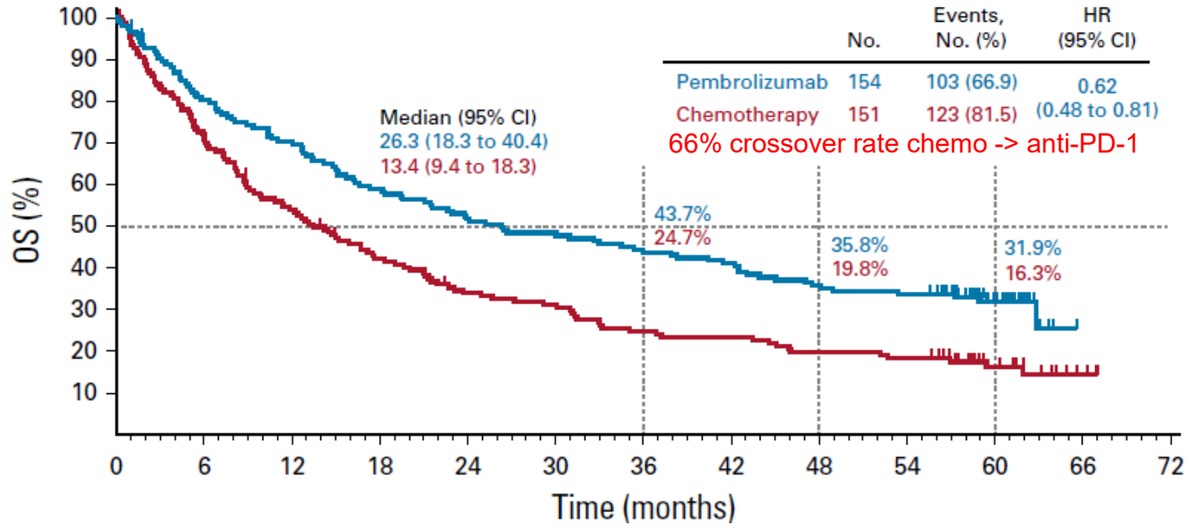
| | Nivo + Ipi (n = 314) | Nivo (n = 316) | Ipi (n = 315) |
|---|---|---|---|
| Median OS, mo (95% CI) | 72.1 (38.2-NR) | 36.9 (28.2-58.7) | 19.9 (16.8-24.6) |
| HR (95% CI) vs Ipi | 0.52 (0.43-0.64) | 0.63 (0.52-0.76) | -- |
| HR (95% CI) vs Nivo* | 0.84 (0.67-1.04) | -- | -- |




Wolchok. ASCO 2021. Abstr 9506

## Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non–Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50%

**Phase III KEYNOTE-024**



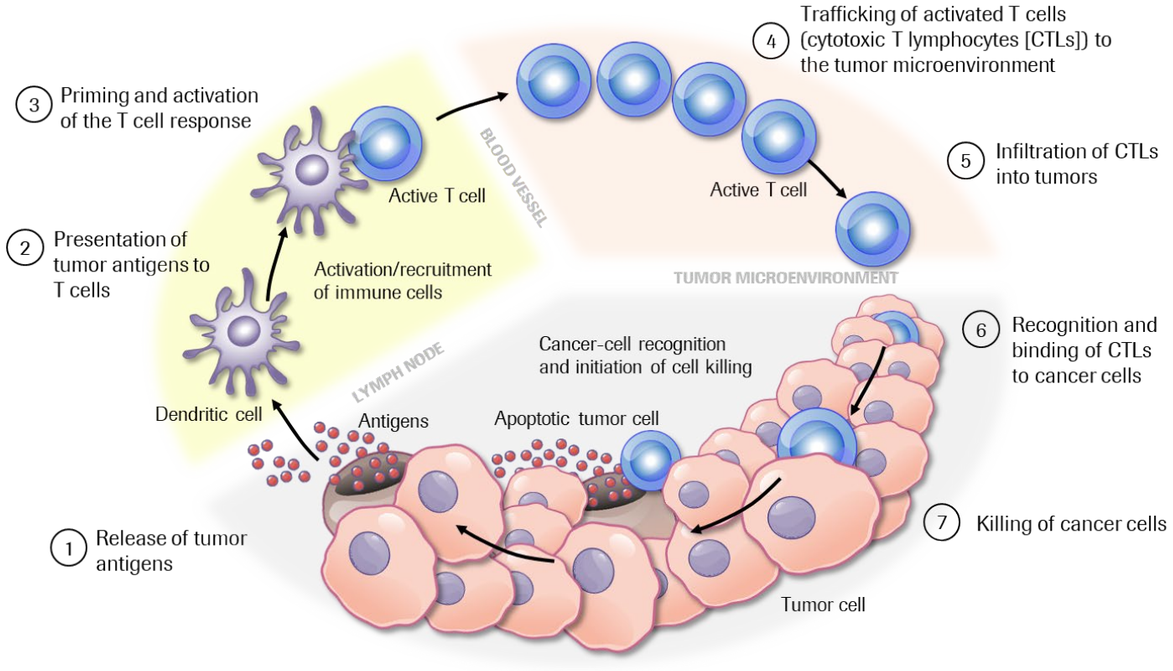

No. at risk:

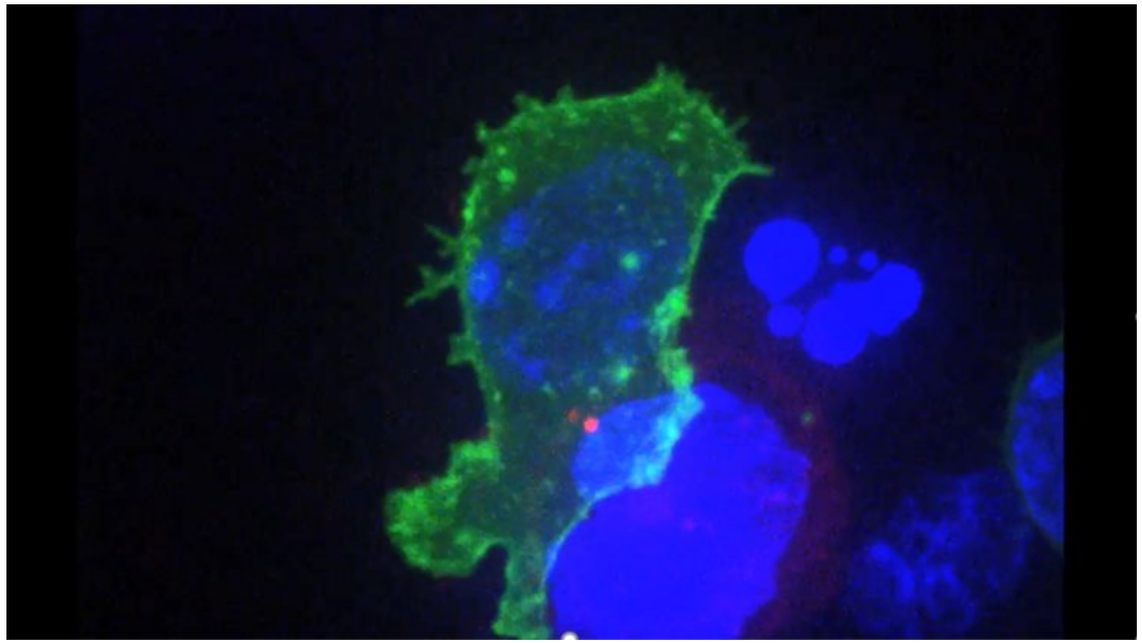
| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pembrolizumab | 154 | 121 | 106 | 89 | 78 | 73 | 66 | 62 | 54 | 51 | 20 | 0 | 0 |
| Chemotherapy | 151 | 108 | 80 | 61 | 48 | 44 | 35 | 33 | 28 | 26 | 13 | 3 | 0 |

Reck et al JCO 2021

# The Cancer Immunity Cycle

*Cytotoxic T-cell killing of cancer cells as the final common pathway*



CD8+ cytotoxic T-cell (green) killing a cancer cell (purple/blue)

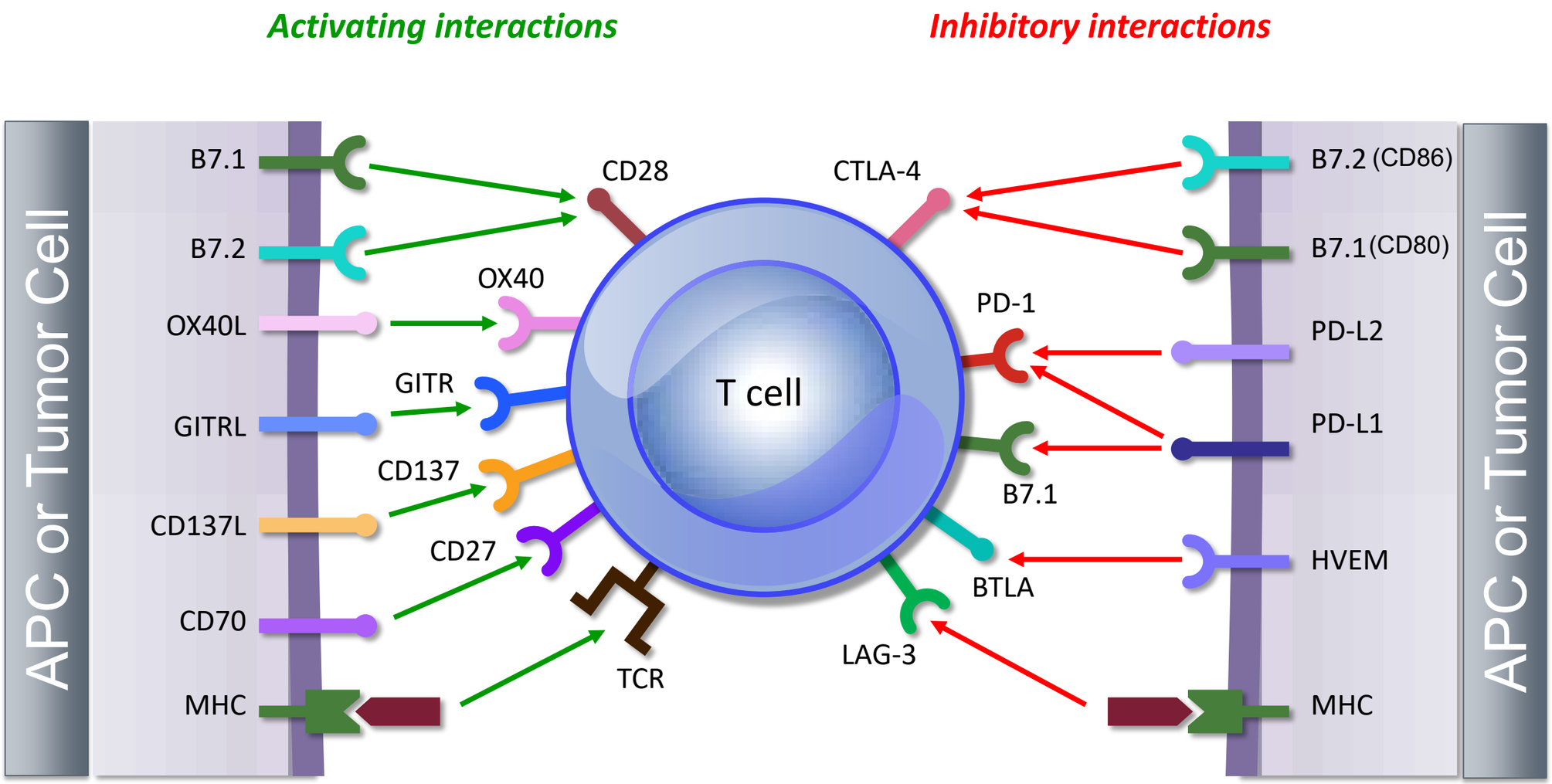


Chen DS, Mellman I. Immunity. 2013

Cambridge University – “Under the Microscope”

# Regulation of T-cell Activation via ‘Checkpoints’

*Balancing activating and inhibitory signals*



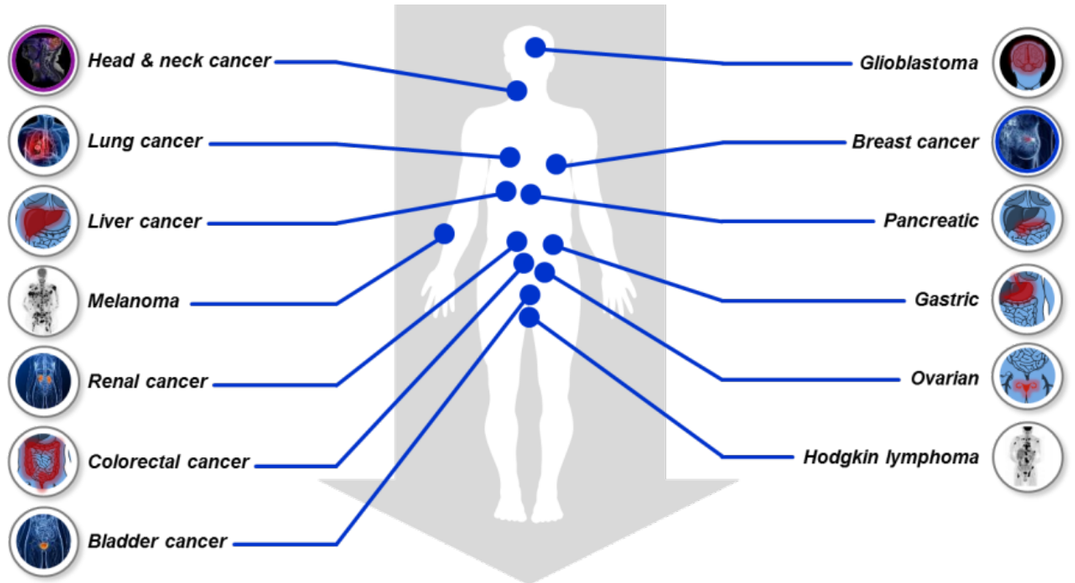



Pardoll. Nat Rev Cancer 2012

# Cancer Immunotherapy Clinical Activity

*Broad clinical activity across multiple cancer types*

| Cancer Type | FDA Approval |
|---|---|
| Melanoma | Yes |
| Lung cancer | Yes |
| Renal cell cancer | Yes |
| Bladder cancer | Yes |
| Head and neck cancer | Yes |
| Hodgkin lymphoma | Yes |
| Non-Hodgkin lymphoma | Yes |
| Merkel cell carcinoma | Yes |
| MSI/TMB-high solid tumors | Yes |
| Triple-negative breast cancer | Yes |
| Hepatocellular carcinoma | Yes |
| Gastric cancer | Yes |
| Colorectal cancer | Yes |
| Cervical cancer | Yes |
| Endometrial cancer | Yes |
| Esophageal cancer | Yes (3/23/2021) |






Walk et. al Arch Pathol Lab Med-Vol 144, June 2020

# Adjuvant Immune Oncology Approvals Bring Survival Benefits to Earlier Stages of Disease

October 15th, 2021


| Therapy | Indication | Line of therapy | Trial result | FDA approval | CDx |
|---|---|---|---|---|---|
| **Tecentriq (atezolizumab)** | **NSCLC stage II-IIIA** | **Adjuvant** | **HR=0.66 DFS in PD-L1≥1% (IMpower010 Ph3)** | **10/15/21** | **PD-L1 (SP263) IHC** |
| **Opdivo (nivolumab)** | **Urothelial ca resected high-risk** | **Adjuvant** | **HR=0.7 DFS (CheckMate-274 Ph3)** | **8/20/21** | **None** |
| **KEYTRUDA (pembrolizumab) + CT** | **Triple-negative breast cancer** | **Neo-adjuvant & adjuvant** | **HR=0.63 EFS pCR 63% vs. 56% (KEYNOTE-522 Ph3)** | **7/26/21** | **None** |
| **Opdivo (nivolumab)** | **Esophageal/GEJ cancer, resected** | **Adjuvant** | **HR=0.69 DFS (CheckMate-577 Ph3)** | **5/20/21** | **None** |
| KEYTRUDA (pembrolizumab) | Melanoma | Adjuvant | HR=0.57 RFS (KEYNOTE-054 Ph3) | 2/15/19 | None |
| Opdivo (nivolumab) | Melanoma w/LN involvement | Adjuvant | HR=0.65 RFS (CheckMate-238 Ph3) | 12/20/17 | None |



www.fda.gov/drugs/resources-information-approved-drugs

# Recent IO Accelerated Approval Withdrawals

## *Based on failure of confirmatory studies*

March 11, 2021

U.S. FOOD & DRUG ADMINISTRATION

### FDA In Brief: FDA Oncologic Drugs Advisory Committee to Review Status of Six Indications Granted Accelerated Approval

"**We are committed to ensuring the integrity of the accelerated approval program, which is designed to bring safe and effective drugs to patients with unmet medical needs as quickly as possible**. The program allows the FDA to approve a drug or biologic product intended to treat a serious or life-threatening condition based on an outcome that can be measured earlier than survival that demonstrates a meaningful advantage over available therapies. **However, when confirmatory trials do not confirm clinical benefit, a reevaluation must be performed to determine if the approval should be withdrawn**.

https://www.fda.gov/news-events/fda-brief/fda-brief-fda-oncologic-drugs-advisory-committee-review-status-six-indications-granted-accelerated

**Anti-PD-(L)1 drugs with accelerated US approvals and failed confirmatory trials**

| Drug (company) | Indication | Failed potentially confirmatory trial(s) | Regulatory outcome | Advanced potentially confirmatory trials remaining? |
|---|---|---|---|---|
| Keytruda (Merck & Co) | Urothelial bladder cancer (2L/1L) | Keynote-361 (1L) | US label narrowed 3 Jul 2018 | Keynote-676 (BCG combo in non-muscle invasive bladder cancer) |
| | Liver cancer (2L) | Keynote-240 (2L) | None | Keynote-394 (2nd-line Asian patients) |
| | Gastric/GEJ adenocarcinoma (3L) | Keynote-061 (2L) & 062 (1L, inconclusive) | None | Keynote-585 (neoadjuvant/adjuvant chemo combo) |
| | SCLC (3L) | Keynote-604 (1L) | Withdrawn 1 Mar 2021 | No |
| Tecentriq (Roche) | Urothelial bladder cancer (1L) | Imvigor-211 (2L) | US label narrowed 3 Jul 2018; withdrawn 8 Mar 2021 | Imvigor-130 final readout |
| | TNBC (1L) | Impassion-131 (1L) | US indication withdrawn 8/27/21 | Impassion-132 (note OS benefit in Impassion-130 not statistically tested) |
| Opdivo (BMS) | Liver cancer (2L) | Checkmate-459 (1L) | None | Checkmate-9DX (adjuvant) |
| | SCLC (3L) | Checkmate-331 (2L) & 451 (1L) | Withdrawn 29 Dec 2020 | No |
| Imfinzi (Astrazeneca) | Urothelial bladder cancer (2L) | Danube (1L, tremelimumab combo) | Withdrawn 22 Feb 2021 | Nile (tremelimumab combo) |

*Source: company information.*

https://www.evaluate.com/vantage/articles/news/policy-and-regulation/us-fda-gets-tough

# PD-L1 Expression and Response Rate to Checkpoint Inhibition

*Increased response rate vs. unselected patients across multiple cohorts*

| | **Nivolumab Solid Tumors** Topalian et al. NEJM 2012 | **Nivolumab Melanoma** Weber ASCO 2013 | **Nivolumab Melanoma** Grosso et al. ASCO 2013 | **MPDL3280A Solid Tumors** Herbst et al. ASCO 2013 | **MPDL3280A Melanoma** Hamid et al. ASCO 2013 | **MPDL3280A NSCLC** Sorial et al. ECC 2013 | **Pembrolizumab Melanoma** Daud et al. AACR 2014 | **Pembrolizumab NSCLC** Ghandi et al. AACR 2014 | **MPDL3280A Bladder** Powels et al. ASCO 2014 | **Pembrolizumab Head & Neck** Selwet et al. ASCO 2014 | **Pembrolizumab NSCLC** Ribas et al. ASCO 2014 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| N= | 42 | 44 | 34 | 94 | 30 | 53 | 113 | 129 | 64 | 55 | 411 |
| Response rates | | | | | | | | | | | |
| Unselected | 21% | 32% | 29% | 22% | 23% | 23% | 40% | 19% | 26% | 18% | 40% |
| | | | | | | | | | | | |
| PD-L1 + | 36% | 67% | 44% | 39% | 27% | 46% | 49% | 37% | 43% | 46% | 49% |
| PD-L1 - | 0% | 19% | 17% | 13% | 20% | 15% | 13% | 11% | 11% | 11% | 13% |



Adapted from Margaret Callahan, ASCO 2014

# FDA-approved PD-L1 Companion Diagnostic Assays

*Multiple antibody clones approved across indications*

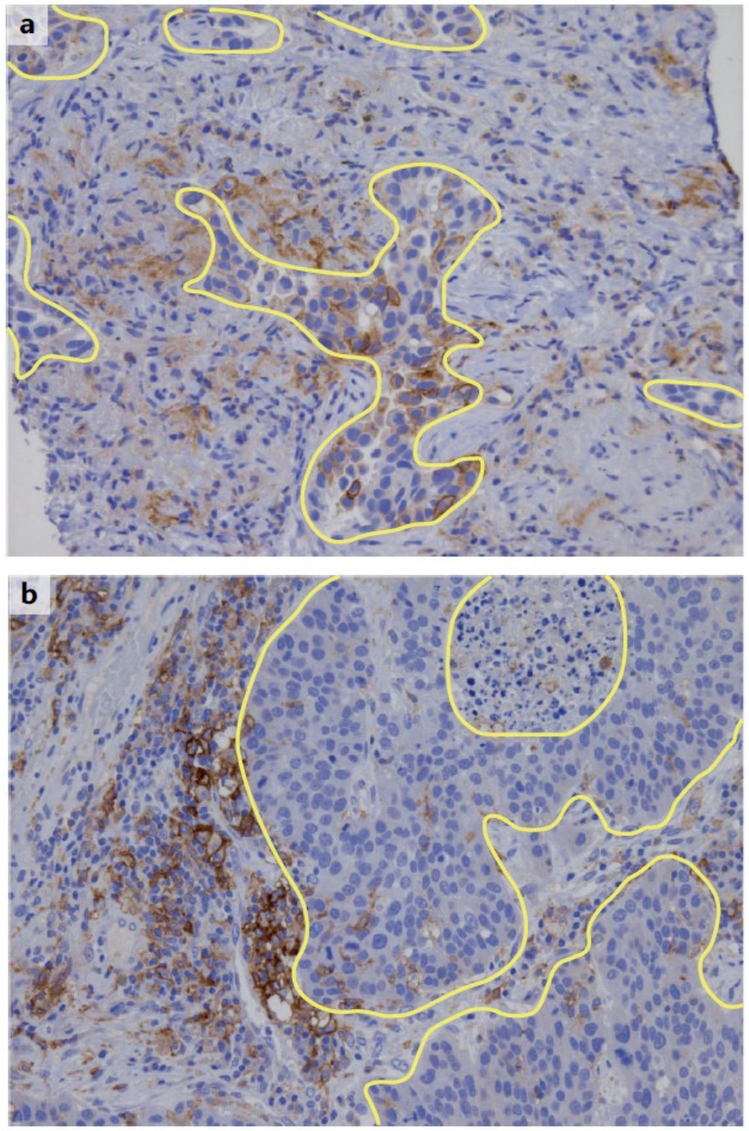
**TABLE 1.** Summary of US Food and Drug Administration–Approved PD-L1 Assays and Associated Scoring Algorithms

| Assay | Dako PD-L1 IHC 28-8 pharmDx Assay[51] | Dako PD-L1 IHC 22C3 pharmDx Assay[53] | Ventana PD-L1 (SP142) Assay[52] | Ventana PD-L1 (SP263) Assay[73] |
|---|---|---|---|---|
| For use with (drug) | Nivolumab ± ipilimumab (Bristol Myers Squibb) | Pembrolizumab (Merck) | Atezolizumab (Roche or Genentech) | Durvalumab (AstraZeneca) |
| Manufacturer | Dako[a] | Dako[a] | Ventana[b] | Ventana[b] |
| Approved PD-L1 scoring algorithm(s) | % TC | TPS,[c] CPS[d] | % IC, % TC, or % IC[e] | % TC or % IC[f] |
| Approval status and cutoffs | Companion<br>1L NSCLC: ≥ 1%[g]<br>Complementary<br>2L NSQ NSCLC: ≥ 1%, ≥ 5%, ≥ 10%<br>2L SCCHN: ≥ 1%<br>2L UC: ≥ 1% | Companion<br>1L or 2L NSCLC: TPS ≥ 1%<br>1L UC: CPS ≥ 10<br>3L+ gastric or GEJ: CPS ≥ 1<br>2L+ CC: CPS ≥ 1<br>2L+ ESCC: CPS ≥ 10<br>1L SCCHN: CPS ≥ 1<br>1L TNBC: CPS ≥ 10 | Companion<br>1L UC[h]: ≥ 5% IC<br>1L TNBC: ≥ 1% IC<br>1L NSCLC: ≥ 50% TC or ≥ 10% IC<br>Complementary<br>2L NSCLC: ≥ 50% TC or ≥ 10% IC | Complementary[i]<br>2L UC: ≥ 25% TC or ICP > 1% and IC+ ≥ 25% or ICP = 1% and IC+ = 100% |

**Prince et al. Analytical Concordance of PD-L1 Assays Utilizing Antibodies From FDA-Approved Diagnostics in Advanced Cancers: A Systematic Literature Review. JCO Precis Oncol 5:953-973.**

# PD-L1 Immunohistochemistry (IHC)

*Expression on both tumor and immune cells*




Doroshow et al. Nature Reviews Clinical Oncology 2021

$$\text{TPS (\%)} = \frac{\text{Number of PD-L1-stained tumour cells}}{\text{Total number of viable tumour cells}} \times 100\% \text{ (for 22C3 or SP263)}$$

$$\text{TC (\%)} = \frac{\text{Number of PD-L1-stained tumour cells}}{\text{Total number of viable tumour cells}} \times 100\% \text{ (for SP142)}$$

$$\text{IC (\%)} = \frac{\text{Area of tumour infiltrated by PD-L1-stained immune cells}}{\text{Total tumour area}} \times 100\% \text{ (for SP142)}$$

$$\text{CPS} = \frac{\text{Number of PD-L1-stained cells (tumour cells, lymphocytes and macrophages)}}{\text{Total number of viable tumour cells}} \times 100 \text{ (for 22C3)}$$

**TPS: Tumor Proportion Score, TC: Tumor Cells, IC: tumor-infiltrating Immune Cells; CPS: Combined Positive Score**

# Clinical Use of PD-L1 IHC Assays Has Become Very Complex

*40 different disease indications with various clone, scoring system, and cut-off combinations*

Last Updated Sept 2021

**PD-L1 (Immune Checkpoint Inhibitors) Ordering Guide**

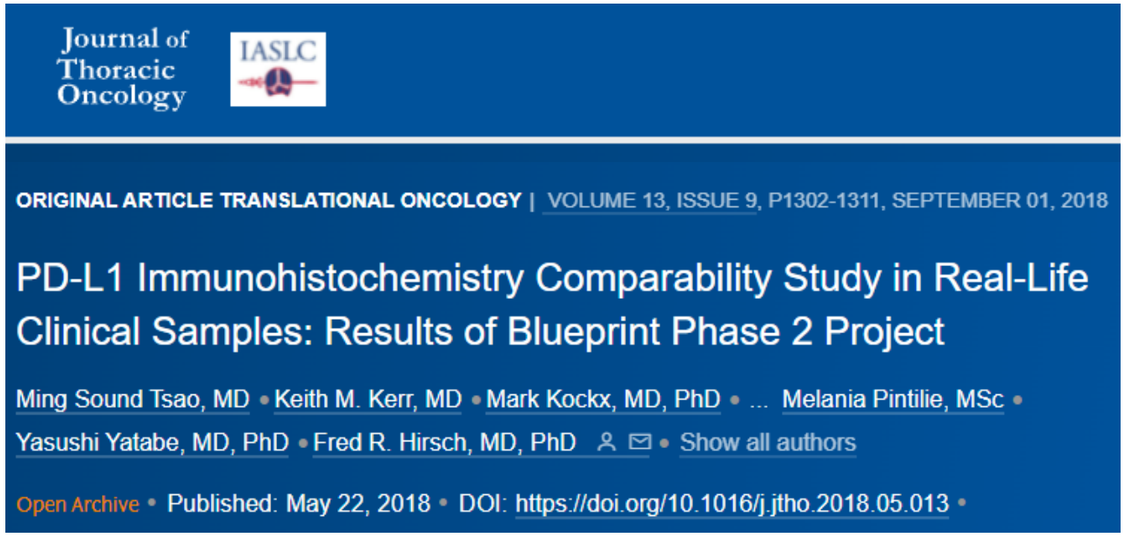
ACL Laboratories / Great Lakes Pathologists

Frank Zuehl, MD
franklin.zuehl@aah.org

| Drug and Tumor Types | ORDER THIS AB/TEST | Scoring system | Cut Off Values | Test Type | Treatment Settings | Studies |
|---|---|---|---|---|---|---|
| **Pembroluzimab (KEYTRUDA)** - PD-1 inhibitor | | | | | | |
| Non-Small Cell Lung Cancer (NSCLC) | 22C3 | TPS | >1% = Expression; >50% = High Expression * | Companion | Multiple * NO SCORE NEEDED WITH CARBOPLATIN OR PEMETREXED & PLATINUM - KEYNOTE-021 & 407 | KEYNOTE-010, 024, 042, 048, 189 |
| Esophageal Squamous Cell Carcinoma | 22C3 | CPS | ≥10 = Expression * | Companion | Recurrent, locally advanced or metastatic * NO SCORE NEEDED IF WITH PLATINUM OR FU | KEYNOTE-181 |
| Breast Carcinoma (Triple Negative) | 22C3 | CPS | ≥10 = Expression | Companion | Locally recurrent, unresectable or metastatic TNBC | KEYNOTE-355 |
| Gastric or GEJ Carcinomas | 22C3 | CPS | >1 = Expression * | Companion | Recurrent, locally advanced or metastatic * NO SCORE NEEDED FOR GEJ IF WITH PLATINUM OR FU | KEYNOTE-059, 590 (181 with SCC) |
| Cervical cancer (SCC or adenocarcinoma) | 22C3 | CPS | >1 = Expression | Companion | Recurrent or metastatic with disease progression on or after chemotherapy | KEYNOTE-158 |
| Head and Neck Squamous Cell Carcinoma | 22C3 | CPS | ≥1 = Expression | Companion | Unresectable/ mets * NO SCORE NEEDED WITH PLATINUM & FU OR PROGRESSION WITH PLATINUM | KEYNOTE-040, 048 |
| Any MSI/MMR deficient tumors | MMR (IHC) | Intact / Def | Deficient MMR or MSI-H | N/A | Tumor progression following Rx with no satisfactory alternative treatment options | KEYNOTE-012, 016, 028, 158, 164 |
| Tumor Mutation Burden-High | Foundation1 | TMB | >10 mut/Mb | Companion | Adult and pediatric unresectable or metastatic tumors TMB-H | KEYNOTE-158 |
| Primary Mediastinal Large B-Cell Lymphoma | Testing Not Indicated - scoring not evaluated in studies (most of these tumors express) | | | | Refractory disease | KEYNOTE-013 and 170 |
| Urothelial Carcinoma (including NMIBC) | Testing Not Indicated - status not predictive of response or not studied in studies | | | | Locally advanced / mets not eligible for Platinum or tumor progression / NMIBC with no cystectomy | KEYNOTE-052, 361, and 045 |
| Hodgkin Lymphoma (Classical type) | | | | | Refractory disease | KEYNOTE-087 |
| Endometrial Carcinoma (Not MSI-H/dMMR) | | | | | With Lenvatinib if progression following systemic therapy & not candidates for surgery or XRT | KEYNOTE-146 |
| Melanoma | | | | | Unresectable or metastatic; adjuvant use if positive nodes | KEYNOTE-001, 002, 006, 054 |
| Small Cell Lung Cancer | | | | | Tumor progression after 2 lines of therapy | KEYNOTE-028 and 158 |
| Hepatocellular Carcinoma | | | | | Previously treated with Sorafenib (KeyNote 240 showed not effective) | KEYNOTE-224 and 240 |
| Merkel Cell Carcinoma | | | | | Recurrent, locally advanced or metastatic with no prior systemic Rx | KEYNOTE-017 |
| Renal Cell Carcinoma | | | | | Combination with axitinib, for first-line treatment with advanced RCC | KEYNOTE-426 |
| Cutaneous SCC | | | | | Recurrent or metastatic that is unresectable or not curable with radiation | KEYNOTE-629 |
| **Cemiplimab-rwlc (LIBTAYO)** - PD-1 inhibitor | | | | | | |
| Non-small Cell Lung Cancer (NSCLC) | 22C3 | TPS | >50% = Expression | Companion | First-line locally advanced or metastatic; Only patients with TPS ≥ 50% were eligible | EMPOWER-Lung 1 |
| Cutaneous SCC & BCC | Testing Not Indicated | | | | SCC = Locally advanced or mets BCC = locally advanced or mets after hedgehog inh or cannot take | EMPOWER-CSCC1 & BCC1 |
| **Atezolizumab (TECENTRIQ)** - PD-L1 inhibitor | | | | | | |
| Non-small Cell Lung Cancer (NSCLC) | SP142 | TC & IC | ≥50% Tumor cells (TC) or ≥10% Immune Cells (IC) * | Companion | First-line mets * NO SCORE NEEDED IF WITH BEVA,PACL, CARBO OR PROGRESSION AFTER PLATINUM | IMpower 110, 150, POPLAR, OAK |
| Urothelial Carcinoma | SP142 | IC | >5% tumor-infiltrating immune cells (IC) * | Companion | Locally advanced or metastatic * NO SCORE NEEDED IF NOT ELIGIBLE FOR PLATINUM | IMvigor130 |
| Small Cell Lung Cancer | Testing Not Indicated - status not predictive of response or not studied in studies | | | | Extensive SCLC - use with Carbo/Etop | IMpower 133 |
| Hepatocellular carcinoma | | | | | Unresectable or metastatic HCC with no prior systemic therapy - combo with Bevacizumab | IMbrave150 |
| Melanoma | | | | | BRAF V600 mutation unresectable or metastatic - combo with Cobimetinib and Vemurafenib | IMspire150 |
| **Nivolumab (OPDIVO)** - PD-1 inhibitor | | | | | | |
| Non-Small Cell Lung Cancer (NSCLC) | 28-8 | TPS | ≥1% = Expression * | Companion | First-line in mets with YERVOY * NO SCORE NEEDED WITH YERVOY & PLAT OR PROGRESS AFTER PLAT | CheckMate-227 |
| Colorectal Adenocarcinoma | MMR(IHC) | Intact / Def | Deficient MMR or MSI-H | N/A | With or without Yervoy | CheckMate-142 |
| Esophageal SCC | Testing Not Indicated - status not predictive of response or not studied in studies | | | | Unresectable, recurrent, or metastatic after fluoropyrimidine- and platinum | CheckMate-577 |
| Gastric, GEJ and Esophageal Adenocarcinoma | | | | | Advanced or metastatic - treat along with chemotherapy (fluorpyrimidine and platinum-based) | CheckMate-649 |
| Mesothelioma | | | | | Untreated, unresectable, treat with Yervoy | CheckMate-743 |
| Renal Cell Carcinoma | | | | | Advanced or unresectable, with Yervoy or Cabozantinib or received anti-aniogenic | CheckMate-214, 9Er |
| Urothelial Carcinoma | | | | | High risk of recurrence after resction regardless of neoadj, nodal involvement or PD-L1 score | CheckMate-032 and 275 |
| Head and Neck Squamous Cell Carcinoma | | | | | Recurrent or metastatic with progression and platinum | CheckMate-141 |
| Melanoma | | | | | Unresectable or metastatic; adjuvant use if positive nodes; with Ipilimumab (YERVOY) | CheckMate-0671, 067 and 238 |
| Hepatocellular Carcinoma | | | | | Previously treated with Sorafenib, as single agent or with Yervoy | CheckMate-040 |
| Hodgkin Lymphoma (Classic type) | | | | | Refractory disease | CheckMate-039 and 205 |
| **Durvalumab (IMFINZI)** - PD-L1 inhibitor | | | | | | |
| Non-Small Cell Lung Cancer (NSCLC) | SP263 | TC | ≥1% = Expression | Complementary | Unresectable Stage III after CRT; adjuvant (respond better if TC ≥1%) | PACIFIC |
| Small cell lung cancer | Testing Not Indicated - status not predictive of response or not studied in studies | | | | With etoposide or carbo/cis | CASPIAN |
| **Dostarlimab (JEMPERLI)** - PD-1 inhibitor | | | | | | |
| Solid Tumors and Endometrial Carcinoma | MMR (IHC) | Intact / Def | Deficient MMR (by Roche IHC stains) | Companion | Recurrent or advanced disease | GARNET |
| **Avelumab (BAVENCIO)** - PD-L1 inhibitor | | | | | | |
| Renal Cell Carcinoma | SP263 | TPS | ≥1% = Expression | Complementary | First-line therapy with axitinib with advanced RCC | JAVELIN Renal 101 |
| Urothelial Carcinoma | Testing Not Indicated - status not predictive of response or not studied in studies | | | | First-line maintenance therapy with advanced disease that has not progressed on platinum-based | JAVELIN Bladder 100 |
| Merkel Cell Carcinoma | | | | | Metastatic | JAVELIN Merkel 200 |
| **Ipilimumab (YERVOY)** - CTLA-4 inhibitor | | | | | | |
| Mesothelioma | 28-8 | TPS | ≥1% = Expression | Complementary | Untreated, unresectable, treat with Yervoy | CheckMate-743 |
| Melanoma, RCC, Colorectal, NSCLC, and HCC | Testing Not Indicated - status not predictive of response | | | | Combination therapy with Opdivo | See Opdivo |
| **Testing Not Indicated** = No good cut offs or scoring system since trials didn't measure PD-L1 in these tumors, didn't randomized based on results or may not have found the scores to be predictive of response; may still test to help assess response if requested | | | | | Reasons listed for not studying score - often expected scant sampling due to FNA/biopsy type, low PD-L1 expression on this tumor cell type, or prior studies showed no response based on score (ex. - Impower 133) | |

Courtesy Dr. Frank Zuehl – St. Luke's Hospital, Milwaukee, WI

# PD-L1 IHC Clone Analytic Comparisons



Journal of Thoracic Oncology

IASLC

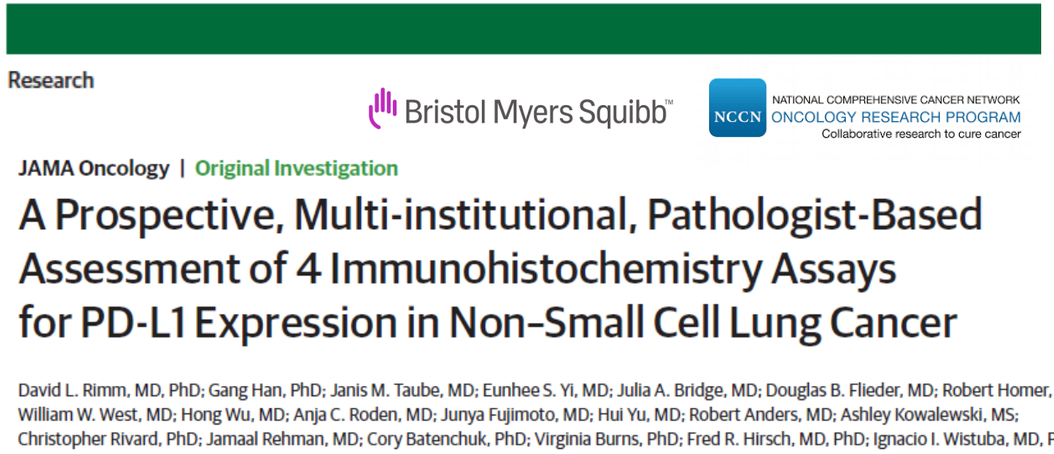
ORIGINAL ARTICLE TRANSLATIONAL ONCOLOGY | VOLUME 13, ISSUE 9, P1302-1311, SEPTEMBER 01, 2018

PD-L1 Immunohistochemistry Comparability Study in Real-Life Clinical Samples: Results of Blueprint Phase 2 Project

Ming Sound Tsao, MD • Keith M. Kerr, MD • Mark Kockx, MD, PhD • ... Melania Pintilie, MSc • Yasushi Yatabe, MD, PhD • Fred R. Hirsch, MD, PhD • Show all authors

Open Archive • Published: May 22, 2018 • DOI: https://doi.org/10.1016/j.jtho.2018.05.013 •

- 81 lung cancer specimens
- 5 PD-L1 assays: 22C3, 28-8, SP142, SP263, 73-10
- Highly comparable staining by the 22C3, 28-8 and SP263 assays
- Less sensitivity with the SP142 assay
- Higher sensitivity with the 73-10 assay to detect PD-L1 expression on TCs.



Research

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NCCN NATIONAL COMPREHENSIVE CANCER NETWORK ONCOLOGY RESEARCH PROGRAM Collaborative research to cure cancer

JAMA Oncology | Original Investigation

A Prospective, Multi-institutional, Pathologist-Based Assessment of 4 Immunohistochemistry Assays for PD-L1 Expression in Non–Small Cell Lung Cancer

David L. Rimm, MD, PhD; Gang Han, PhD; Janis M. Taube, MD; Eunhee S. Yi, MD; Julia A. Bridge, MD; Douglas B. Flieder, MD; Robert Homer, MD, PhD; William W. West, MD; Hong Wu, MD; Anja C. Roden, MD; Junya Fujimoto, MD; Hui Yu, MD; Robert Anders, MD; Ashley Kowalewski, MS; Christopher Rivard, PhD; Jamaal Rehman, MD; Cory Batenchuk, PhD; Virginia Burns, PhD; Fred R. Hirsch, MD, PhD; Ignacio I. Wistuba, MD, PhD

**JAMA Oncology August 2017 Volume 3, Number 8**

- 90 archival NSCLC samples
- 4 PD-L1 assays: 22C3, 28-8, SP142, E1L3N
- Scores from the 28-8 and E1L3N were not significantly different but that the 22c3 test showed a slight but statistically significant reduction in labeling of PD-L1 expression in tumor cells.
- SP142 antibody is an outlier that detected significantly less PD-L1 expression in tumor cells and immune cells.

# PD-L1 IHC Clone Analytic Comparisons

Journal of Thoracic Oncology | IASLC

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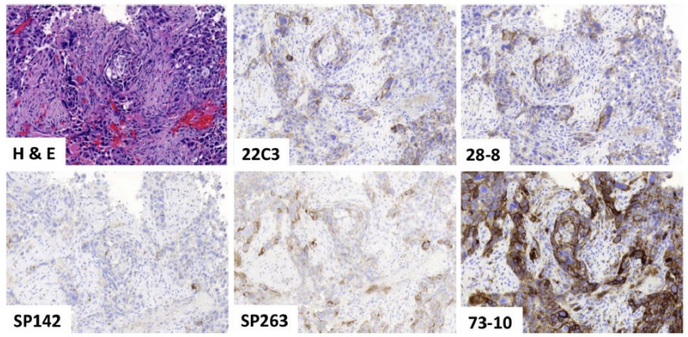


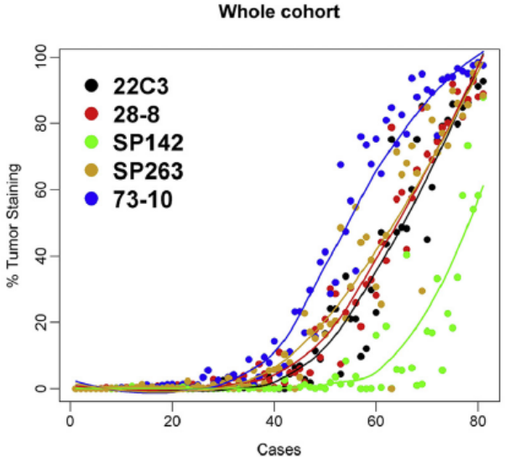


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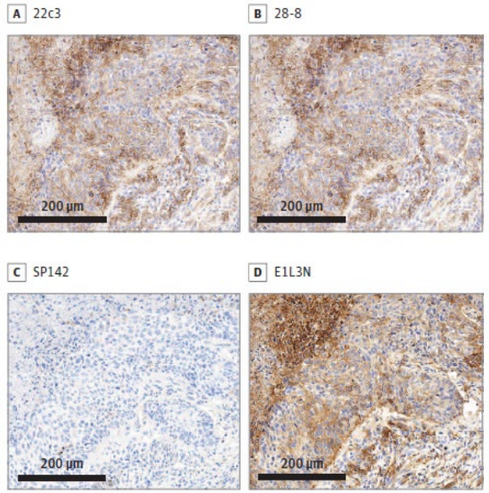


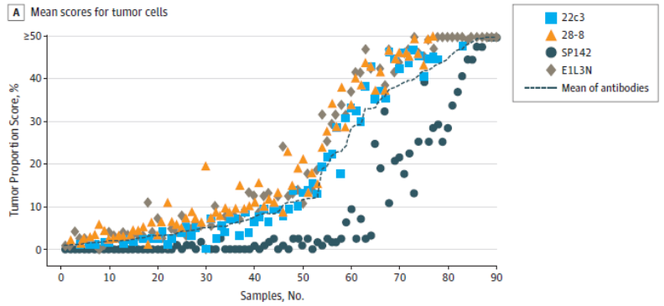

# PD-L1 IHC Scoring Reproducibility

ORIGINAL ARTICLE TRANSLATIONAL ONCOLOGY | VOLUME 13, ISSUE 9, P1302-1311, SEPTEMBER 01, 2018

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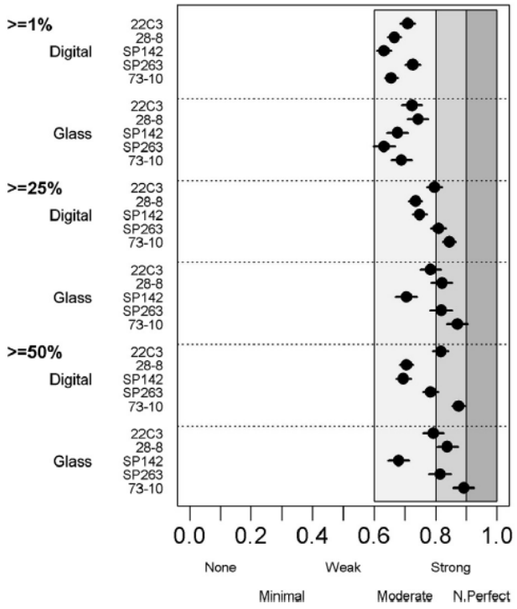
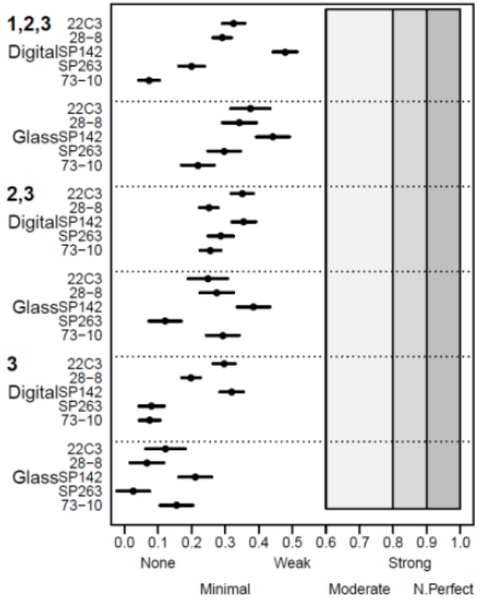
**Reliability (Fleiss κ statistics) of Scoring PD-L1 Expression**

### Tumor cells




### Immune cells

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**JAMA Oncology August 2017 Volume 3, Number 8**

**Table 2. ICC for the Pathologist Scores and Concordance Statistics**

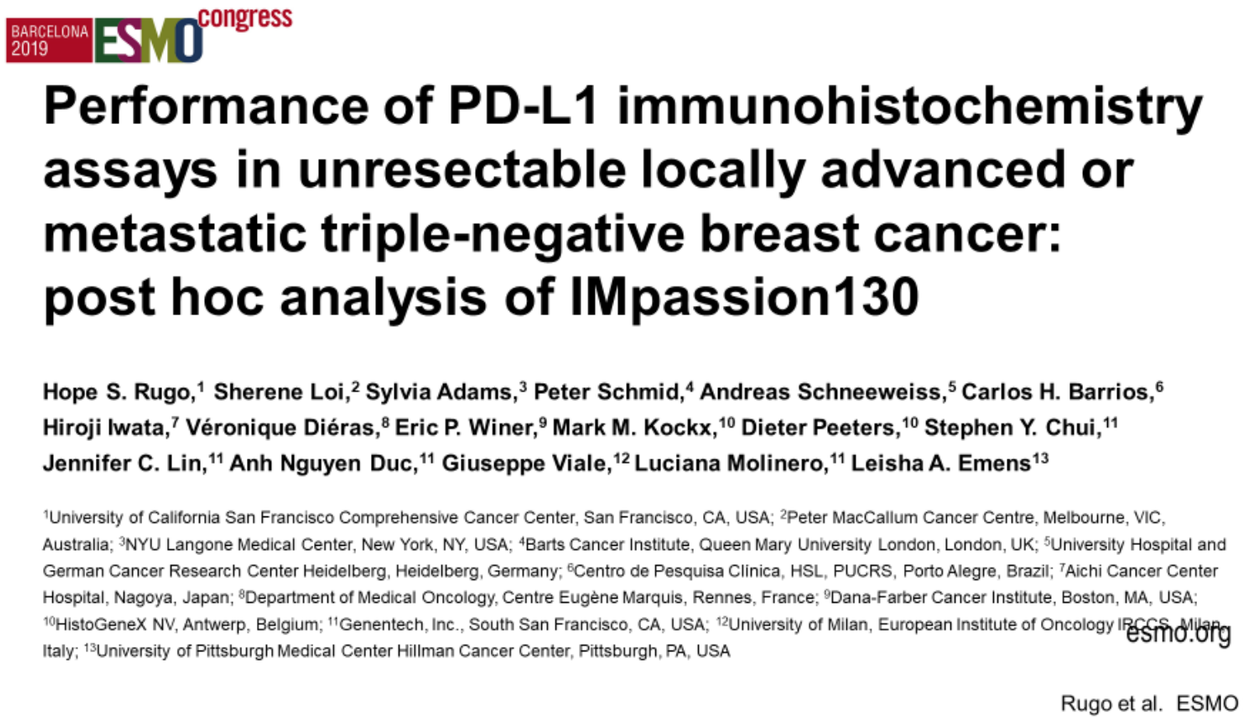
| | Antibody, ICC (95% CI) | | |
|---|---|---|---|
| Cells[a] | 22c3 | 28-8 | SP142 |
| Tumor cells | 0.882 (0.873-0.891) | 0.832 (0.820-0.844) | 0.869 (0.859-0.879) |
| Immune cells | 0.207 (0.190-0.226) | 0.172 (0.156-0.189) | 0.185 (0.169-0.203) |

Abbreviation: ICC, intraclass correlation coefficient.

[a] N = 90.

| Cells[a] | E1L3N | Summary, Mean (SD) |
|---|---|---|
| Tumor cells | 0.859 (0.849-0.869) | 0.86 (0.02) |
| Immune cells | 0.229 (0.211-0.248) | 0.19 (0.03) |

# Comparison of PD-L1 Clones with Clinical Endpoints



BARCELONA 2019 ESMO congress

**Performance of PD-L1 immunohistochemistry assays in unresectable locally advanced or metastatic triple-negative breast cancer: post hoc analysis of IMpassion130**

Hope S. Rugo,[1] Sherene Loi,[2] Sylvia Adams,[3] Peter Schmid,[4] Andreas Schneeweiss,[5] Carlos H. Barrios,[6] Hiroji Iwata,[7] Véronique Diéras,[8] Eric P. Winer,[9] Mark M. Kockx,[10] Dieter Peeters,[10] Stephen Y. Chui,[11] Jennifer C. Lin,[11] Anh Nguyen Duc,[11] Giuseppe Viale,[12] Luciana Molinero,[11] Leisha A. Emens[13]

[1]University of California San Francisco Comprehensive Cancer Center, San Francisco, CA, USA; [2]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [3]NYU Langone Medical Center, New York, NY, USA; [4]Barts Cancer Institute, Queen Mary University London, London, UK; [5]University Hospital and German Cancer Research Center Heidelberg, Heidelberg, Germany; [6]Centro de Pesquisa Clinica, HSL, PUCRS, Porto Alegre, Brazil; [7]Aichi Cancer Center Hospital, Nagoya, Japan; [8]Department of Medical Oncology, Centre Eugène Marquis, Rennes, France; [9]Dana-Farber Cancer Institute, Boston, MA, USA; [10]HistoGeneX NV, Antwerp, Belgium; [11]Genentech, Inc., South San Francisco, CA, USA; [12]University of Milan, European Institute of Oncology IRCCS, Milan, Italy; [13]University of Pittsburgh Medical Center Hillman Cancer Center, Pittsburgh, PA, USA

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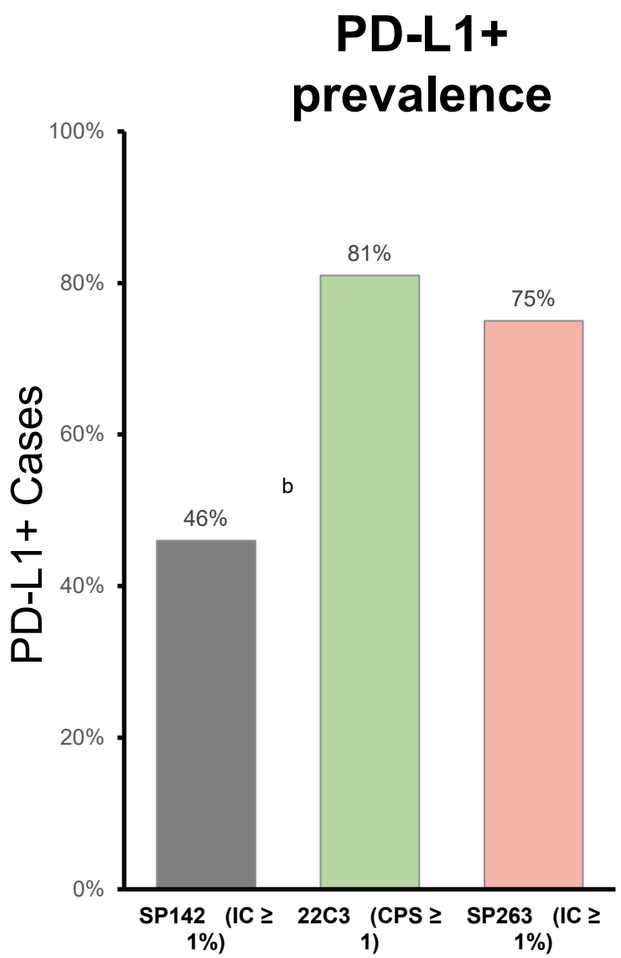
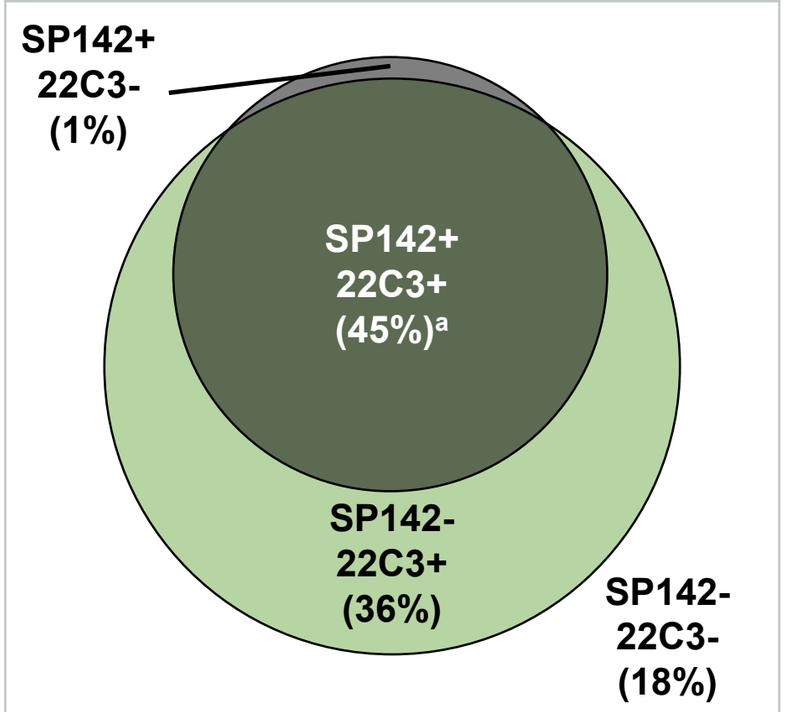
- IMpassion130: Phase III accelerated approval study of atezolizumab + nab-paclitaxel vs. placebo + nab-paclitaxel in mTNBC .
- Exploratory post hoc sub-study: SP142, 22C3 and SP263 PD-L1 IHC assays were evaluated for PD-L1 prevalence, analytical concordance and estimates of clinical activity.
- The US indication for atezolizumab was subsequently withdrawn based on IMpassion 131 study results.

# PD-L1 IHC Assays: Prevalence and Analytical Concordance

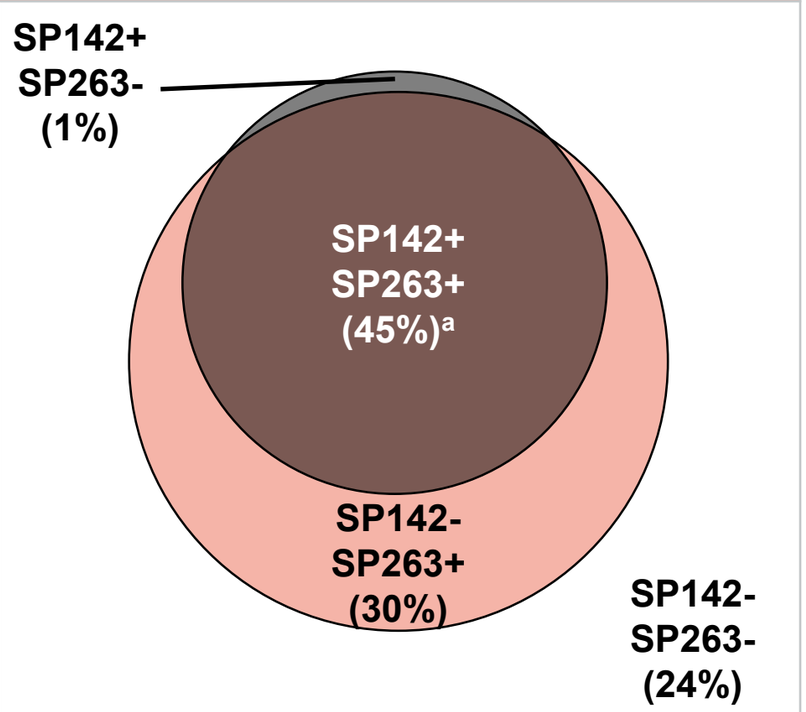



## SP142 (IC 1%) and 22C3 (CPS 1)




| OPA[c] | 64% |
|---|---|
| PPA | 98% |
| NPA | 34% |

## SP142 (IC 1%) and SP263 (IC 1%)




| OPA[c] | 69% |
|---|---|
| PPA | 98% |
| NPA | 45% |

NPA, negative percentage agreement; OPA, overall percentage agreement; PPA, positive percentage agreement.

[a] > 97% of SP142+ samples included in 22C3+ or SP263+ samples. [b] Compared with 41% in ITT (Schmid, *New Engl J Med* 2018).

[c] ≥ 90% OPA, PPA *and* NPA required for analytical concordance.



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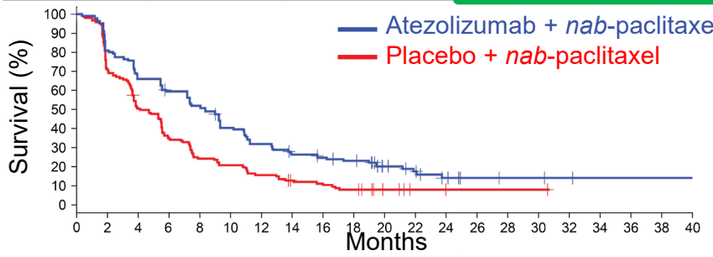
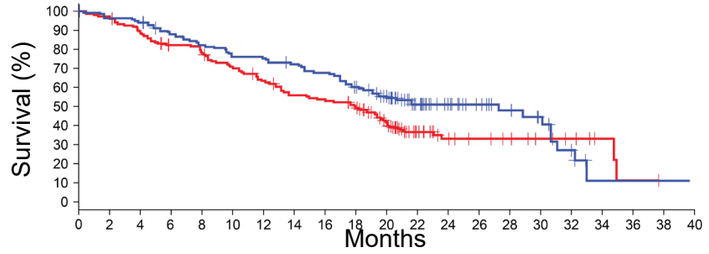
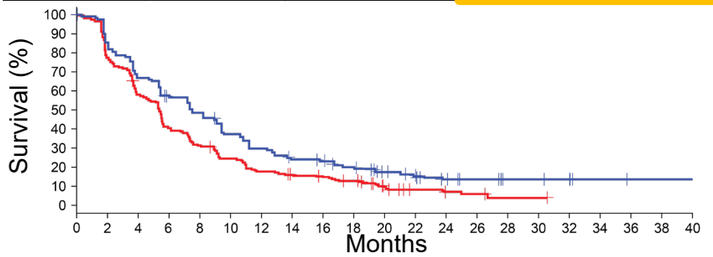
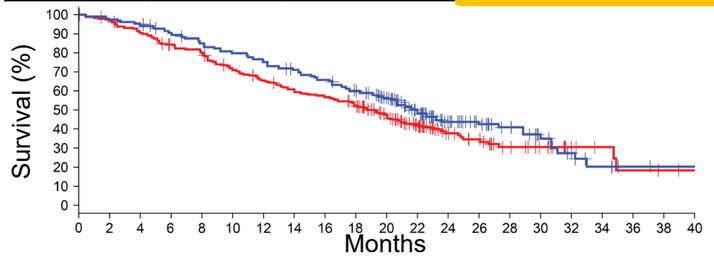
# Clinical outcomes in PD-L1+ populations per SP142 (IC 1%), 22C3 (CPS 1) and SP263 (IC 1%)

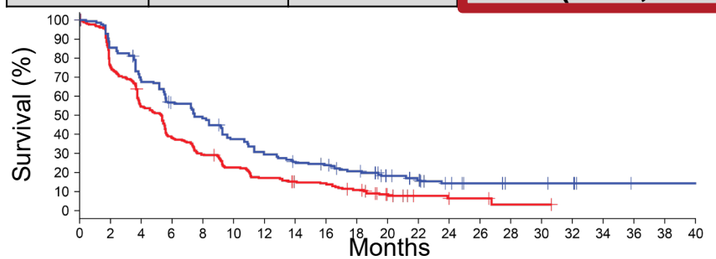
| Population | PFS | | | | OS | | | |
|---|---|---|---|---|---|---|---|---|
| | Median PFS, mo | | | HR (95% CI) | Median OS, mo | | | HR (95% CI) |
| | A + nP | P + nP | Δ | | A + nP | P + nP | Δ | |
| **SP142 IC ≥ 1%: 46% (285/614)** | 8.3 | 4.1 | 4.2 | 0.60 (0.47, 0.78) | 27.3 | 17.9 | 9.4 | 0.74 (0.54, 1.01) |
| **22C3 CPS ≥ 1: 81% (497/614)** | 7.5 | 5.4 | 2.1 | 0.68 (0.56, 0.82) | 21.6 | 19.2 | 2.4 | 0.78 (0.62, 0.99) |
| **SP263 IC ≥ 1%: 75% (460/614)** | 7.5 | 5.3 | 2.2 | 0.64 (0.53, 0.79) | 22.0 | 18.7 | 3.3 | 0.75 (0.59, 0.96) |

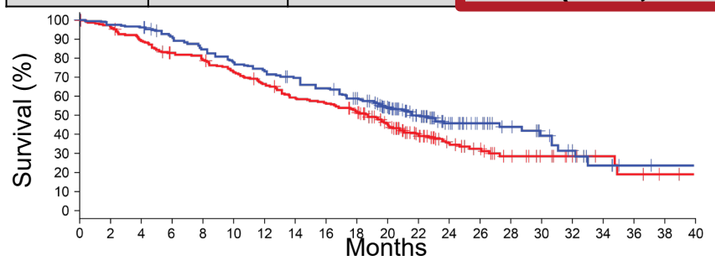







HR adjusted for prior taxanes, presence of liver metastases, age and ECOG PS.

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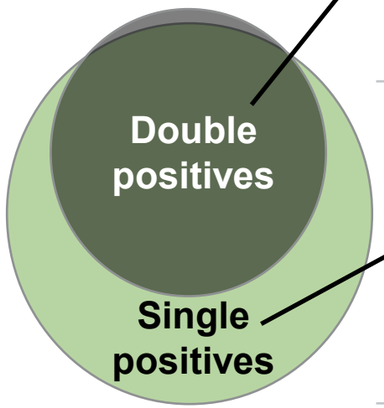
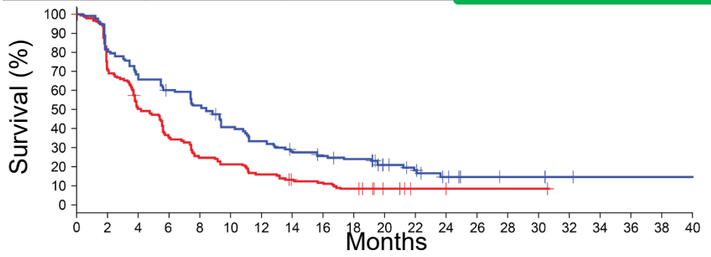
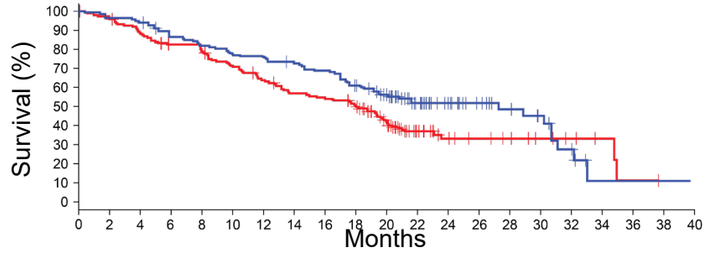
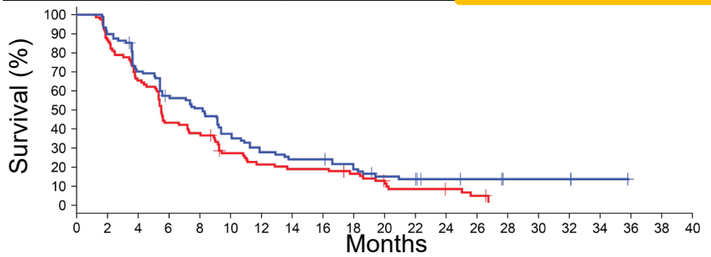
# Clinical Outcomes Defined by SP142 (IC 1%) and 22C3 (CPS 1)

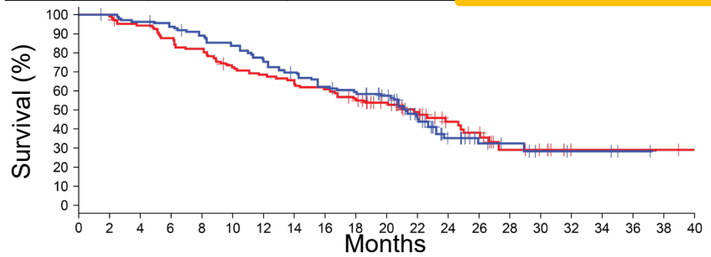


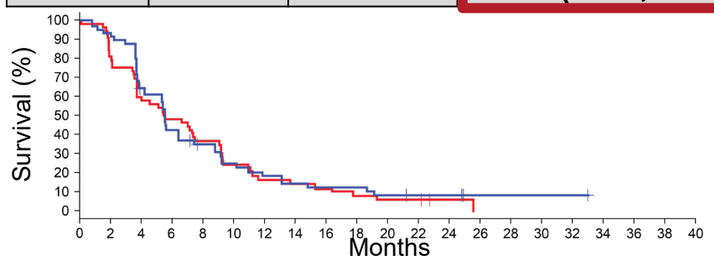

| Population | Median PFS, mo A + nP | Median PFS, mo P + nP | Median PFS, mo Δ | PFS HR (95% CI) | Median OS, mo A + nP | Median OS, mo P + nP | Median OS, mo Δ | OS HR (95% CI) |
|---|---|---|---|---|---|---|---|---|
| SP142+ 22C3+ (45%; 279/614) | 8.3 | 3.9 | 4.4 | 0.60 (0.46, 0.78) | 27.3 | 18.0 | 9.3 | 0.71 (0.52, 0.98) |
| SP142- 22C3+ (36%; 218/614) | 7.3 | 5.6 | 1.7 | 0.81 (0.61, 1.09) | 21.3 | 21.8 | −0.5 | 0.92 (0.64, 1.31) |
| SP142- 22C3- (18%, 111/614) | 5.5 | 5.6 | −0.1 | 1.00 (0.66, 1.51) | 14.7 | 19.6 | −4.9 | 1.08 (0.67, 1.76) |

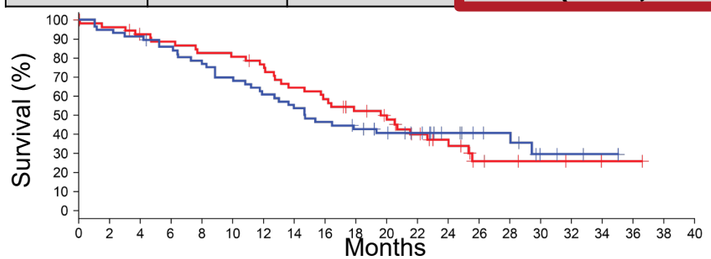



Double positive: SP142 IC ≥ 1%, 22C3 CPS ≥ 1; single positive: SP142 IC < 1%, 22C3 CPS ≥ 1; double negative: SP142 IC < 1%, 22C3 CPS < 1.

HR adjusted for prior taxanes, presence of liver metastases, age and ECOG PS.



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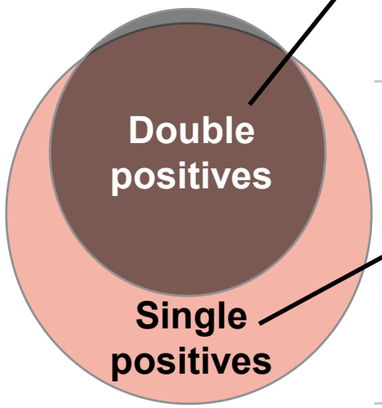
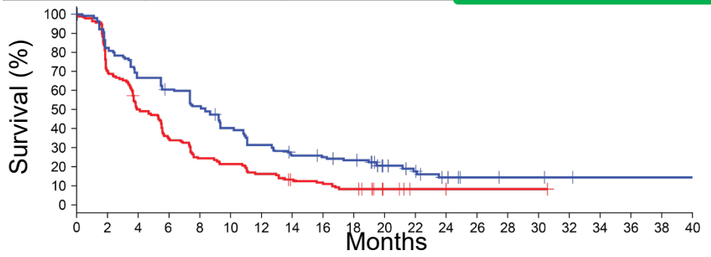
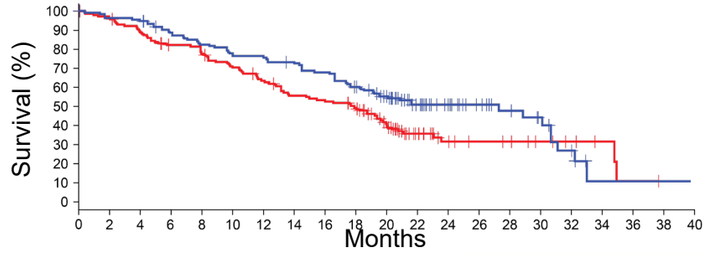
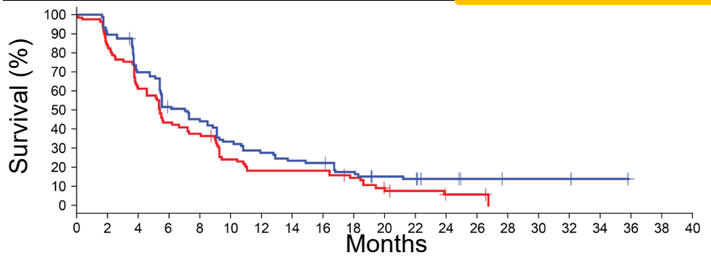
# Clinical Outcomes Defined by SP142 (IC 1%) and SP263 (IC 1%)

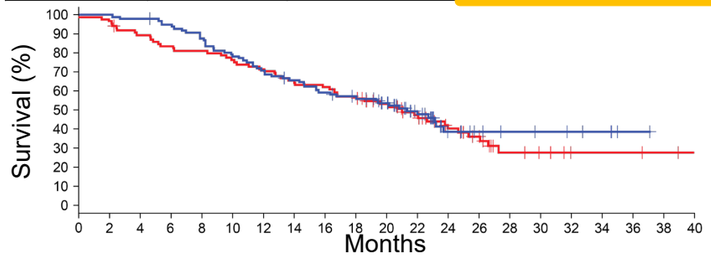


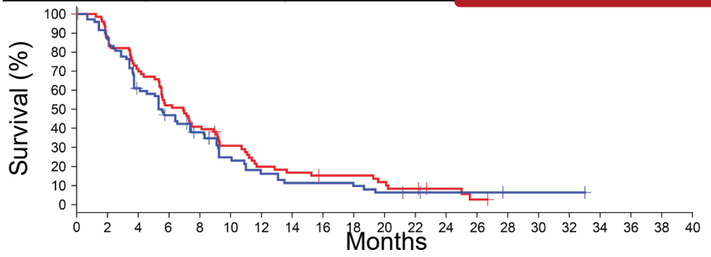

| Population | Median PFS, mo A + nP | Median PFS, mo P + nP | Median PFS, mo Δ | PFS HR (95% CI) | Median OS, mo A + nP | Median OS, mo P + nP | Median OS, mo Δ | OS HR (95% CI) |
|---|---|---|---|---|---|---|---|---|
| SP142+ SP263+ (45%; 278/614) | 8.3 | 4.1 | 4.2 | 0.61 (0.47, 0.79) | 27.3 | 17.9 | 9.4 | 0.71 (0.52, 0.97) |
| SP142- SP263+ (30%; 182/614) | 7.0 | 5.4 | 1.6 | 0.68 (0.49, 0.94) | 21.4 | 21.0 | 0.4 | 0.87 (0.58, 1.29) |
| SP142- SP263- (24%; 147/614) | 5.5 | 6.9 | −1.4 | 1.13 (0.79, 1.61) | 17.9 | 20.5 | −2.6 | 1.10 (0.72, 1.68) |

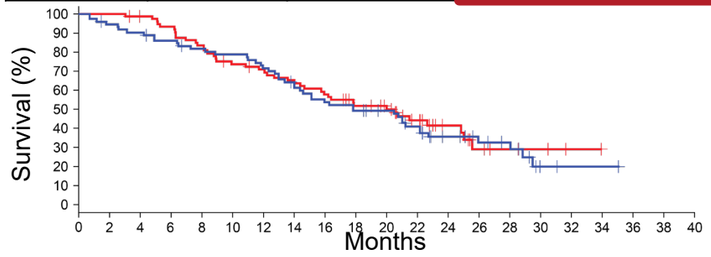



Double positive: SP142 IC ≥ 1%, SP263 IC ≥ 1%; single positive: SP142 IC < 1%, SP263 IC ≥ 1%; double negative: SP142 IC < 1%, SP263 IC < 1%.

HR adjusted for prior taxanes, presence of liver metastases, age and ECOG PS.



Rugo et al. ESMO 2019.

# PD-L1 IHC Clones: Analytic vs. Clinical Comparisons

- **In the post hoc exploratory biomarker sub-study of the IMpassion130 trial:**
  - **The analytical concordance of SP142, 22C3 and SP263 were subpar (< 90%).**
  - **The assays are not equivalent with overall percentage agreements (OPA) of 64% (22C3 vs. SP142) and 69% (SP263 vs. SP142).**
  - **The clinical benefit in 22C3+ and SP263+ subgroups was driven by the SP142+ subgroup.**
- **This data represents a post hoc exploratory analysis of a single trial with a single therapy and indication combination.**
- **While analytic clone comparison data is useful, more clinical comparison data is needed to enable optimal decision making for patients.**

# Why do PD-L1 Negative Patients Respond to PD-(L)1 Inhibition?

*Up to 20% response rate in PD-L1-negative population*

| | **Nivolumab Solid Tumors** Topalian et al. NEJM 2012 | **Nivolumab Melanoma** Weber ASCO 2013 | **Nivolumab Melanoma** Grosso et al. ASCO 2013 | **MPDL3280A Solid Tumors** Herbst et al. ASCO 2013 | **MPDL3280A Melanoma** Hamid et al. ASCO 2013 | **MPDL3280A NSCLC** Sorial et al. ECC 2013 | **Pembrolizumab Melanoma** Daud et al. AACR 2014 | **Pembrolizumab NSCLC** Ghandi et al. AACR 2014 | **MPDL3280A Bladder** Powels et al. ASCO 2014 | **Pembrolizumab Head & Neck** Selwet et al. ASCO 2014 | **Pembrolizumab NSCLC** Ribas et al. ASCO 2014 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| N= | 42 | 44 | 34 | 94 | 30 | 53 | 113 | 129 | 64 | 55 | 411 |
| Response rates | | | | | | | | | | | |
| Unselected | 21% | 32% | 29% | 22% | 23% | 23% | 40% | 19% | 26% | 18% | 40% |
| | | | | | | | | | | | |
| PD-L1 + | 36% | 67% | 44% | 39% | 27% | 46% | 49% | 37% | 43% | 46% | 49% |
| PD-L1 - | 0% | 19% | 17% | 13% | 20% | 15% | 13% | 11% | 11% | 11% | 13% |

Adapted from Margaret Callahan, ASCO 2014

# Intratumoral Heterogeneity of PD-L1 Expression in NSCLC

*48% PD-L1 discordance between biopsy and resection*

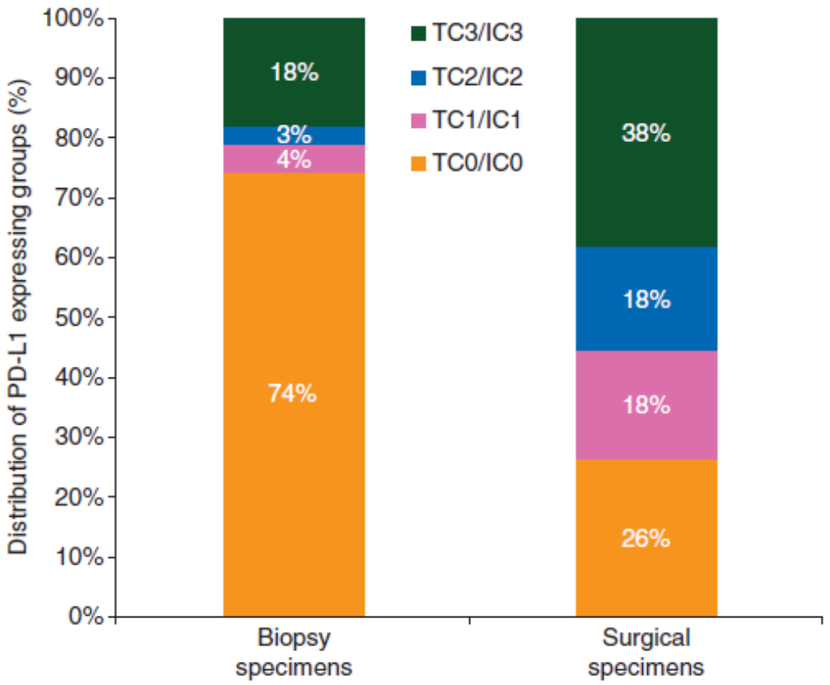
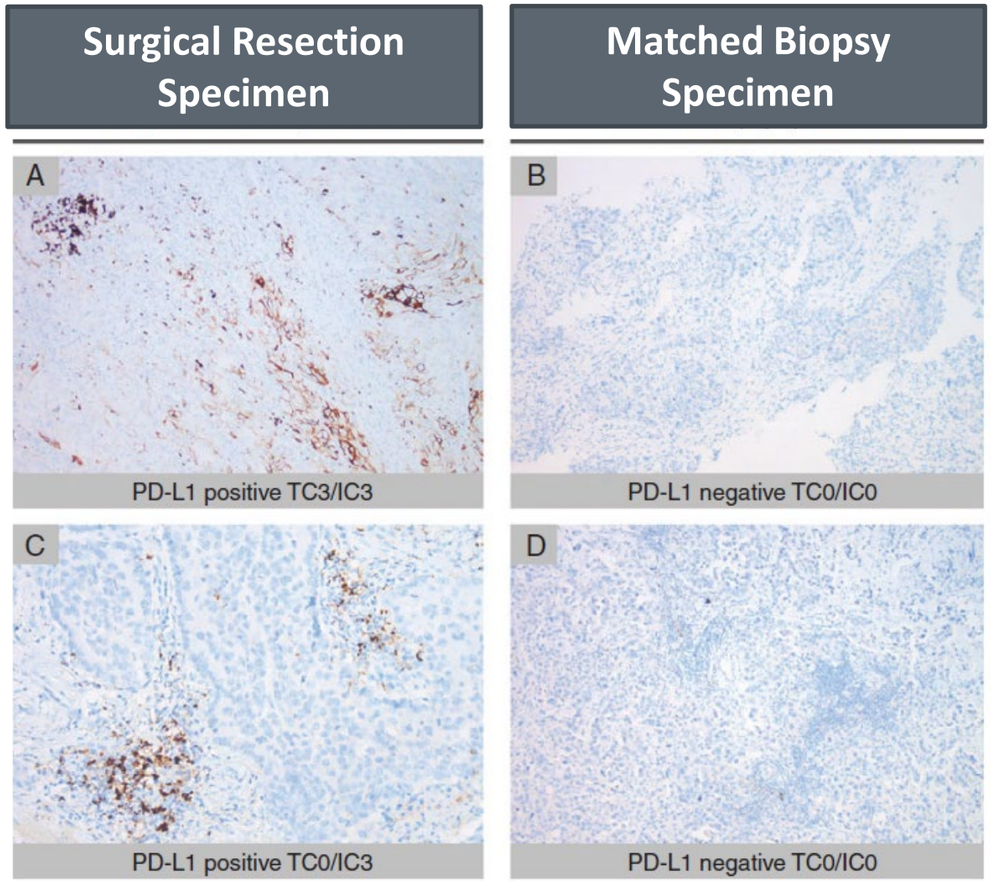



**Figure 1.** Distribution (%) of 160 NSCLC patients included in the study according to the expression of PD-L1 in tumor cells (TC) and immune cells (IC) in either surgical specimens or matched biopsy specimens.




**In all cases, the biopsy specimens underestimated the PD-L1 status observed on the whole tissue sample. The discrepancies were mainly related to the lack of a PD-L1-positive IC component in matched biopsies.**

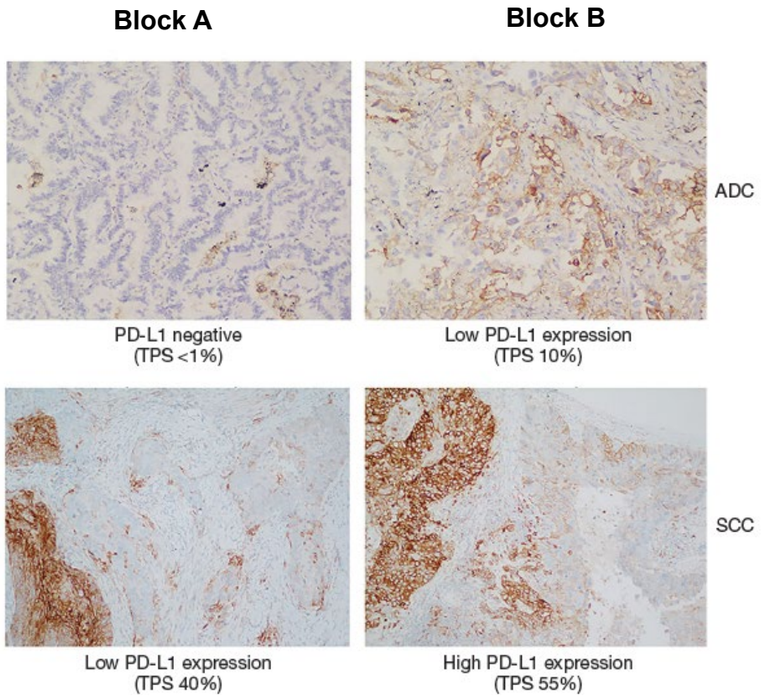


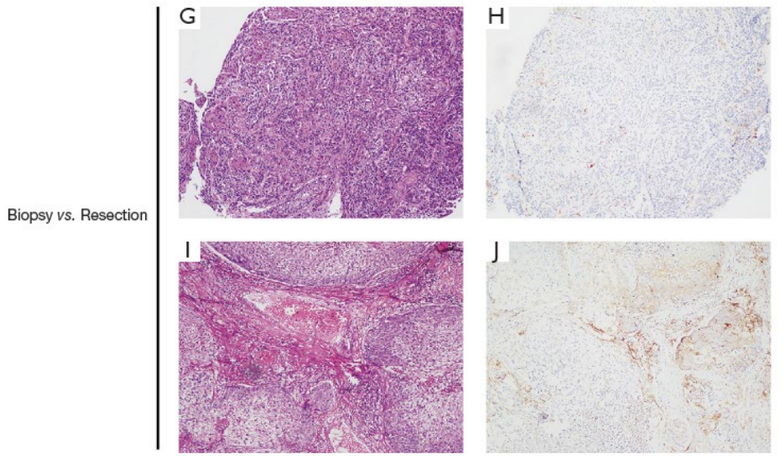


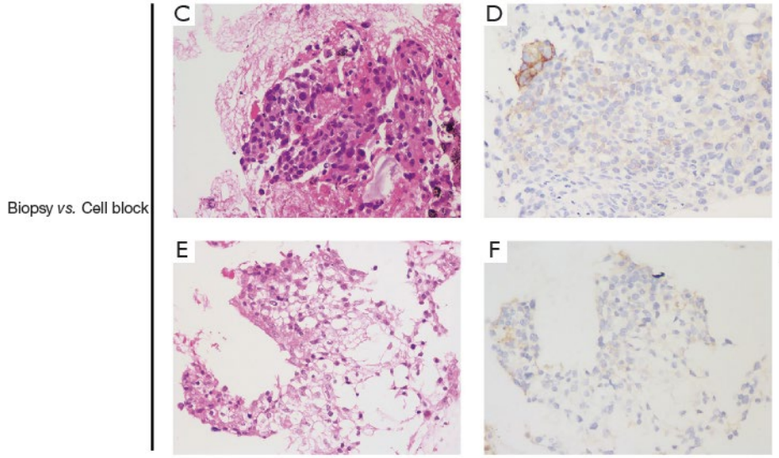
Illie et al. Annals of Oncology 2015

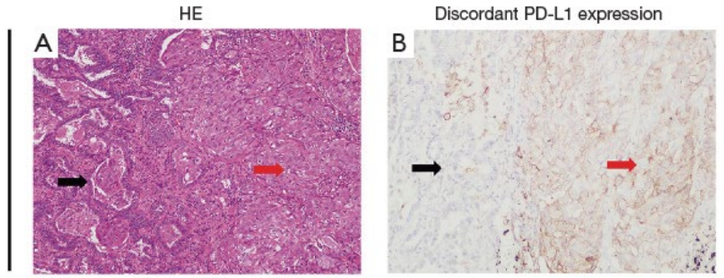
# PD-L1 Expression in NSCLC: Heterogeneity by Pathologic Types, Tissue Sampling and Metastasis

- 1,002 NSCLC samples stained with PD-L1 22C3 and scored w/TPS
- Discordance
  - Biopsy vs. resection: 31.4% (11/35)
  - Primary tumor vs. LN mets: 28.6% (14/49)
  - Cell blocks vs. biopsy: 11.1% (6/54)
  - Different FFPE blocks from same case: 35.8% (19/53)






Shen et al. Thorac Dis 2021;13(7):4360-4370

# Digital Quantification of PD-L1 Expression

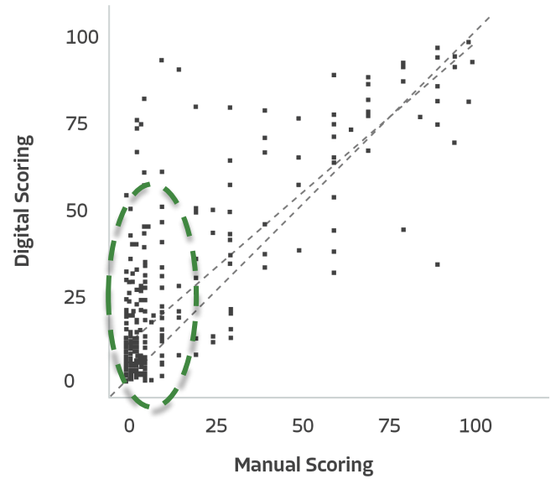
## Abstract 2017: Association of digital and manual quantification of tumor PD-L1 expression with outcomes in nivolumab-treated patients

Chunzhe Duan, Michael Montalto, George Lee, Dimple Pandya, Daniel Cohen, Han Chang, Hao Tang, Nishant Agrawal, Hunter Elliott, Benjamin Glass, Ilan Wapinski, Robin Edwards, Andrew H. Beck, and Vipul Baxi

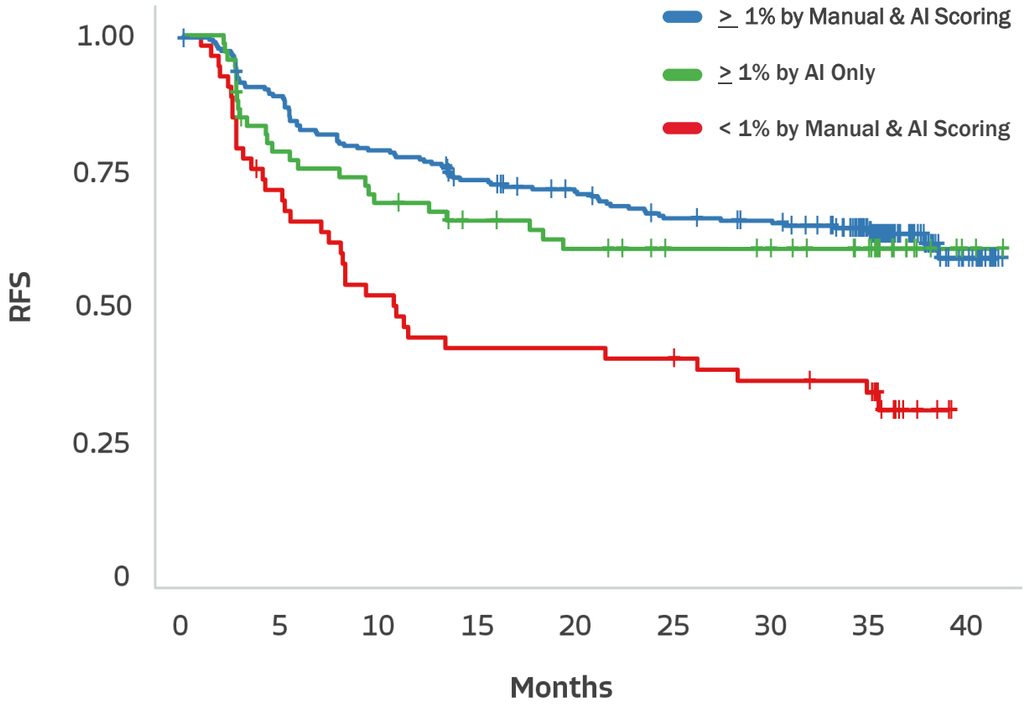
**DOI:** 10.1158/1538-7445.AM2020-2017 Published August 2020 Check for updates

| | Evaluable samples, n | Prevalence, n (%) | | Additional samples identified by digital only, n (%)[a] | Additional samples identified by manual only, n (%) |
|---|---|---|---|---|---|
| | | Digital | Manual | | |
| | | ≥ 1% PD-L1+ TCs | | | |
| CheckMate 275 (UC) | 241 | 166 (69) | 113 (47) | 58 (24) | 5 (2) |
| CheckMate 067 (MEL) | 264 | 173 (66) | 160 (61) | 36 (14) | 23 (9) |
| CheckMate 238 (MEL) | 377 | 307 (81) | 259 (69) | 66 (18) | 18 (5) |
| | | ≥ 5% PD-L1+ TCs | | | |
| CheckMate 275 (UC) | 241 | 90 (37) | 74 (31) | 28 (12) | 12 (5) |
| CheckMate 067 (MEL) | 264 | 103 (39) | 76 (29) | 36 (14) | 9 (3) |
| CheckMate 238 (MEL) | 377 | 234 (62) | 139 (37) | 104 (28) | 9 (2) |

CheckMate 238: Digital vs Manual Scoring




CheckMate 238: Recurrence-Free Survival



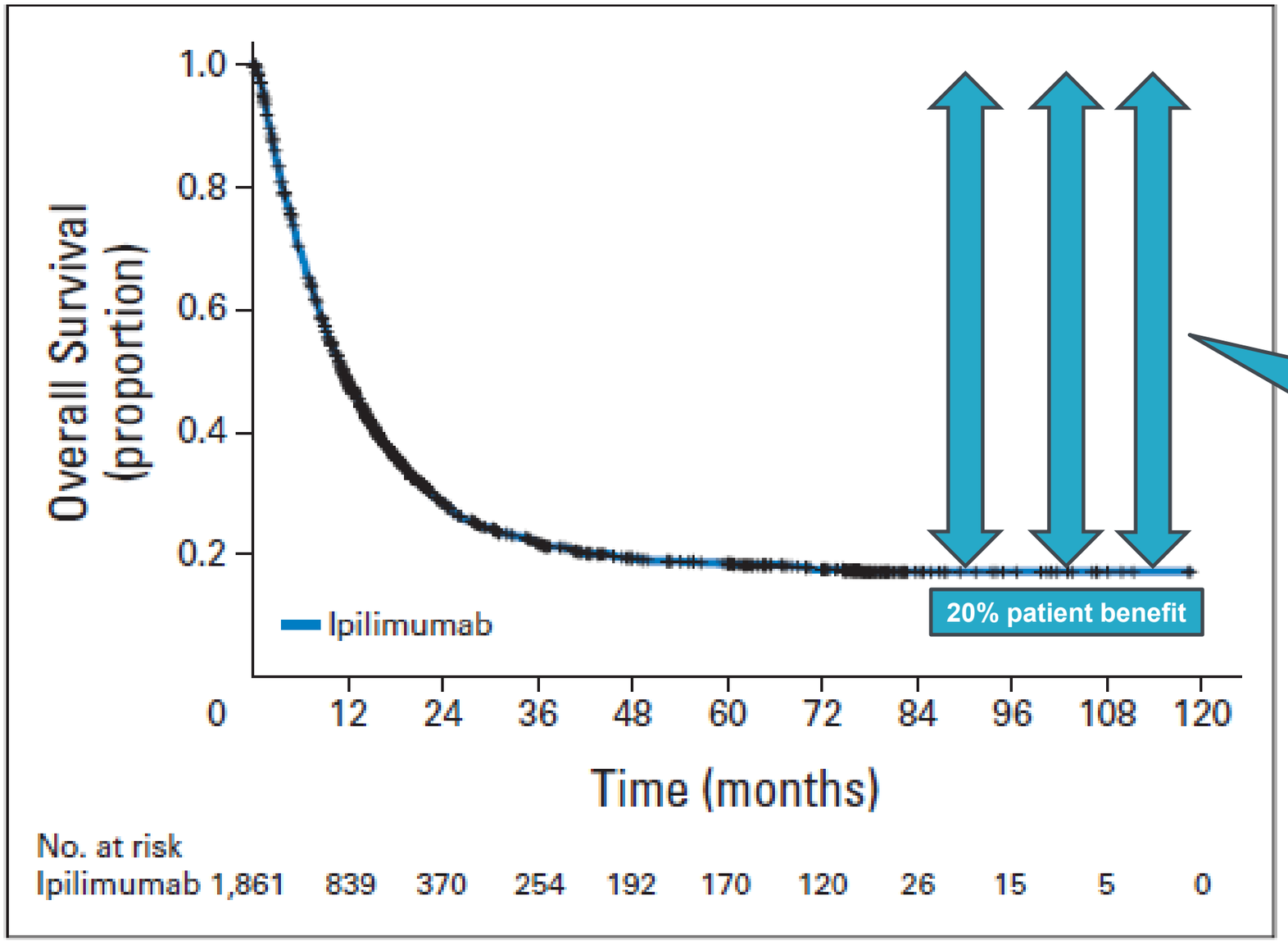





Duan et al., Association of digital and manual quantification of tumor PD-L1 expression with outcomes in nivolumab-treated patients. Poster presented at AACR 2020

# Cancer Immunotherapy Challenges

*Why do only ~20% of patients benefit?*

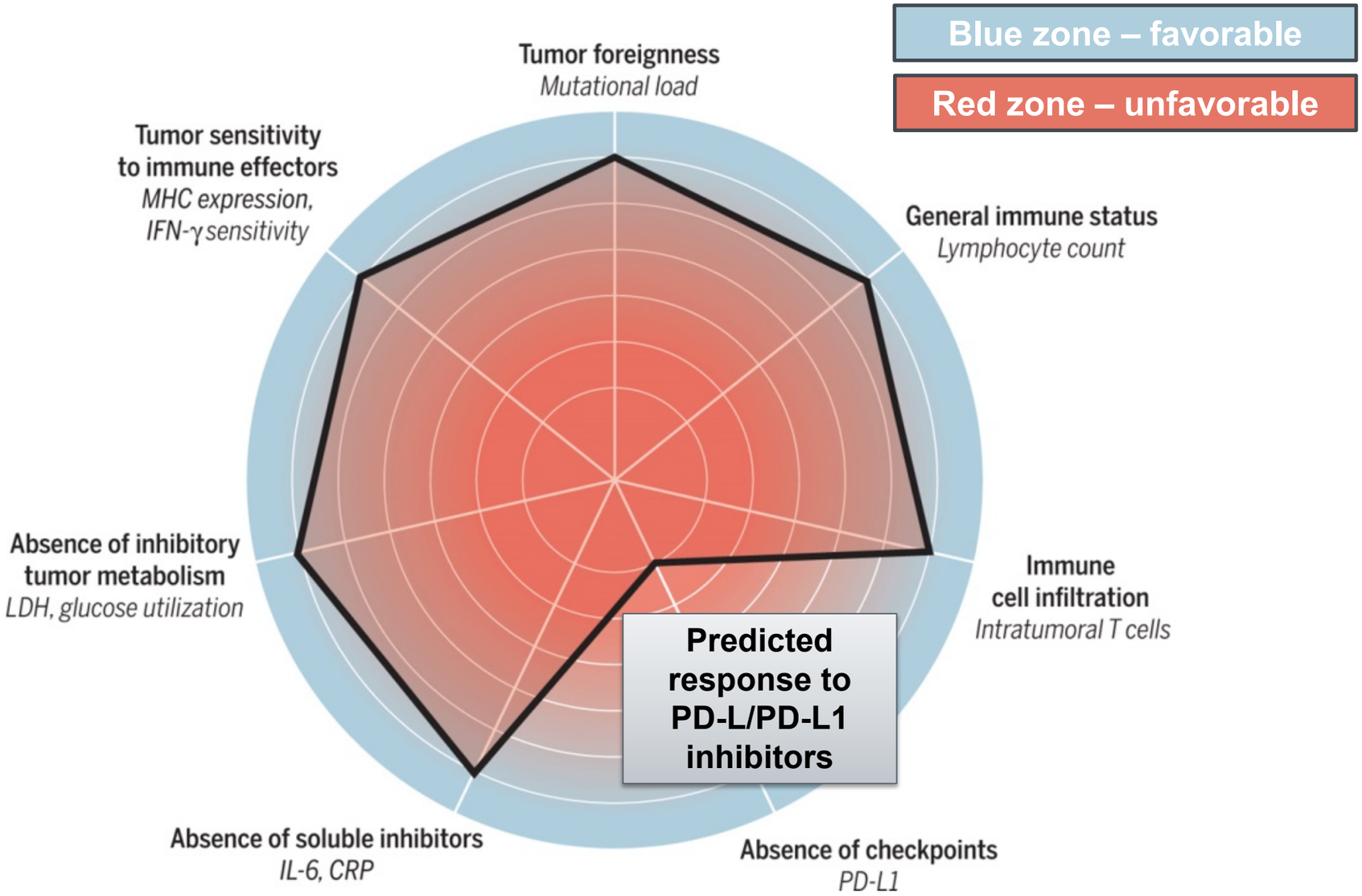





Schadendorf et al. JCO 2015

# Tumor and Host Factors Favoring Immune Responsiveness

*Cancer Immunogram - Schumacher et al.*



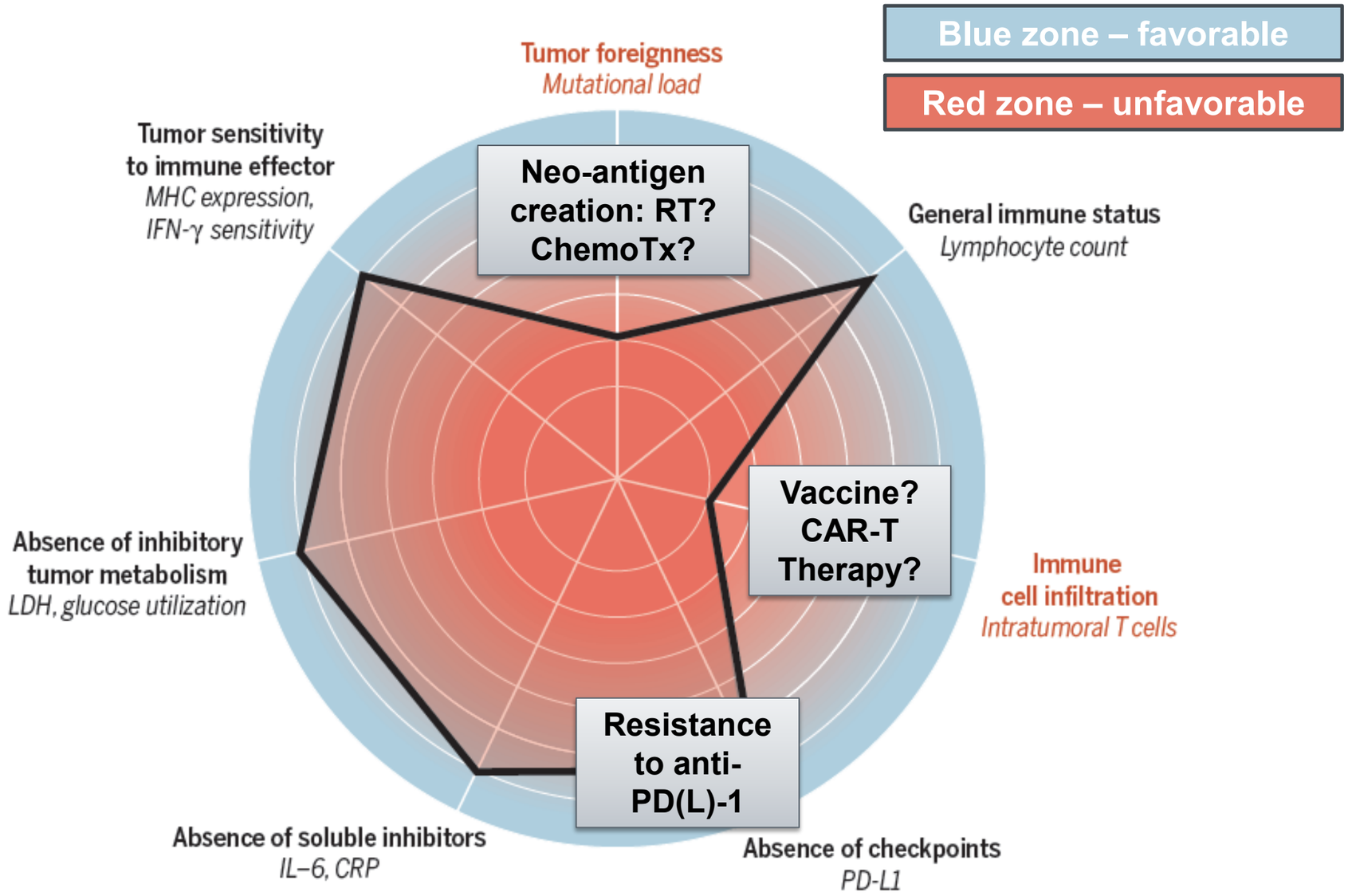





Blank, Haanen, Ribas, Schumacher – Science 2016.

# Tumor and Host Factors Favoring Immune Responsiveness

*Cancer Immunogram - Schumacher et al.*



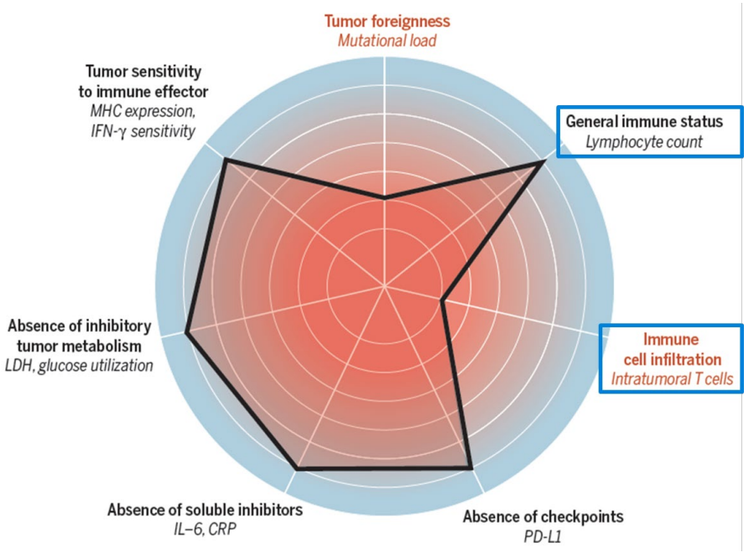


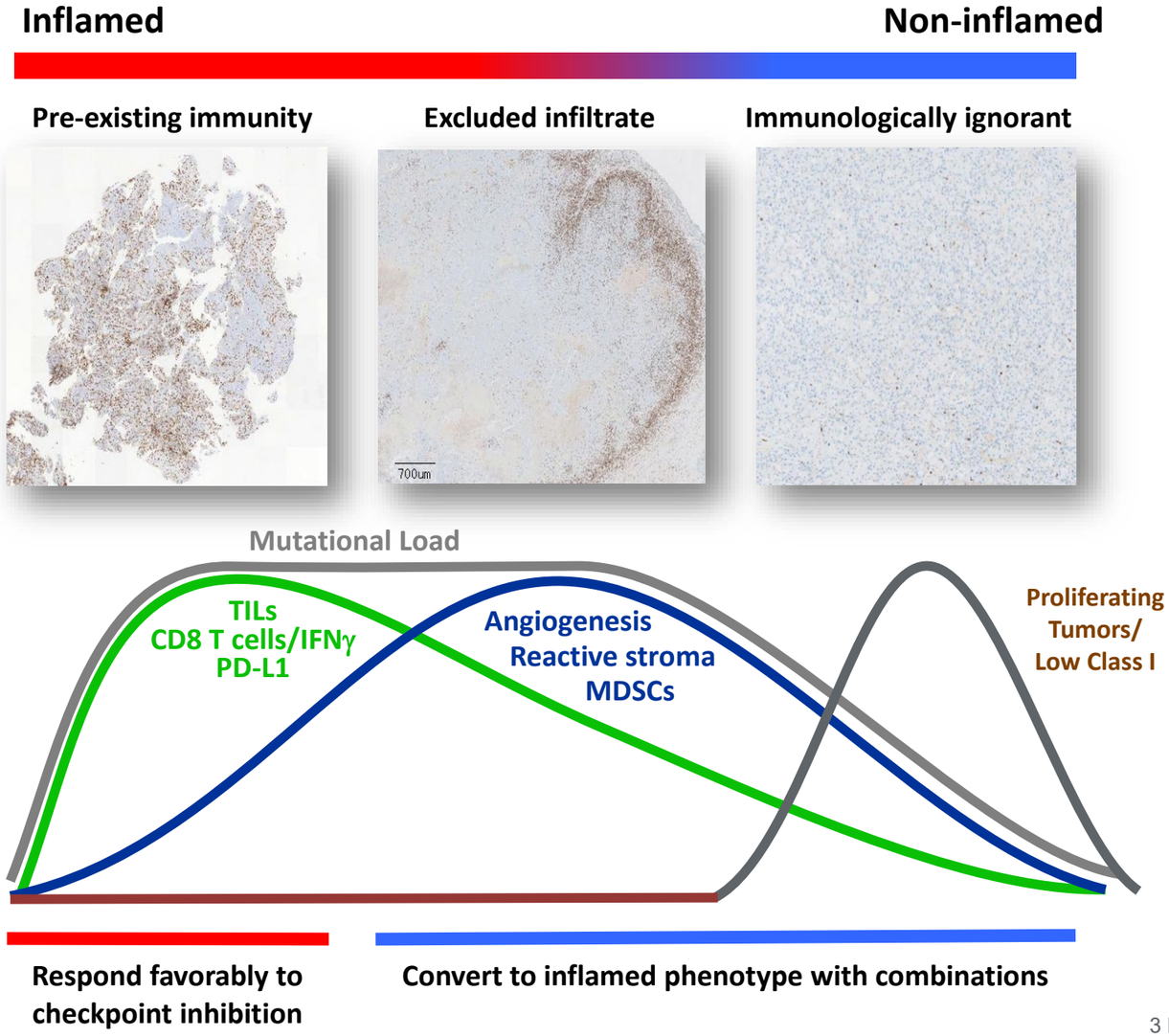



Blank, Haanen, Ribas, Schumacher – Science 2016.

# General Immune Status & Infiltration

*Understanding the root causes of immune oases vs deserts*






Hegde, et al. Clin Cancer Res 2016

TILs: Tumor Infiltrating Lymphocytes MDSCs: Myeloid Derived Suppressor Cells

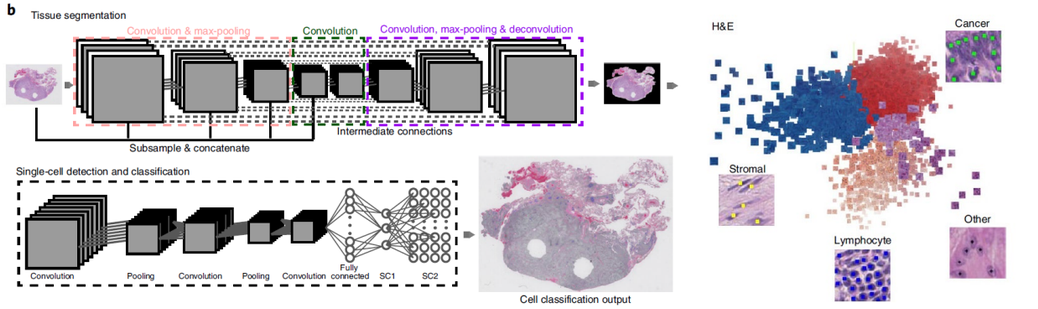
# Prognostic Significance of Immune Infiltration Status in NSCLC

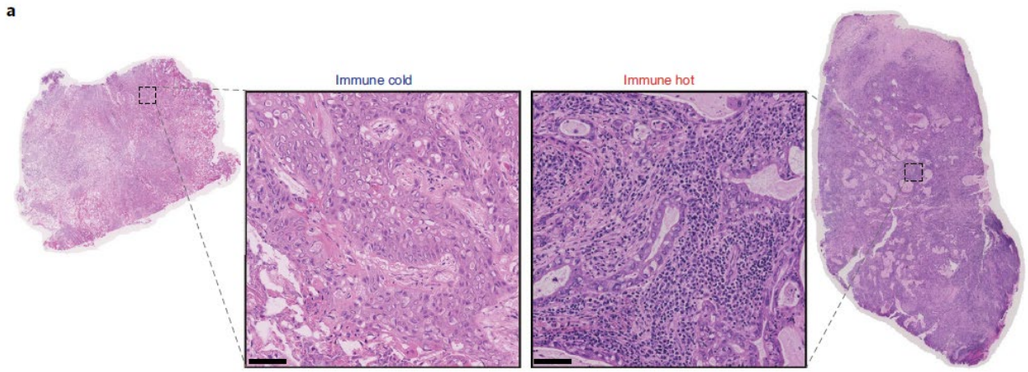
*>1 cold region associated with significantly higher risk of relapse*

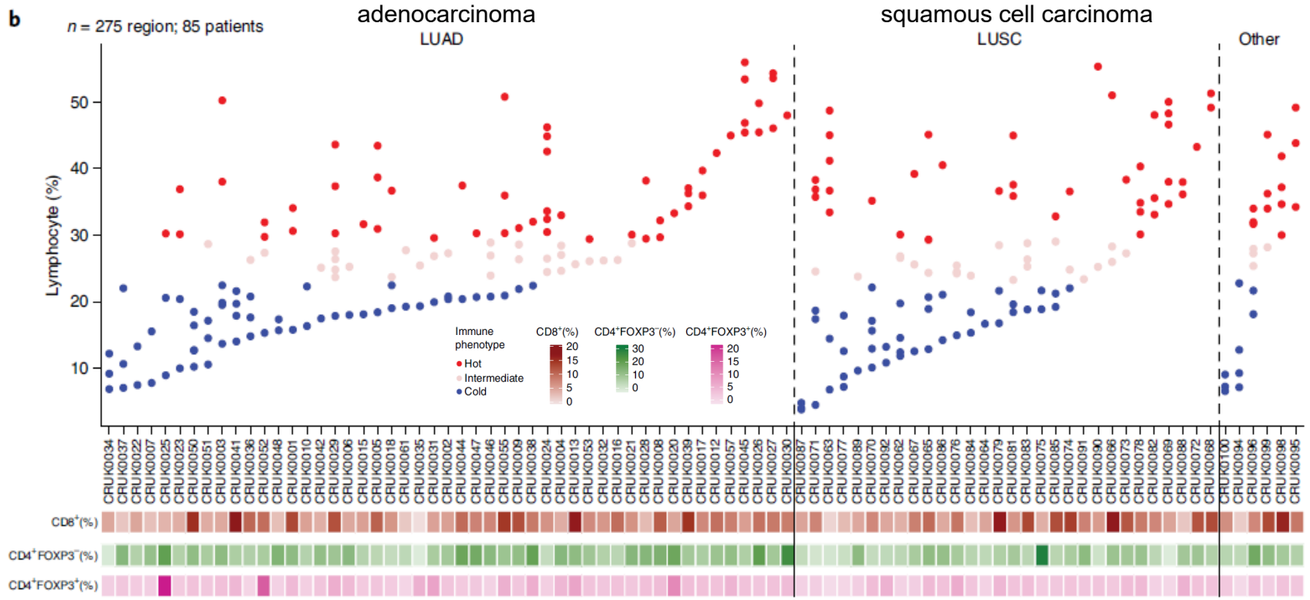
LETTERS
https://doi.org/10.1038/s41591-020-0900-x
nature medicine

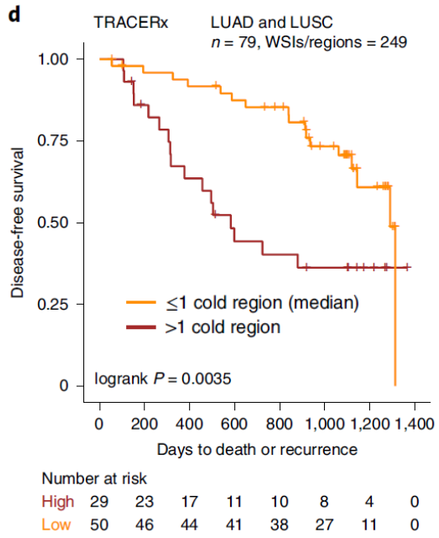
## Geospatial immune variability illuminates differential evolution of lung adenocarcinoma

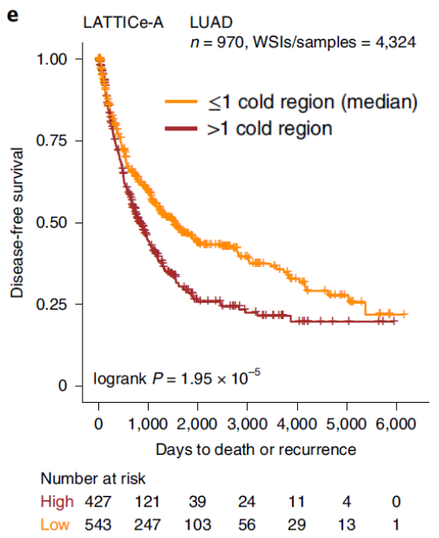
Khalid AbdulJabbar[1,2,53], Shan E. Ahmed Raza[1,2,53], Rachel Rosenthal[3,4], Mariam Jamal-Hanjani[3,5], Selvaraju Veeriah[3,4], Ayse Akarca[6], Tom Lund[7], David A. Moore[3,6], Roberto Salgado[8,9], Maise Al Bakir[4], Luis Zapata[1,2], Crispin T. Hiley[3,4], Leah Officer[10], Marco Sereno[11], Claire Rachel Smith[11], Sherene Loi[9], Allan Hackshaw[12], Teresa Marafioti[6], Sergio A. Quezada[13], Nicholas McGranahan[3,14], John Le Quesne[10,11,15] ✉, TRACERx Consortium*, Charles Swanton[3,4,5,54] ✉ and Yinyin Yuan[1,2,54] ✉



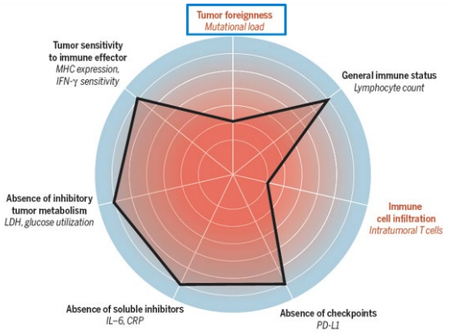



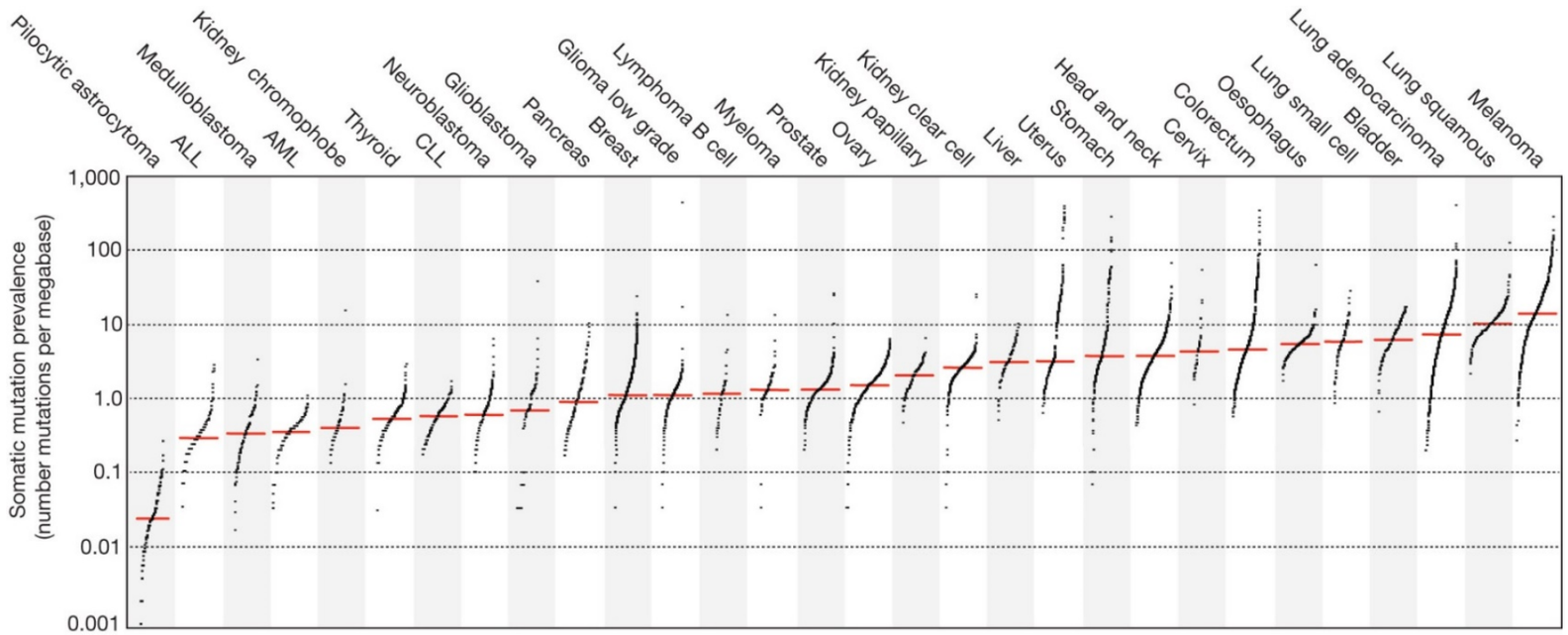

**Independent of:**

- **Total # regions sampled**
- **Tumor size**
- **Stage**

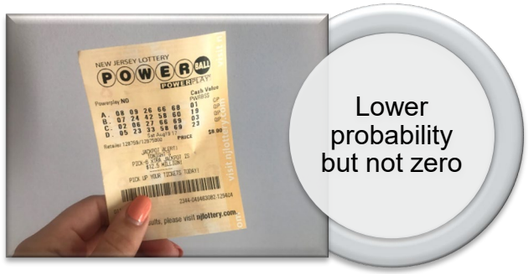
# Tumor Mutational Burden (TMB) – Surrogate of Tumor Foreignness

*Higher mutational load increases probability of immunogenic neo-antigens*




The prevalence of somatic mutations across human cancer types.







LB Alexandrov et al. Nature 000, 1-7 (2013) doi:10.1038/nature12477

# Tumor Mutational Burden (TMB)

## *Predictive or Prognostic?*

REVIEW

ESMO OPEN | CANCER HORIZONS

**The prognostic impact of tumor mutational burden (TMB) in the first-line management of advanced non-oncogene addicted non-small-cell lung cancer (NSCLC): a systematic review and meta-analysis of randomized controlled trials**


**A. Galvano[1†], V. Gristina[1†], U. Malapelle[2], P. Pisapia[2], F. Pepe[2], N. Barraco[1], M. Castiglia[1], A. Perez[1], C. Rolfo[3], G. Troncone[2], A. Russo[1*] & V. Bazan[4]**

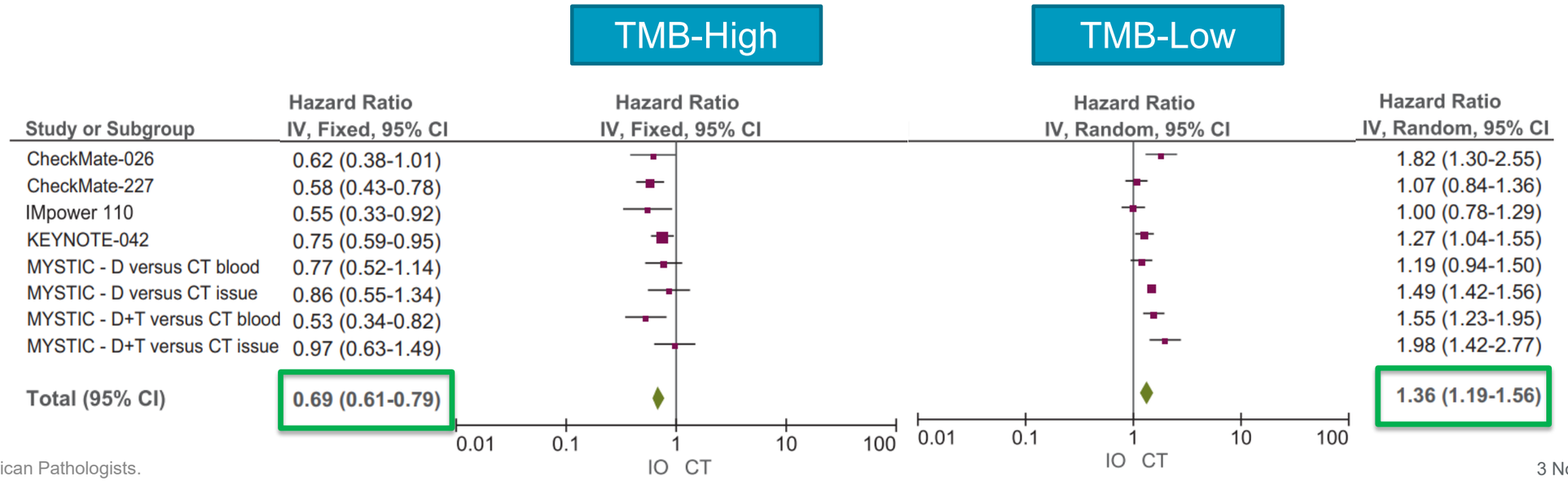
[1]Department of Surgical, Oncological and Oral Sciences, University of Palermo, Palermo; [2]Department of Public Health, University Federico II of Naples, Naples, Italy; [3]Marlene and Stewart Greenebaum Comprehensive Cancer Center, University of Maryland School of Medicine, Baltimore, USA; [4]Department of Experimental Biomedicine and Clinical Neurosciences, University of Palermo, Palermo, Italy


**Table 2. Clinical outcomes measures stratified according to tissue TMB status**

| Study | ORR (TMB-high) *n* (%) | ORR (TMB-low) *n* (%) | PFS (TMB-high) HR (95% CI) | PFS (TMB-low) HR (95% CI) | OS (TMB-high) HR (95% CI) | OS (TMB-low) HR (95% CI) |
|---|---|---|---|---|---|---|
| KEYNOTE-042[28] | 62/180 (34.4) versus 51/165 (30.9) | 44/234 (18.8) versus 48/214 (22.4) | 0.75 (0.59-0.95) | 1.27 (1.04-1.55) | 0.62 (0.48-0.80) | 1.09 (0.88-1.36) |
| CheckMate 227 part 1[31]-2[10] | 63/139 (45.3) versus 43/160 (26.9) | N.A. | 0.58 (0.43-0.77) | 1.07 (0.84-1.35) | 0.68 (0.51-0.91) | 0.75 (0.59-0.94) |
| CheckMate 026[13] | N.A. | N.A. | 0.62 (0.38-1.00) | 1.82 (1.30-2.55) | 1.1 (0.64-1.88) | 0.99 (0.71-1.4) |
| MYSTIC[32] tissue D + T versus CT | N.A. | N.A. | 0.97 (0.63-1.49) | 1.98 (1.42-2.78) | 0.72 (0.48-1-09) | 1.39 (1.00-1.92) |
| MYSTIC[32] tissue D versus CT | N.A. | N.A. | 0.86 (0.55-1.33) | 1.49 (1.95-2-13) | 0.70 (0.47-1.06) | 1.26 (0.90-1.77) |
| MYSTIC[32] blood D + | 31/64 (48.4) versus 15/70 (21.4) | 34/204 (16.7) versus 58/185 (31.4) | 0.53 (0.34-0.81) | 1.55 (1.23-1.94) | 0.49 (0.32-0.74) | 1.16 (0.93-1.45) |
| MYSTIC[32] blood D versus CT | 23/77 (29.9) versus 15/70 (21.4) | 43/209 (20.6) versus 58/185 (31.4) | 0.77 (0.52-1.13) | 1.19 (0.94-1.50) | 0.72 (0.50-1.05) | 0.93 (0.74-1.16) |
| IMpower110[33] | N.A. | N.A. | 0.55 (0.33-0.92) | 1.00 (0.78-1.29) | 0.75 (0.41-1.35) | 1.07 (0.77-1.47) |

CI, confidence interval; CT, platinum-based chemotherapy; D, durvalumab; HR, hazard ratio; N.A., not available; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; T, tremelimumab; TMB, tumor mutational burden.

PFS





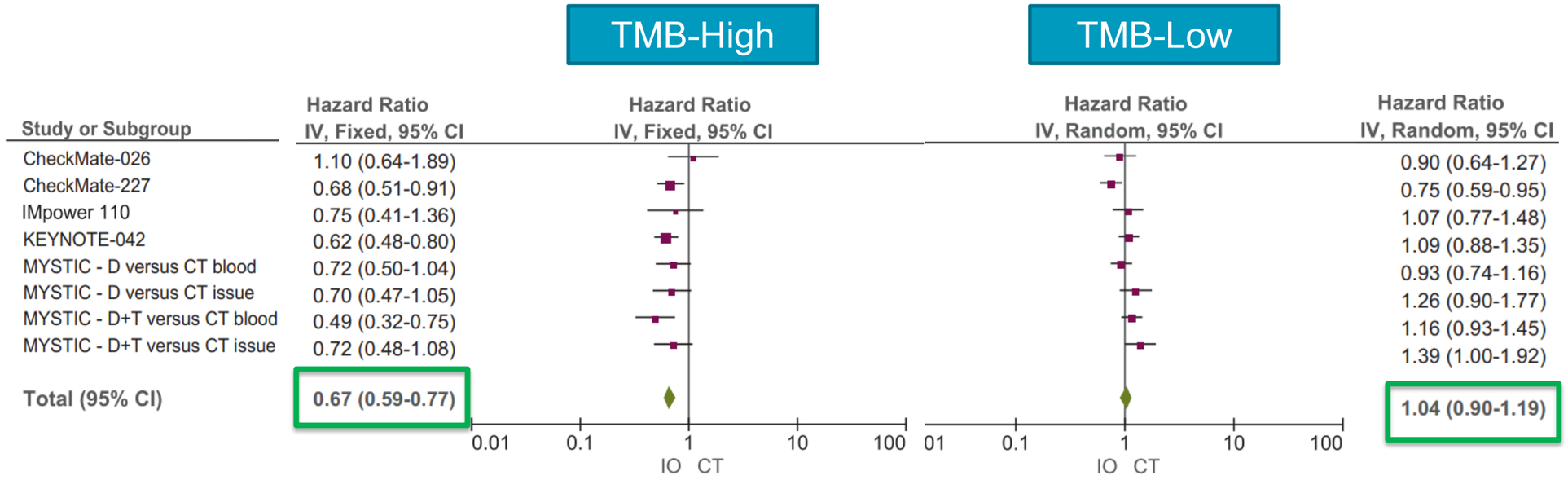



Galvano et al. ESMO Open. 2021 Jun;6(3):100124.

# Tumor Mutational Burden (TMB)

*Predictive or Prognostic?*

OS

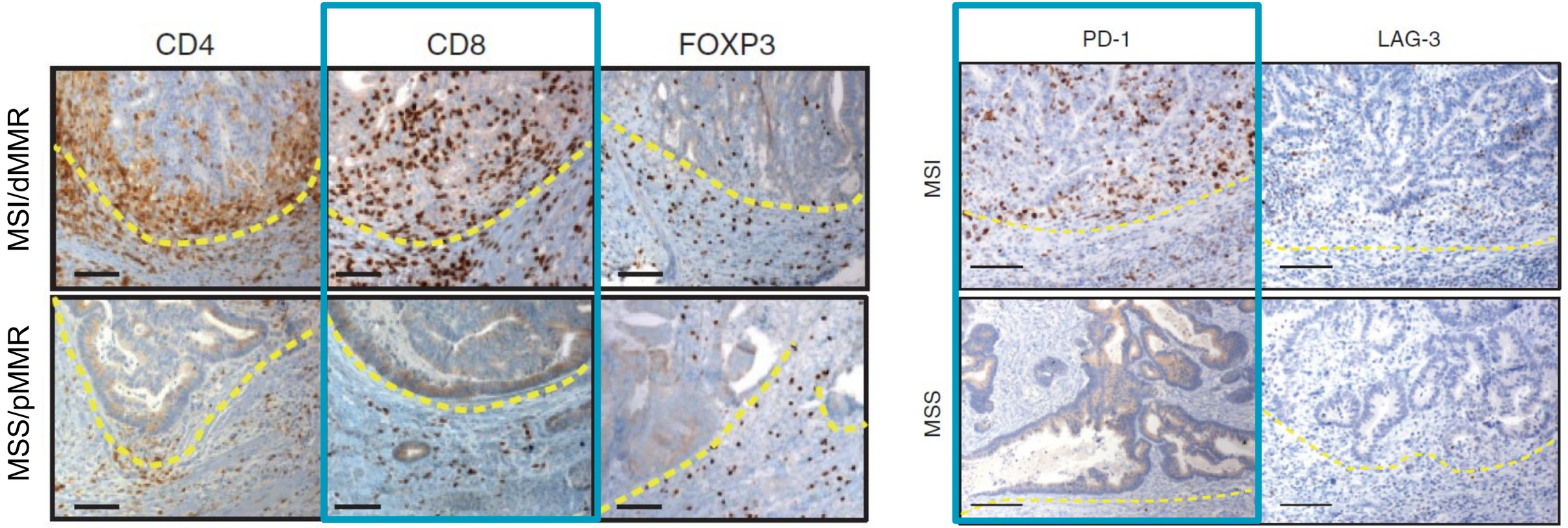



- **TMB-high patients showed a remarkable effect in ORR (data not shown) and a statistically significant benefit in PFS along with an unprecedented OS improvement compared with those patients featuring a low-TMB status.**
- **A possible predictive role of high TMB for IO regimens could be inferred given the ORR and PFS benefit favoring CT vs IO in the TMB-low subgroup**
- **TMB may act as a predictive biomarker in addition to PD-L1 expression for the selection of the most appropriate patients treated with ICIs in the first-line management of advanced non-oncogene-addicted NSCLC.**

**Galvano et al. ESMO Open. 2021 Jun;6(3):100124.**

# MMR/MSI Status - Surrogate of Tumor Foreignness

*Status correlates with immune infiltration*




**CD8+, PD-L1+ T-cells Present at Invasive Front of dMMR/MSI but Not pMMR/MSS Colon Cancer**



Llosa, Pardoll, Cancer Discovery 2015

# Pembrolizumab for MSI-high/dMMR and TMB-High Cancers

*1st tumor agnostic FDA approvals*

FDA U.S. FOOD & DRUG ADMINISTRATION

**FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication**

**[dMMR or MSI-H solid tumors]**

May 23, 2017

FDA U.S. FOOD & DRUG ADMINISTRATION

← Home / Drugs / Development & Approval Process | Drugs / Drug Approvals and Databases

**FDA approves pembrolizumab for adults and children with TMB-H solid tumors**

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June 16, 2020

The NEW ENGLAND JOURNAL of MEDICINE

## PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

**Table 2. Objective Responses According to RECIST Criteria.**

| Type of Response | Mismatch Repair–Deficient Colorectal Cancer (N=10) | Mismatch Repair–Proficient Colorectal Cancer (N=18) | Mismatch Repair–Deficient Noncolorectal Cancer (N=7) |
|---|---|---|---|
| Objective response rate (95% CI) — % | 40 (12–74) | 0 (0–19) | 71 (29–96) |
| Disease control rate (95% CI) — %§ | 90 (55–100) | 11 (1–35) | 71 (29–96) |

| Noncolorectal Cancer Types | |
|---|---|
| Ampullary or cholangiocarcinoma | 4 |
| Endometrial | 2 |
| Small bowel | 2 |
| Gastric | 1 |

Le et al. N Engl J Med 372;26 2015

# FDA Approval of Foundation One CDx TMB

**Approval Date: October 23, 2020**

U.S. FOOD & DRUG ADMINISTRATION

**FoundationOne® CDx - P170019/S017**

**FoundationOne CDx (F1CDx) is a laboratory test designed to detect genetic variations in 324 genes. F1CDx is a companion diagnostic that has been approved for the detection of genetic mutations in patients who may benefit from one of twenty-three FDA-approved therapies for non-small cell lung cancer, melanoma, breast cancer, colorectal cancer, ovarian cancer, cholangiocarcinoma, prostate cancer, and TMB for solid tumors.**

**Therapeutic Efficacy Results**

| Response Evaluation | TMB >=10 mut/Mb (N=102) | | | TMB <10 mut/Mb (N=688) | | |
|---|---|---|---|---|---|---|
| | n | % | 95% CI† | n | % | 95% CI† |
| Complete Response (CR) | 4 | 3.9 | (1.1, 9.7) | 11 | 1.6 | (0.8, 2.8) |
| Partial Response (PR) | 26 | 25.5 | (17.4, 35.1) | 32 | 4.7 | (3.2, 6.5) |
| **Objective Response (CR+PR)** | **30** | **29.4** | **(20.8, 39.3)** | **43** | **6.3** | **(4.6, 8.3)** |
| Stable Disease (SD) | 14 | 13.7 | (7.7, 22.0) | 227 | 33.0 | (29.5, 36.6) |
| Non-CR/Non-PD (NN) | 0 | 0.0 | (0.0, 3.6) | 3 | 0.4 | (0.1, 1.3) |
| Progressive Disease (PD) | 48 | 47.1 | (37.1, 57.2) | 349 | 50.7 | (46.9, 54.5) |
| Non-evaluable (NE) | 1 | 1.0 | (0.0, 5.3) | 13 | 1.9 | (1.0, 3.2) |
| No Assessment | 9 | 8.8 | (4.1, 16.1) | 53 | 7.7 | (5.8, 10.0) |

Central radiology assessed responses per RECIST 1.1 (confirmed) are included in this table.

† Based on binomial exact confidence interval method.

'No Assessment' (NA) counts subjects who had a baseline assessment evaluated by the central radiology assessment but no post-baseline assessment on the data cutoff date including missing, discontinuing or death before the first post-baseline scan.

Subjects with unknown TMB status are not included.

(Database Cutoff Date: 27JUN2019).

**Table 10. Overall TMB concordance summary (weighted average)**

| TMB Cut-off | Overall PPA (95% CI) | Overall NPA (95% CI) |
|---|---|---|
| 10 mut/Mb | 87.28% (64.42%, 96.17%) | 91.56% (85.66%, 95.64%) |





https://www.fda.gov/medical-devices/recently-approved-devices/foundationoner-cdx-p170019s017

# MMR CDx FDA approved to identify endometrial cancer patients eligible for JEMPERLI (dostarlimab-gxly) anti-PD1

- 23Apr2021: Dostarlimab (Jemperli) was granted accelerated approval for the 2nd line treatment of patients with recurrent or advanced deficient mismatch repair (dMMR) endometrial cancer based on an FDA-approved test.

- In 103 patients with dMMR tumors, the objective response rate was 44.7%, made up of 11 CRs and 35 PRs (ESMO 2020 updated results)

- 26Apr2021 FDA approved the VENTANA MMR RxDx Panel, an IHC CDx for dostarlimab

**VENTANA MMR RxDx Panel**

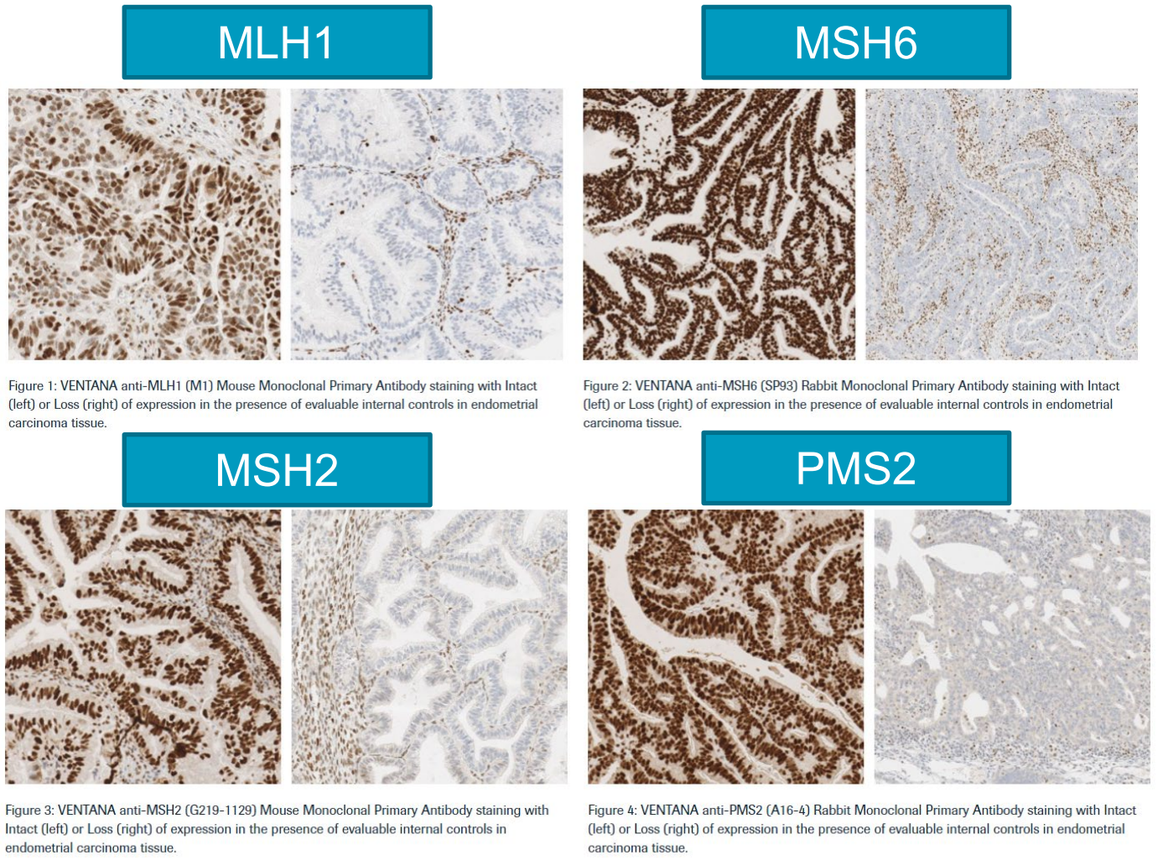



Figure 1: VENTANA anti-MLH1 (M1) Mouse Monoclonal Primary Antibody staining with Intact (left) or Loss (right) of expression in the presence of evaluable internal controls in endometrial carcinoma tissue.

Figure 2: VENTANA anti-MSH6 (SP93) Rabbit Monoclonal Primary Antibody staining with Intact (left) or Loss (right) of expression in the presence of evaluable internal controls in endometrial carcinoma tissue.

Figure 3: VENTANA anti-MSH2 (G219-1129) Mouse Monoclonal Primary Antibody staining with Intact (left) or Loss (right) of expression in the presence of evaluable internal controls in endometrial carcinoma tissue.

Figure 4: VENTANA anti-PMS2 (A16-4) Rabbit Monoclonal Primary Antibody staining with Intact (left) or Loss (right) of expression in the presence of evaluable internal controls in endometrial carcinoma tissue.

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-dostarlimab-gxly-dmmr-endometrial-cancer

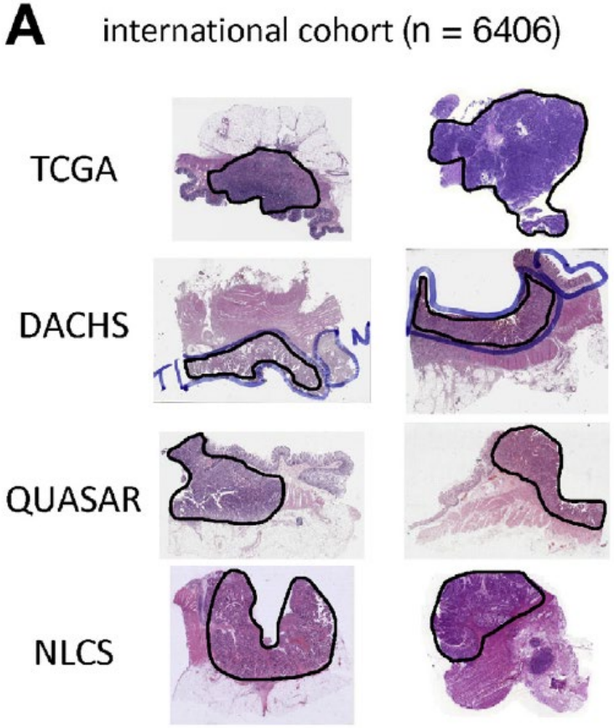


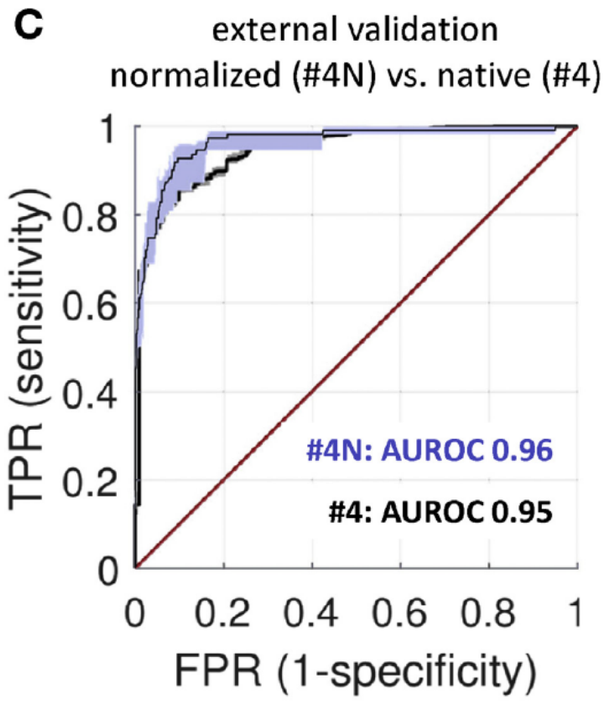


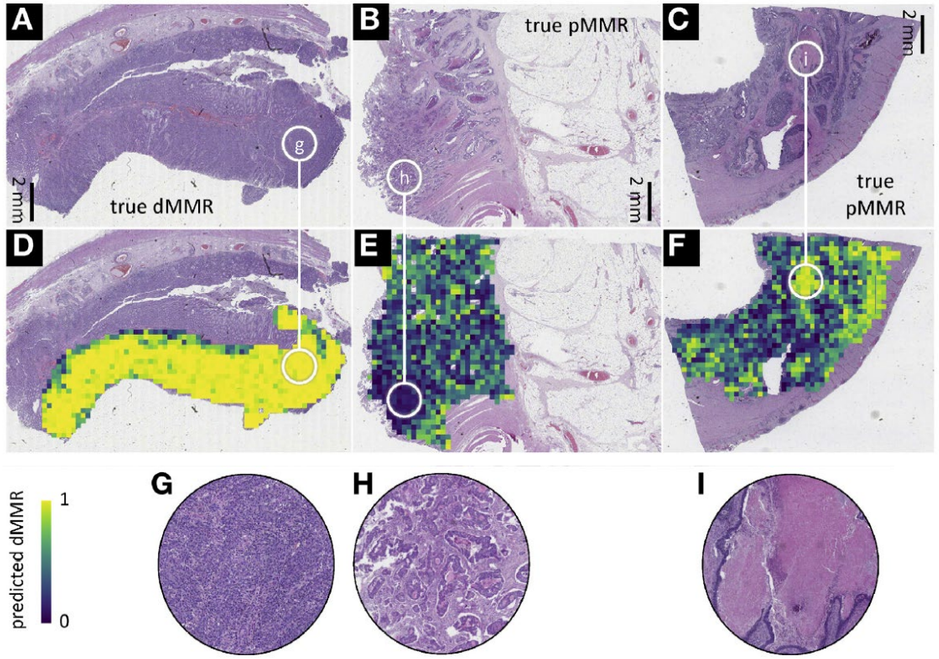
https://diagnostics.roche.com/global/en/products/tests/ventana-mmr-rxdx-panel.html

# Clinical Grade Detection of MSI in CRC by Deep Learning

*AUROC 0.96 using 6,406 patient international training cohort*




## Potential Clinical Implications

- Rapid ID of MSS/pMMR cases with high certainty
- ID high risk MSI/dMMR and Lynch syndrome cases for confirmation via IHC/PCR/NGS

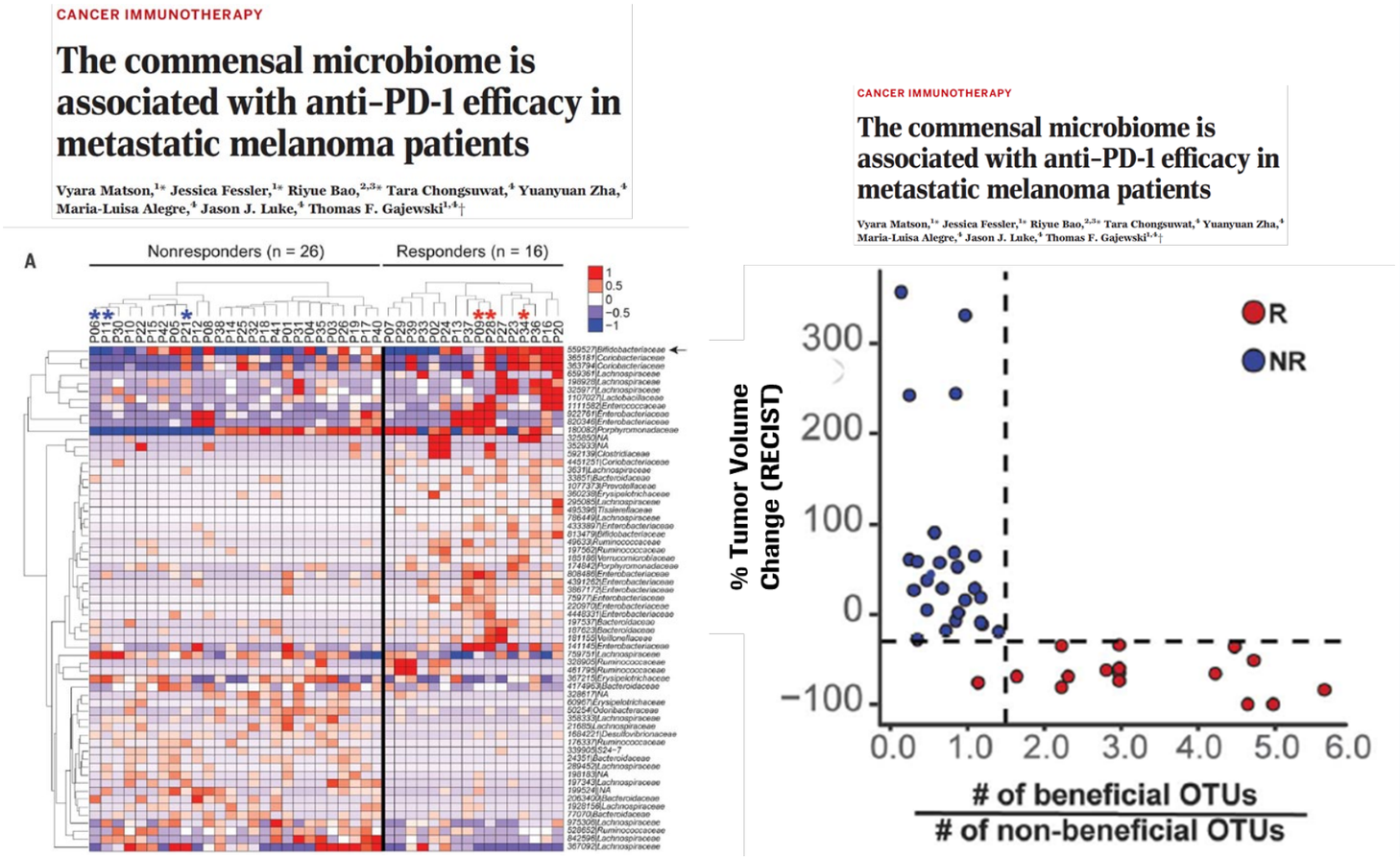


Echle et al. Gastroenterology 2020;159:1406–1416

# Microbiome as a Cancer Immunotherapy Biomarker

*Gut flora diversity and composition predicts response to immunotherapy*

- Baseline stool samples from metastatic melanoma patients analyzed (RNAseq, DNAseq, qPCR) before immunotherapy treatment for selected bacteria.
- Significant association was observed between commensal microbial composition and clinical response.
- Bacterial species more abundant in responders included Bifidobacterium longum, Collinsella aerofaciens, and Enterococcus faecium
- Results suggest that the commensal microbiome may have a mechanistic impact on antitumor immunity in human cancer patients




Matson *et al.*, *Science* **359**, 104–108 (2018) 5 January 2018

# Deep Learning Algorithms to Predict CIT Response

*AUC .707 for anti-PD-1/CTLA-4 response/progression in advanced melanoma*

CLINICAL CANCER RESEARCH | PRECISION MEDICINE AND IMAGING

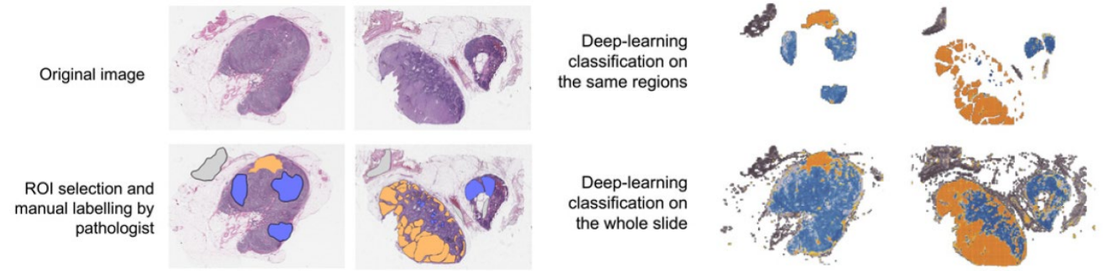
**Using Machine Learning Algorithms to Predict Immunotherapy Response in Patients with Advanced Melanoma** AC

Paul Johannet[1], Nicolas Coudray[2,3], Douglas M. Donnelly[4], George Jour[5], Irineu Illa-Bochaca[4], Yuhe Xia[6], Douglas B. Johnson[7], Lee Wheless[8], James R. Patrinely[7], Sofia Nomikou[5], David L. Rimm[9], Anna C. Pavlick[10], Jeffrey S. Weber[10], Judy Zhong[6], Aristotelis Tsirigos[2,5], and Iman Osman[4]

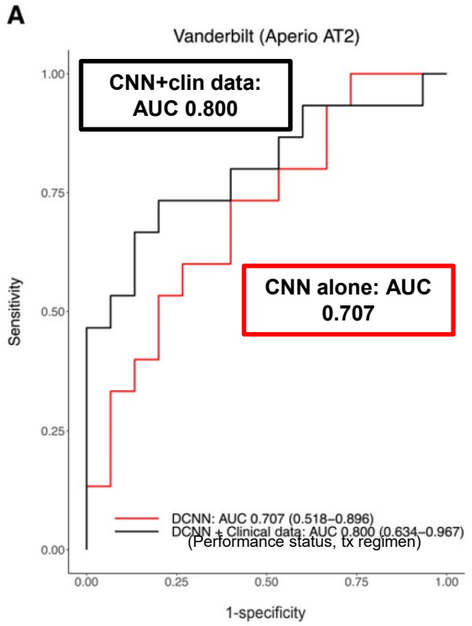
NYU training dataset – 5-fold cross validation

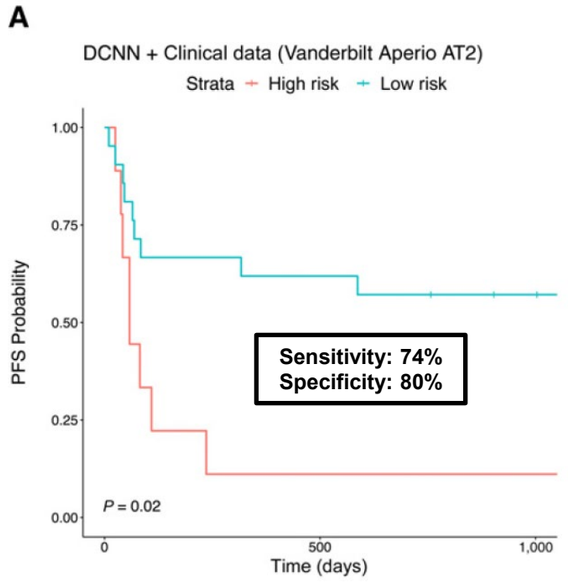
| | Patients | | Slides | | Tiles | |
|---|---|---|---|---|---|---|
| | POD | Response | POD | Response | POD | Response |
| **Set 0** | 18 | 7 | 46 | 24 | 163,393 | 93,197 |
| **Set 1** | 15 | 18 | 30 | 26 | 155,720 | 71,662 |
| **Set 2** | 19 | 10 | 46 | 22 | 151,400 | 100,470 |
| **Set 3** | 10 | 4 | 36 | 14 | 193,583 | 106,325 |
| **Set 4** | 16 | 4 | 42 | 16 | 161,686 | 67,730 |
| **Total** | **78** | **43** | **200** | **102** | **825,782** | **439,384** |

**POD = Progression Of Disease**





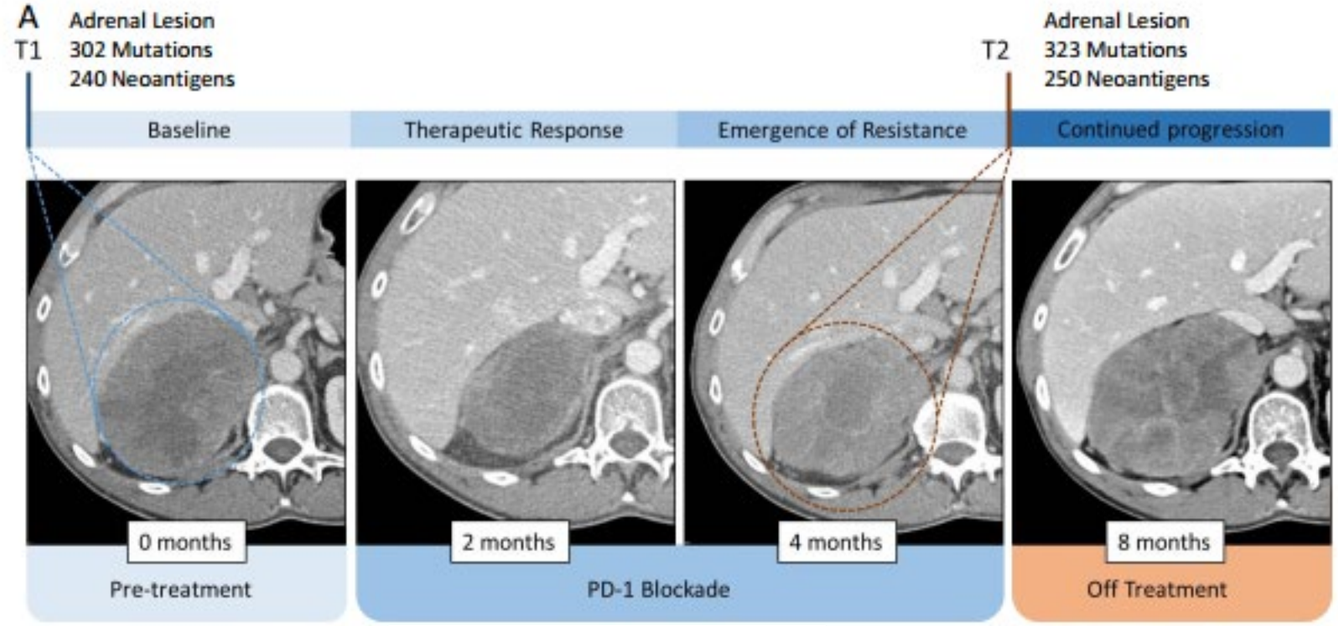

- **CNN+Clin data sensitivity / specificity comparable to PD-L1 IHC**
  - **22C3 (1% cutoff): 80% sensitivity / 60% specificity for pembrolizumab ORR**
  - **28-8 (5% cutoff): 58% sensitivity / 49% specificity for nivolumab monotherapy[1] ORR**
  - **28-8 (5% cutoff): 57% sensitivity / 54% specificity for ipilimumab+nivolumab[1] ORR**

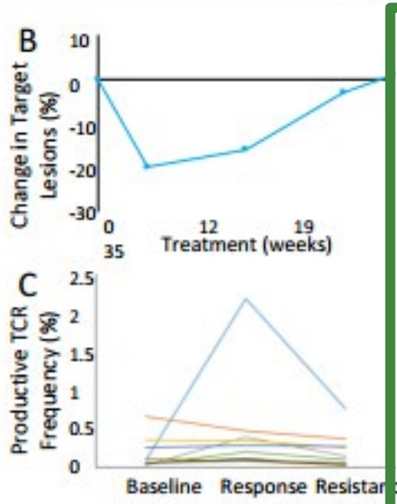
**Conclusions: Histology slides and patients' clinicodemographic characteristics are readily available through standard of care and have the potential to predict ICI treatment outcomes. With prospective validation, we believe our approach has potential for integration into clinical practice.**

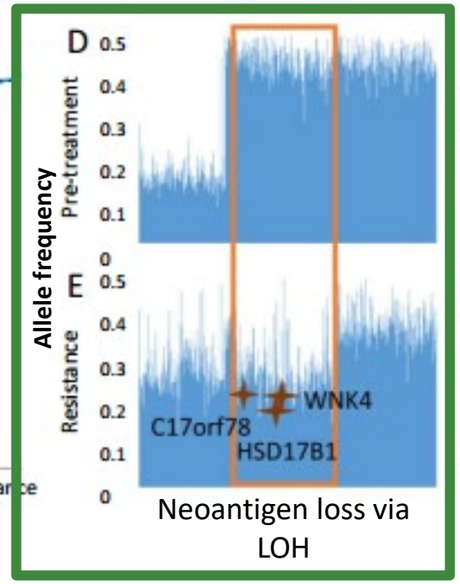
Clin Cancer Res; 27(1) January 1, 2021 [1]Diggs et al. 2017

# Resistance to Checkpoint Inhibitors

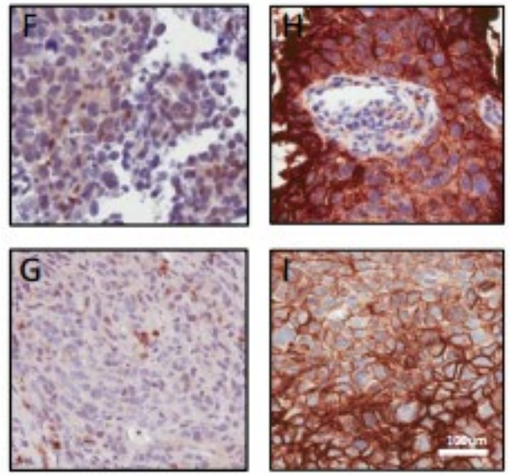
## *Loss of tumor associated neoantigens via LOH in NSCLC*




Neoantigen loss via LOH

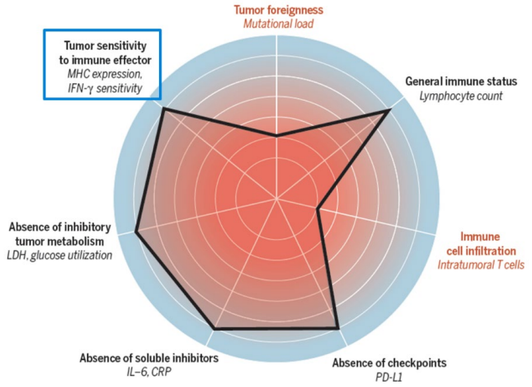


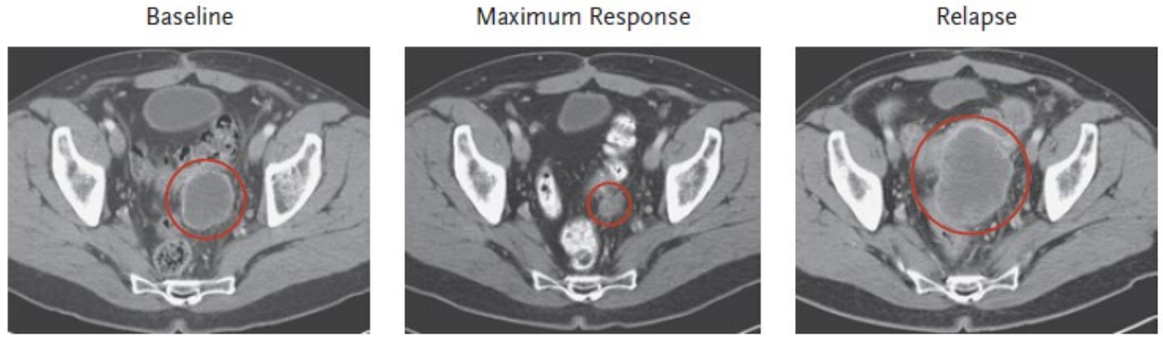


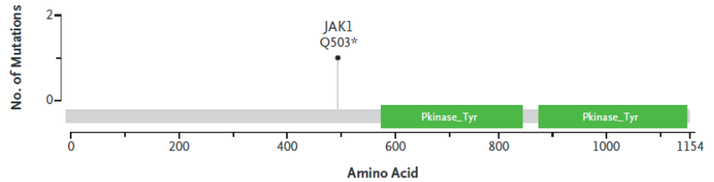

Anagnostou, Velculescu - Cancer Discovery 2017

# Resistance Via Reduced Tumor Sensitivity to Immune Effectors

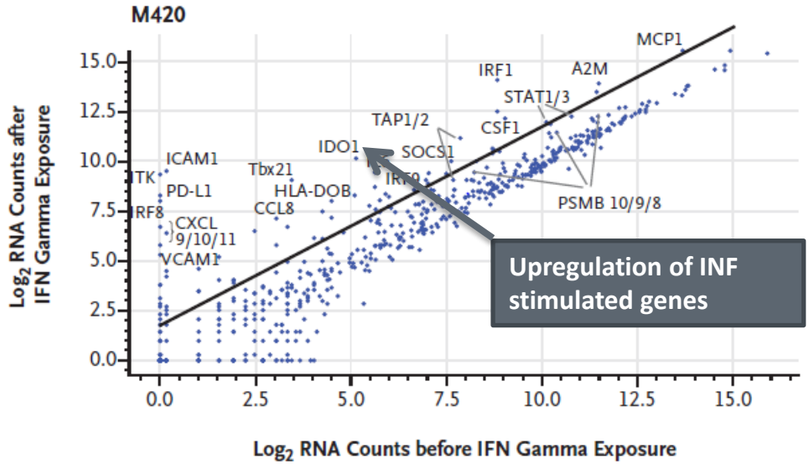
*Inactivating JAK 1/2 mutations abolish INFγ signaling, causing resistance to pembrolizumab in melanoma*



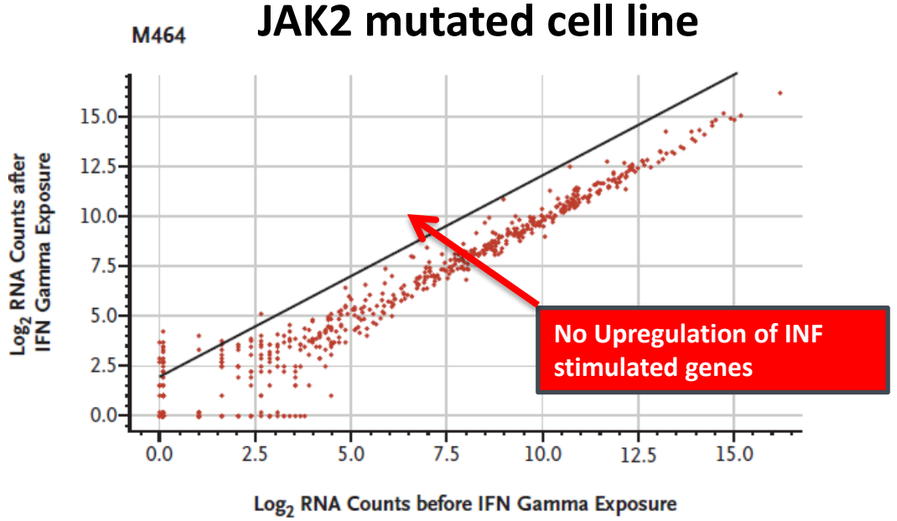




## Baseline cell line




## JAK2 mutated cell line

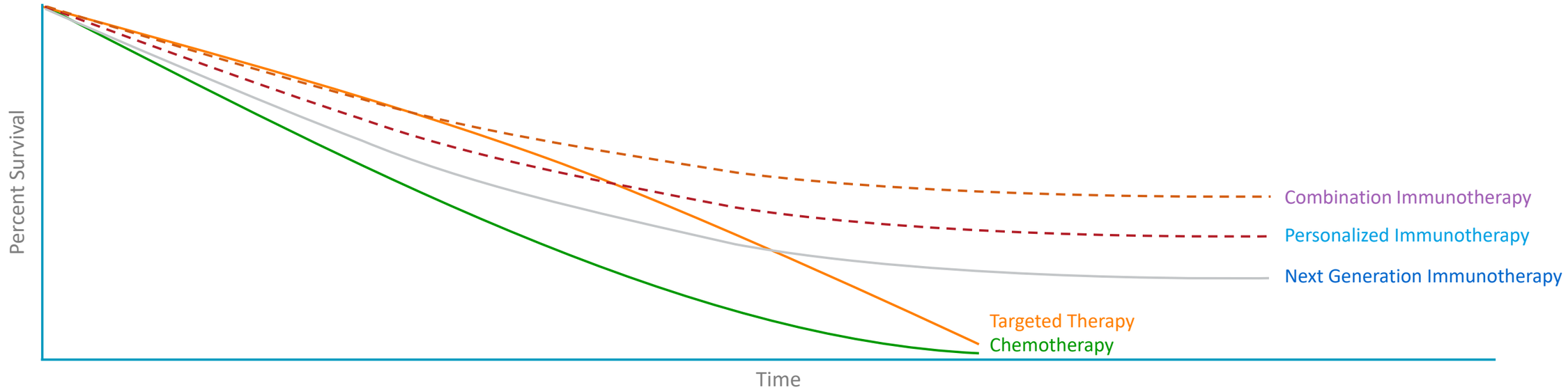



Zaretsky, Ribas NEJM 2016

# Cancer Immunotherapy of Tomorrow Aspires to Cure

*Expand long-term survival benefit to more patients with combo Rx*

**Illustrative KM curve for overall survival**




**Pre-1990s**
Chemotherapy

**1990s+**
Targeted Agents

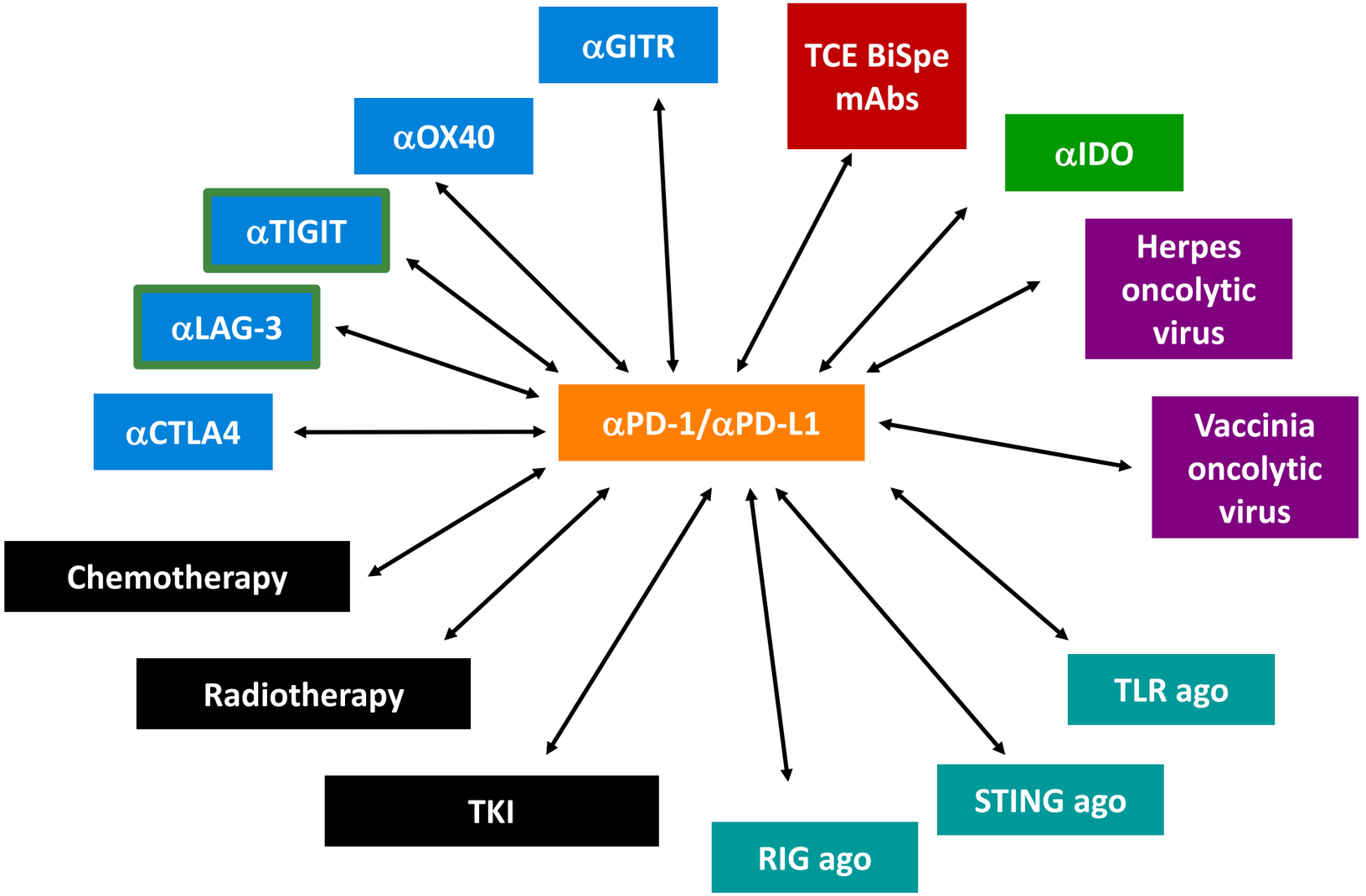
**2010+**
First "Next Gen" Immunotherapy

**2015+**
Personalized Immunotherapy

**2015+**
Combination Immunotherapy

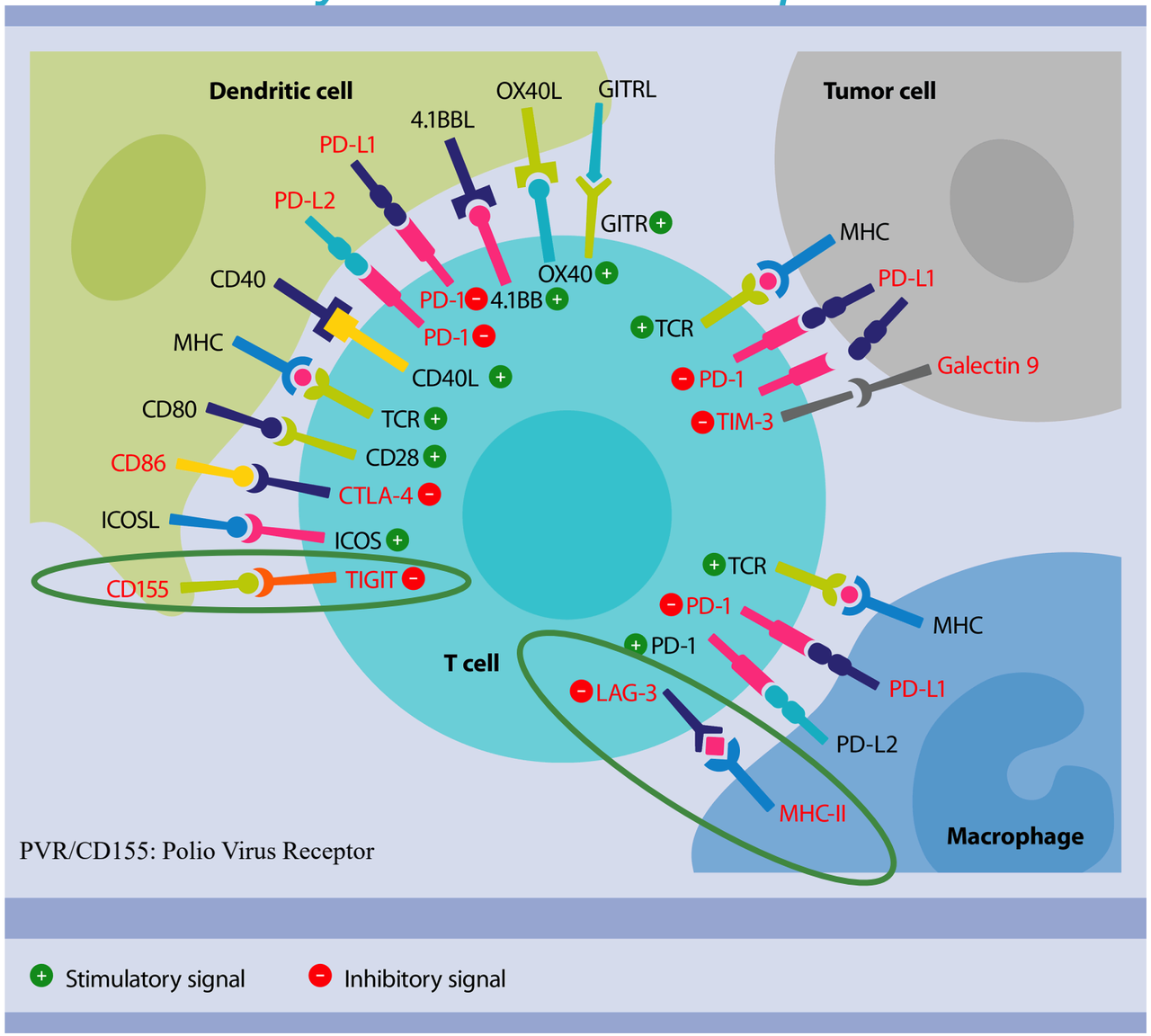
# Combining Immunotherapy With Other Therapies

*Which combinations for which patients?*



# Next Wave of Cancer Immunotherapy Targets

## *TIGIT & LAG-3 are inhibitory immune checkpoints*



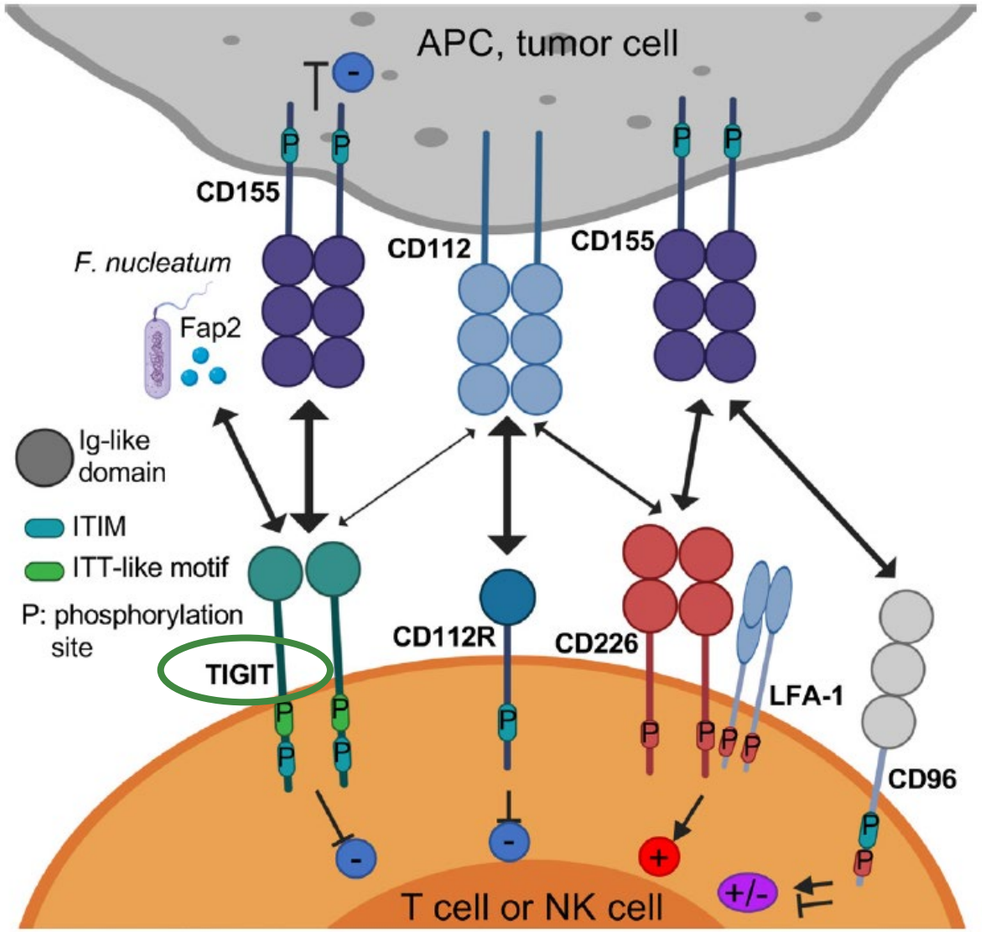



https://www.miltenyibiotec.com/LV-en/applications/flow-cytometry-applications/immune-checkpoint-analysis.html

# TIGIT Immunobiology and Function

## *T cell immunoreceptor with immunoglobulin and ITIM (immunoreceptor tyrosine-based inhibitory motif) domain*

- **TIGIT is upregulated/expressed by immune cells, including activated T cells, natural killer cells, and regulatory T cells.**
- **TIGIT binds to two ligands, CD155 (PVR) and CD112 (PVRL2, nectin-2), that are expressed by tumor cells and antigen-presenting cells in the tumor microenvironment.**
- **TIGIT pathway regulates T cell-mediated (adaptive) and natural killer cell-mediated (innate) tumor recognition in vivo and in vitro.**
- **In cancer, TIGIT is coexpressed with PD-1 on tumor antigen-specific CD8+ T cells and CD8+ tumor-infiltrating lymphocytes (TILs)**

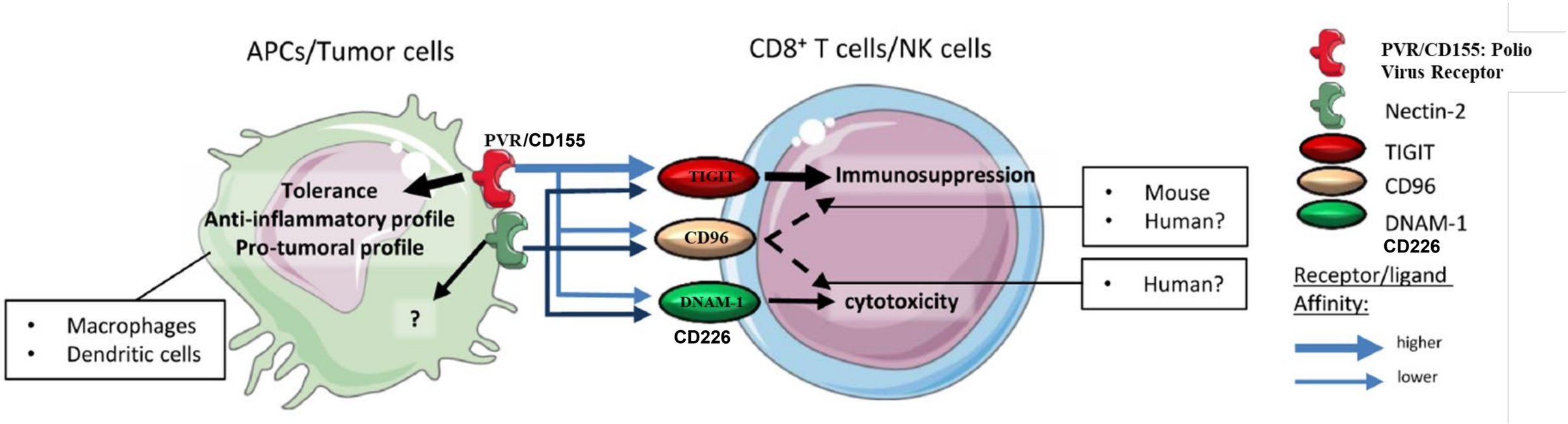





Chauvin et al. TIGIT in cancer immunotherapy. JITC 2020;8e000957

# Regulation of T/NK-cell via TIGIT-PVR Axis

*Differential affinity 'switching' of immunosuppression vs. cytotoxicity/immune effector*

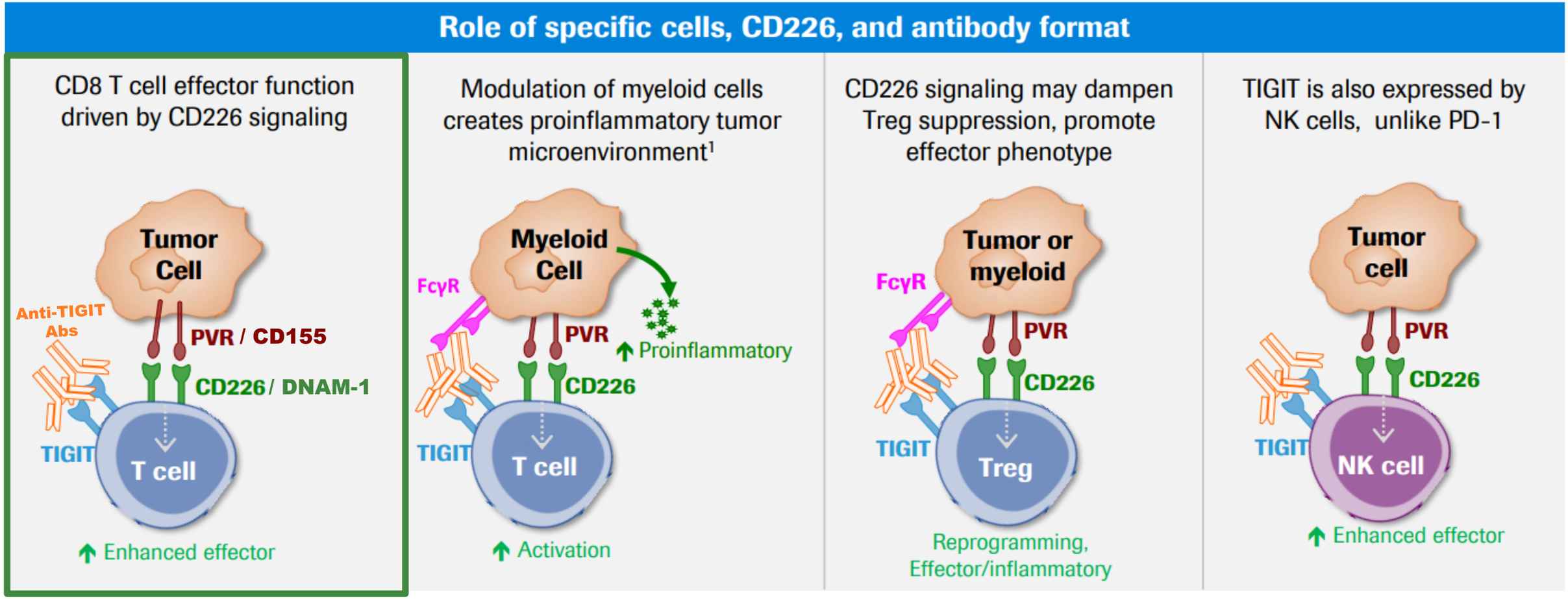





Gorvel et al. F1000Research 2020, 9(F1000 Faculty Rev):354

# Anti-TIGIT Monoclonal Antibody Mechanism of Action

*Sequestration of TIGIT away from PVR-CD226 synapse*




*Anti-TIGIT Fc:FcγR interaction may sequester TIGIT away from the synapse, and play a role in reprogramming of myeloid cells*



Dahan Cancer Cell 2015

NK: natural killer cell; Fc: Fragment crystallizable region

# Anti-TIGIT Programs in Clinical Development

## *Most in phase I with tiragolumab in phase III*

| Programme | Company | Phase | Cancer type | Notes |
|---|---|---|---|---|
| Tiragolumab (MTIG7192A; RG6058) | Genentech/Roche | III | Adv or met NSCLC | Cityscape Phase II promising results in Tecentriq combo at ASCO 20. 500 patient Skyscraper-01 (NSCLC) and 400 patient SS-02 (SCLC). Both ongoing, expected filing date 2022 and 2023+. |
| AB154 | Arcus Bioscience | II | Adv NSCLC | 150 patient Phase II study monotherapy & combination (anti-PD-1 mAb), started Q220 |
| MK-7684 | Merck | II | Solid cancers Melanoma | Various subset studies, with c 90 patients each, of Keynote 01A and 02B, ongoing |
| BMS-986207 | Bristol-Myers Squibb | I/II | Solid tumours Mult myeloma | 170 patient Phase I/II study mono & combo, ongoing 104 patient Phase I/II study combo, start Q320 |
| Etigilimab (OMP-313M32) | Mereo Biopharma | I | Adv or Met solid cancers | 33 patient dose escalation study, completed Q219 |
| ASP8374 | Astellas Pharma, Potenza Therapeutics | I | Adv solid cancers | 363 patient Phase Ib monotherapy & combination study, estimated completion Q321 |
| EOS-448 | Iteos Therapeutics | I | Solid cancers | 30 patient open label study, started Q220 |
| BGB-A1217 | Beigene | I | Adv solid cancers | 39 patient open label study in combination with tislelizumab (anti-PD1), estimated completion Q221 |
| IBI-939 | Innovent | I | Adv solid cancers | 270 patient dose escalation study, started Q220 |
| COM902 | Compugen | I | Solid cancers | 45 patient open label study, started Q220 |

Source: Evaluate, clinicaltrials.gov, Trinity Delta  Note: Adv = advanced, Met = metastatic

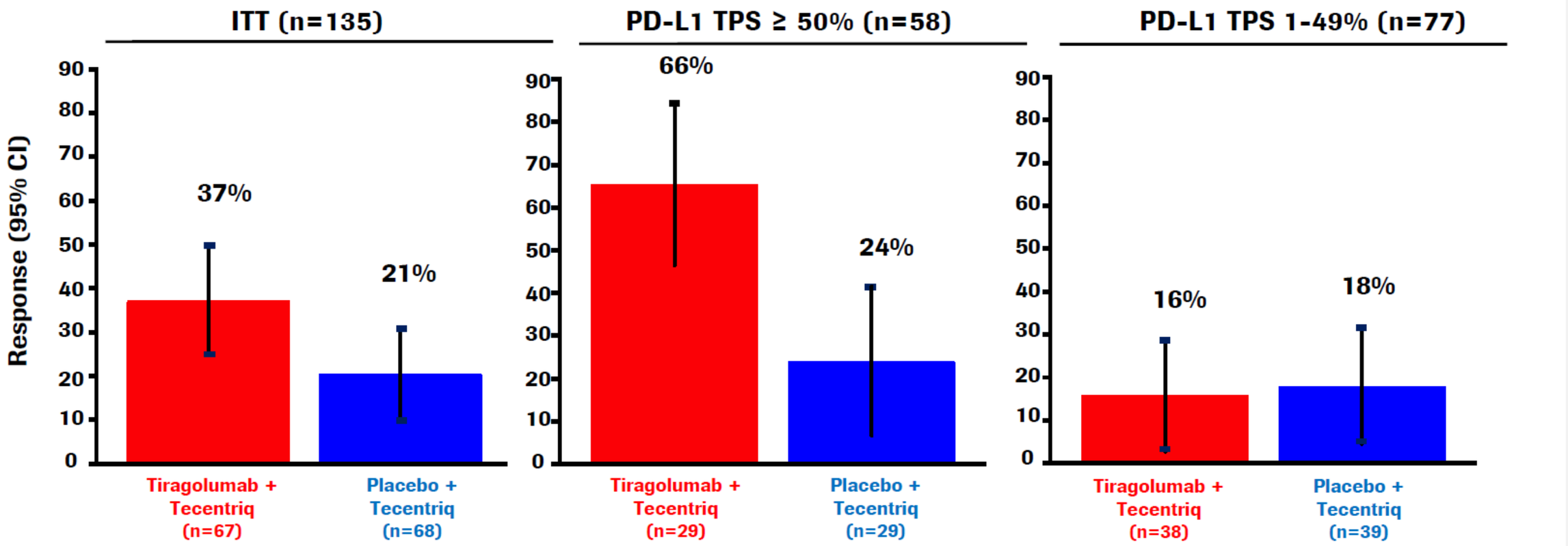




https://www.trinitydelta.org/wp-content/uploads/2020/09/Mereo-BioPharma-Outlook-020920.pdf

# CITYSCAPE rPh II: Tiragolumab plus Tecentriq in 1L Stage IV NSCLC

*Updated ORR analysis with 10.9 months median follow-up*




**Consistent and clinically meaningful overall response rate (ORR), mainly driven by the PD-L1 high population (TPS>50%)**

Rodriguez-Abreu. ASCO 2020. Abstr 9503.

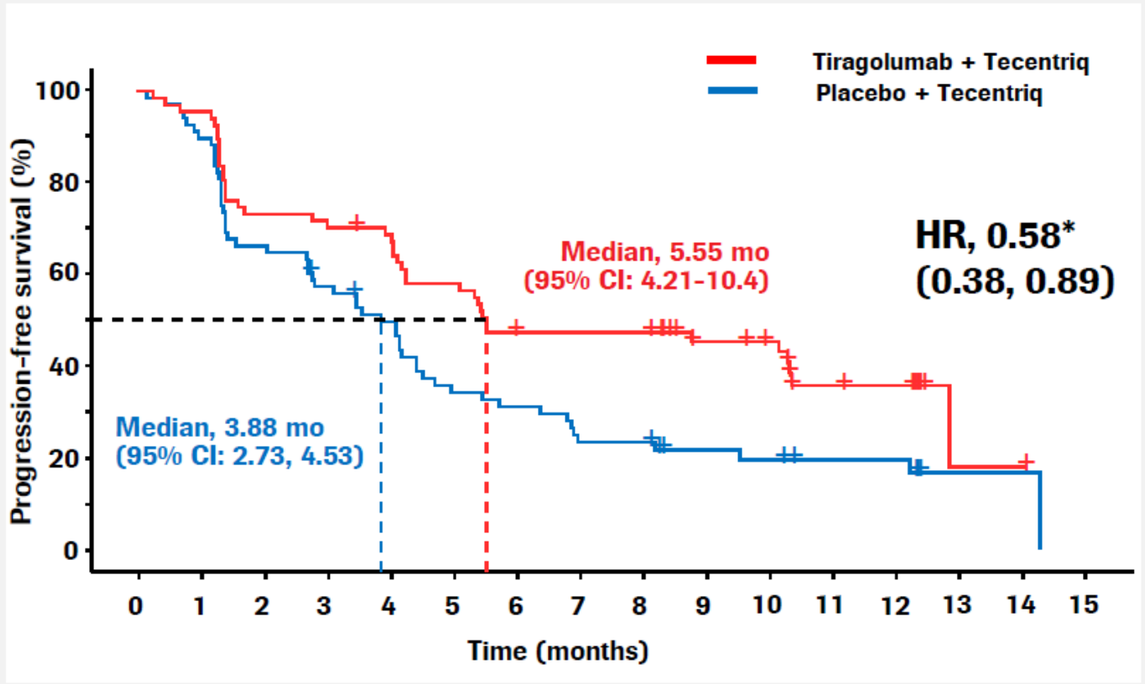


Follow-up data cut-off: 02 December; 2019; ITT=intention-to-treat; TPS=tumor proportion score

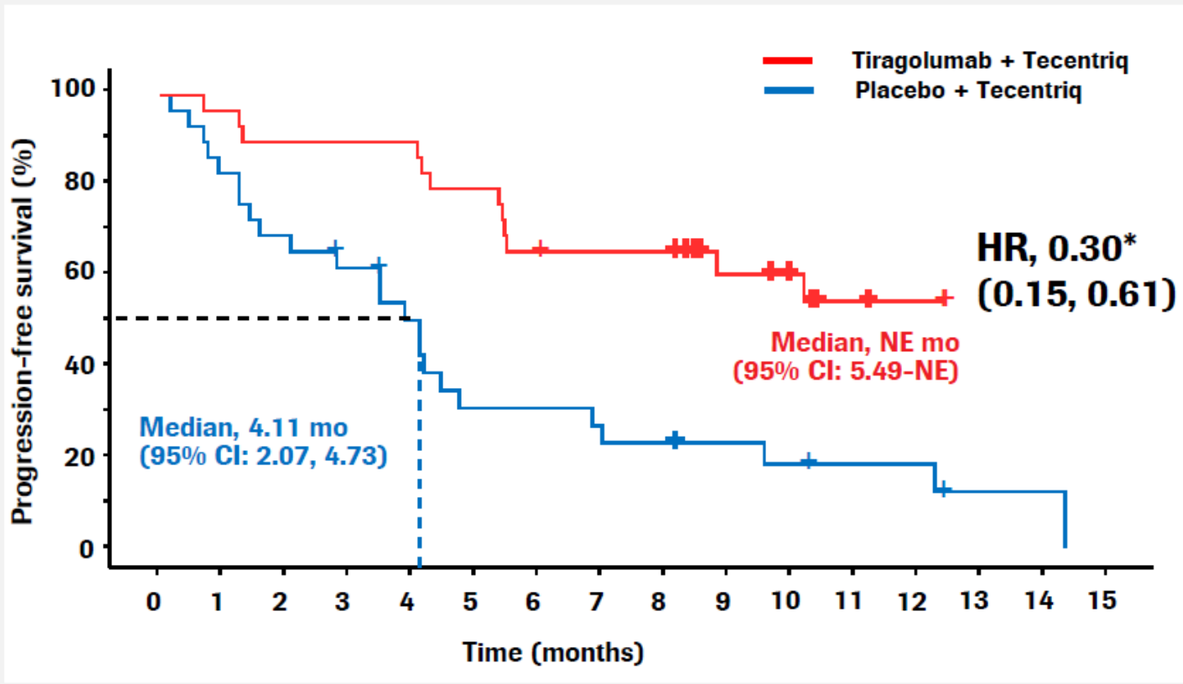
# CITYSCAPE rPh II: Tiragolumab plus Tecentriq in 1L Stage IV NSCLC

*Updated PFS analysis with 10.9 months median follow-up*

## Updated investigator-assessed PFS: ITT




## Updated Investigator-Assessed PFS: PD-L1 TPS ≥ 50%




**Consistent and clinically meaningful PFS at longer follow-up with greater magnitude of improvement in the PD-L1 high population**



Follow-up data cut-off: 02 December; 2019; NE = Non-evaluable; PFS = progression free survival; ITT=intention-to-treat; TPS=tumor proportion score *unstratified HR

# TIGIT Immunohistochemistry

## *Expression of the immune checkpoint receptor TIGIT in Hodgkin's lymphoma*

- **Dianova mouse anti-TIGIT, clone TG-1,1:70**
- **Detected with the DAB-kit (DAKO, Santa Clara, United States)**
- **All analyzed cases (40) of HL contained 9–99% (median: 86%) of TIGIT+ lymphoid cells.**
- **TIGIT localized to the same cells as PD-1**
- **Expression levels of TIGIT and PD-1 were highly variable among the analyzed samples. Highest levels of TIGIT and PD-1 were found in one sample of nodular lymphocytic-predominant HL (NLPHL)**
- **Results encourage further studies evaluating the role of TIGIT as a target for immunotherapies in Hodgkin's lymphoma**

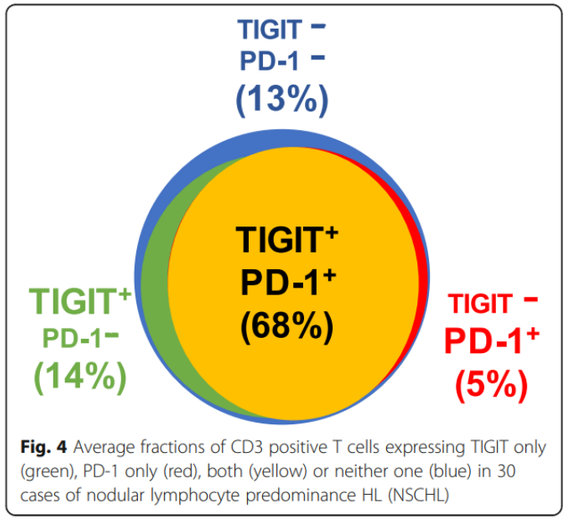
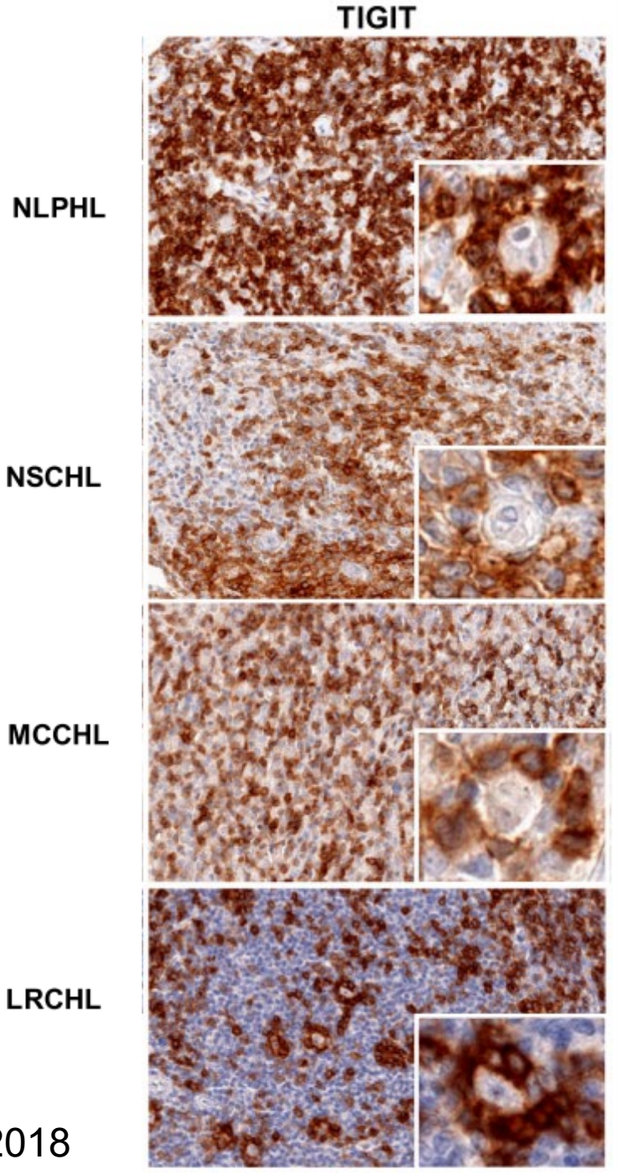



**Fig. 4** Average fractions of CD3 positive T cells expressing TIGIT only (green), PD-1 only (red), both (yellow) or neither one (blue) in 30 cases of nodular lymphocyte predominance HL (NSCHL)



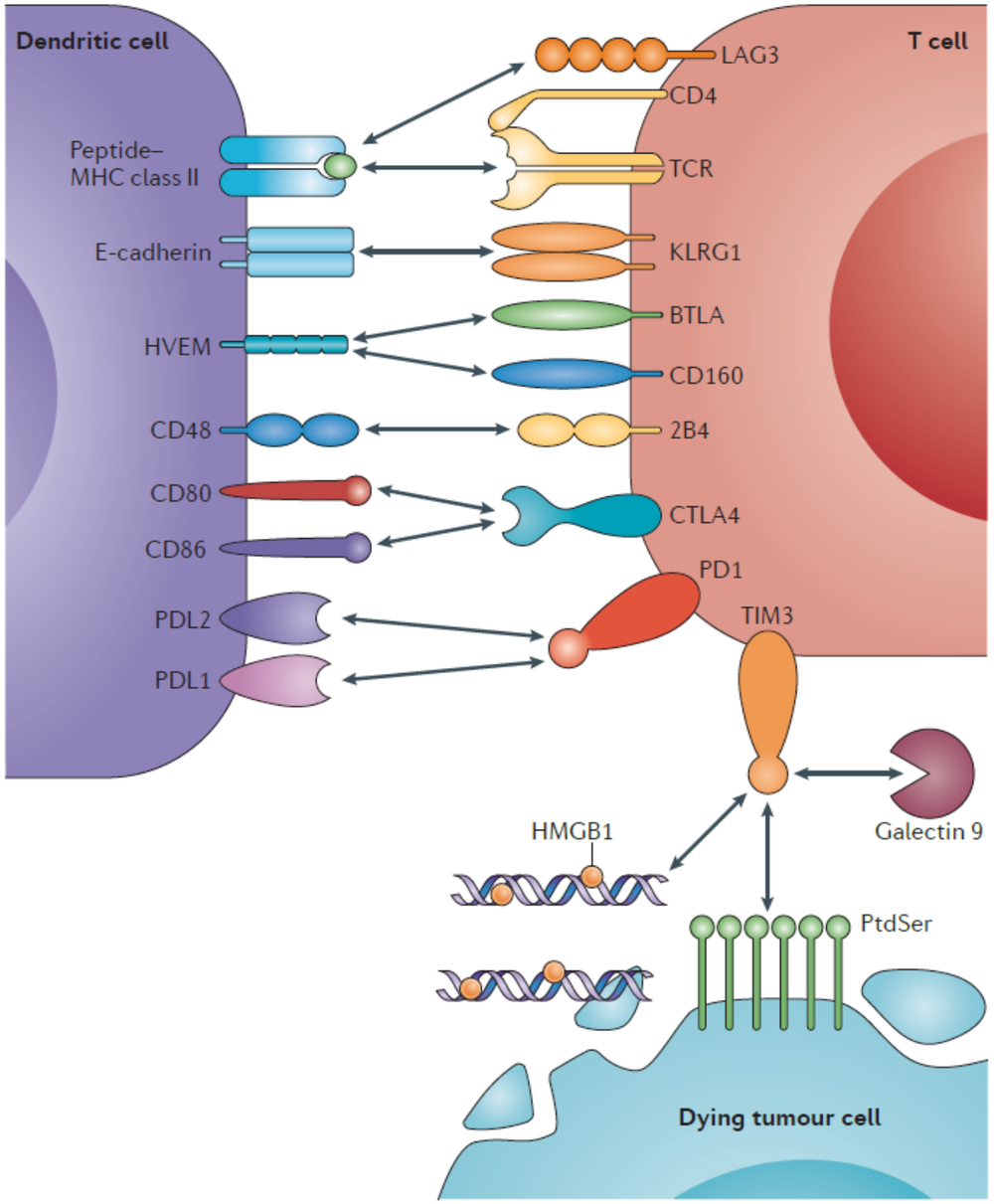



Li et al. Expression of the immune checkpoint receptor TIGIT in Hodgkin's lymphoma. BMC Cancer 2018

# LAG-3 (Lymphocyte Activation Gene-3)

## *Immune biology and mechanism*

- Type I transmembrane protein w/well established role in the negative regulation of T cell function
- Extracellular region has 4 Ig-like domains w/20% identity with CD4
- Binds MHC class II molecules with high affinity; some cancers express MHC class II (e.g. melanoma)
- Not expressed on naive T cells, but can be induced on CD4+ and CD8+ T cells upon antigen stimulation.
- Also expressed on Tregs; inhibition of LAG3 has been shown to inhibit the suppressive activity of Treg cells.
- Pre-clinical synergy of LAG-3 and PD1 blockade led to clinical investigation



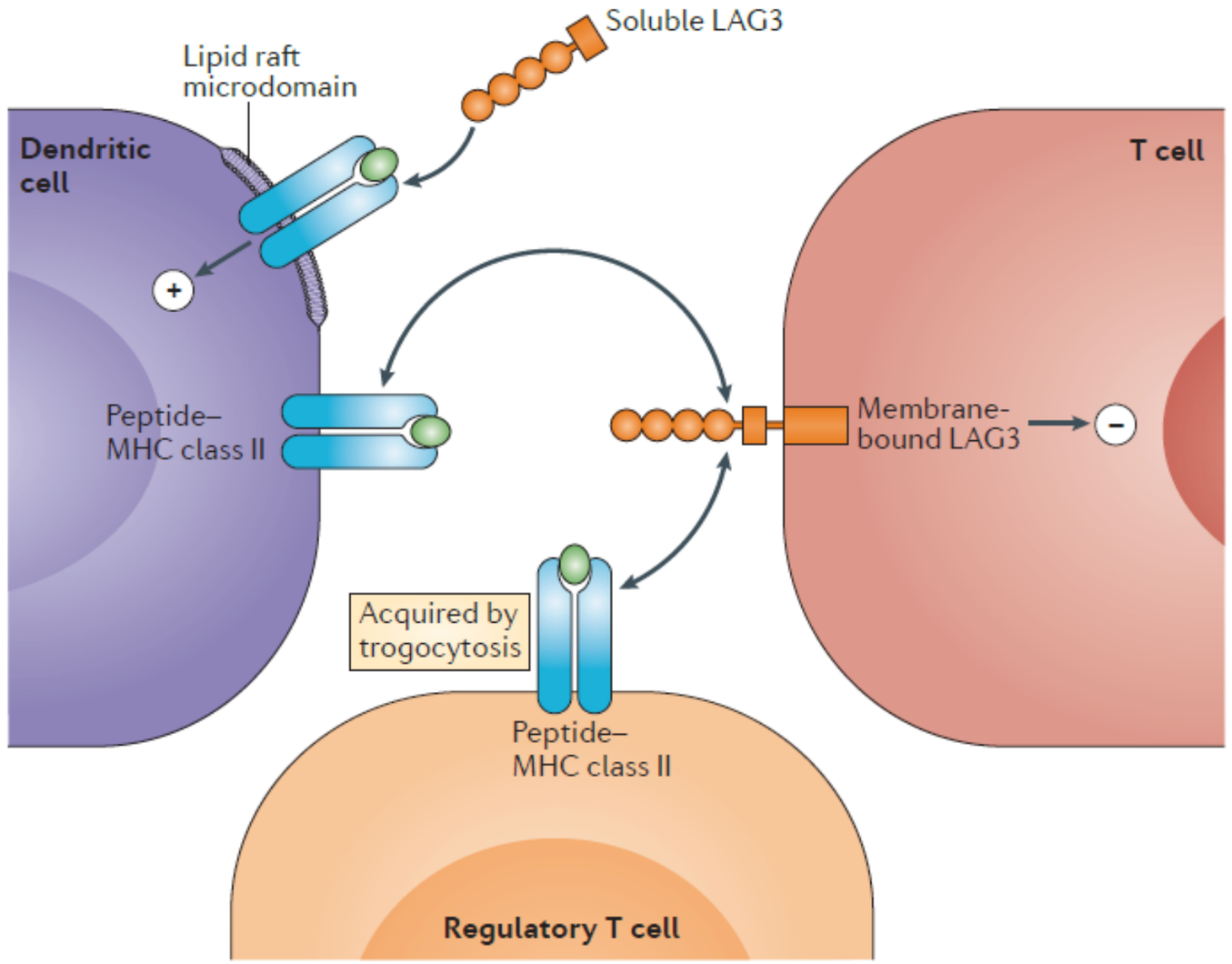



Nguyen et al. Nature Reviews Immunology Jan 2015 v15

# Soluble form of LAG-3

*Not the intended target of anti-LAG3 molecules*

- **LAG3 also encodes an alternative splice variant that is translated to a soluble form of LAG3, which exhibits immune adjuvant activity**
- **The soluble form of LAG3 binds MHC class II molecules in 'lipid raft' micro-domains on a minor subset of APCs**
- **Evidence that sLAG3 has clinical importance in vivo, as overall survival is improved in patients with breast cancer who have higher levels of sLAG3 at the time of diagnosis compared with patients who have lower levels**

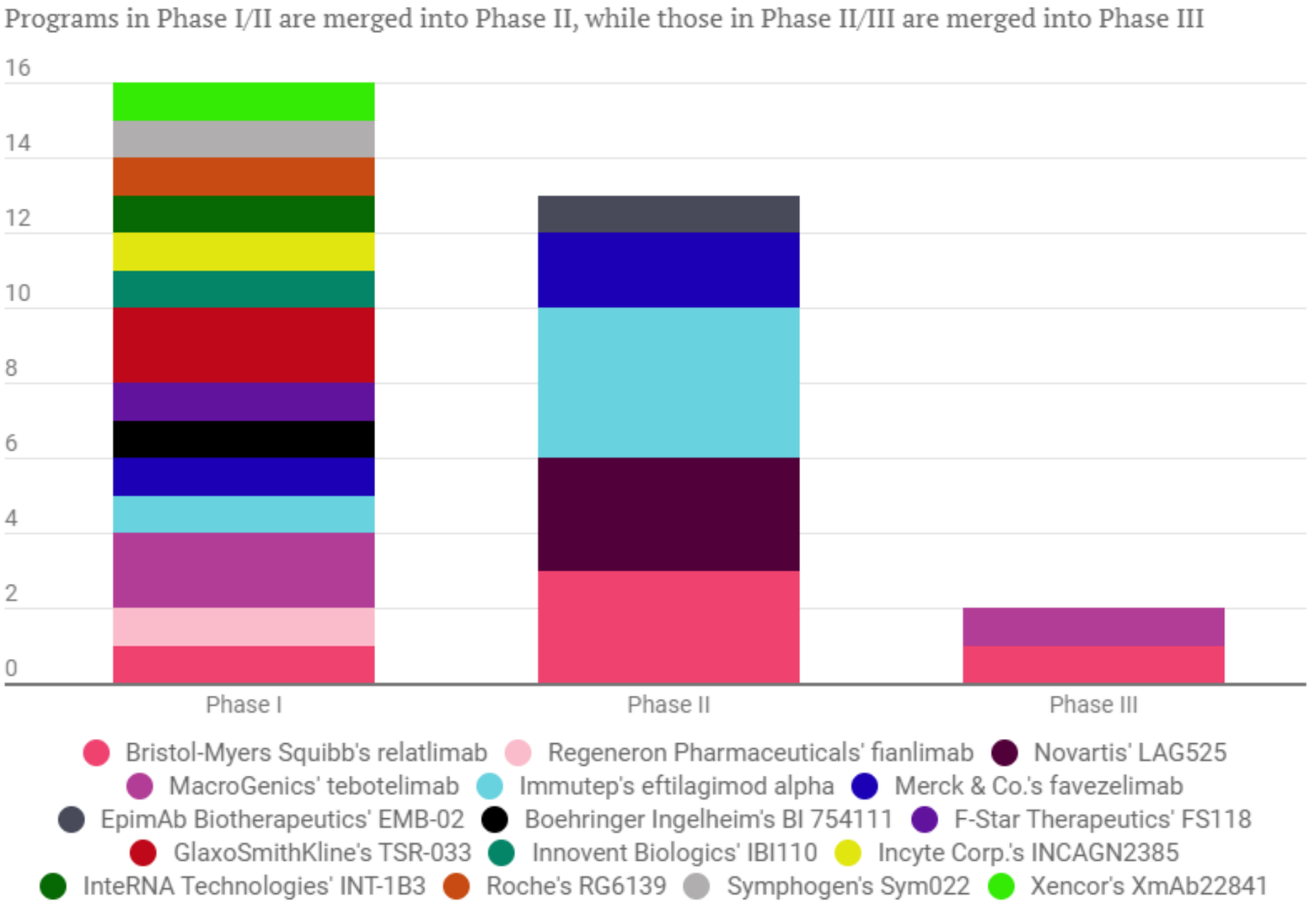





Nguyen et al. Nature Reviews Immunology Jan 2015 v15

# 16 Pharma LAG-3 Programs by Development Phase

*Most molecules in phase I/II with relatlimab and tebotelimab in phase III*

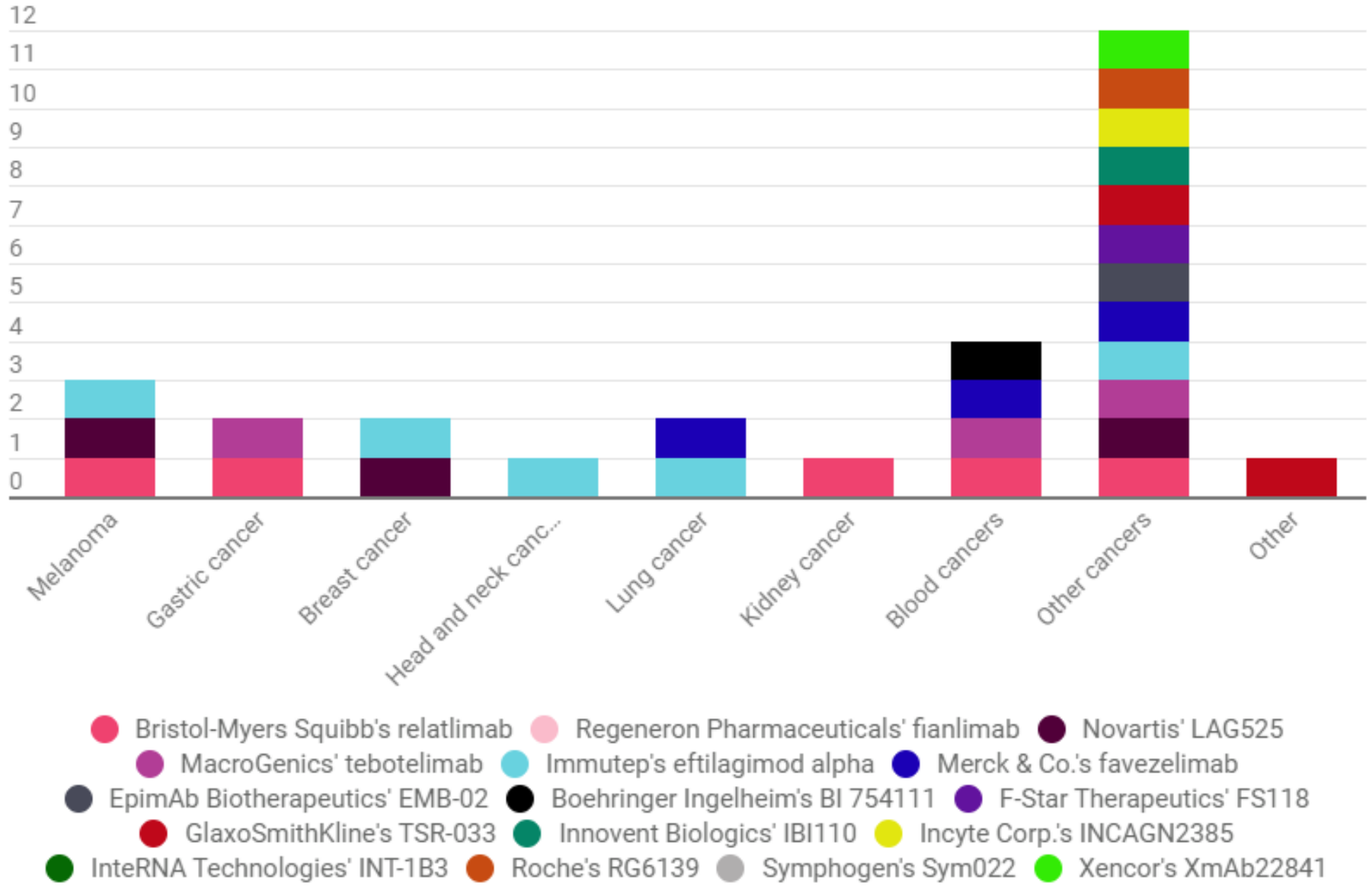





https://scrip.pharmaintelligence.informa.com/SC144491/ASCO-Offers-Glimpse-Of-LAG-3-Inhibitors-Potential-Opportunities--And-Limitations

# Pharma LAG-3 Programs by Indication

*Broad array of disease areas being explored*




Source: Biomedtracker





https://scrip.pharmaintelligence.informa.com/SC144491/ASCO-Offers-Glimpse-Of-LAG-3-Inhibitors-Potential-Opportunities--And-Limitations

# LAG-3 Inhibitor Data @ ASCO 2021

*Broad array of disease areas being explored*

| LAG-3/PD-(L)1 combo | Sponsors/partners | Phase | Disease | Number of patients | Results |
|---|---|---|---|---|---|
| relatlimab/Opdivo | BMS | II/III | advanced melanoma | 714 | Median PFS 10.1 months vs 4.6 months for Opdivo alone |
| relatlimab/Opdivo | MD Anderson | II | neoadjuvant and adjuvant melanoma | 30 | ORR 57%, 1-year EFS 90%, 1-year RFS 93%, 1-year OS 95% |
| fianlimab/Libtayo | Regeneron | I | advanced melanoma | 48 | ORR 63.6%, median PFS not reached |
| favezelimab/Keytruda | Merck & Co. | I | colorectal cancer | 80 | ORR 6.3% |
| eftilagimod alpha/Keytruda | Immutep/Merck & Co. | II | non-small cell lung cancer and head and neck cancer | 73 | ORR 41.7% in NSCLC, 29.7% in HNSCC |
| eftilagimod alpha/Bavencio | Immutep/Pfizer/Merck KGaA | I | solid tumors | 12 | DCR 50% |

PFS = progression-free survival; EFS = event-free survival; RFS = relapse-free survival; OS = overall survival; ORR = objective response rate; DCR = disease control rate

Sources: ASCO, company reports





https://scrip.pharmaintelligence.informa.com/SC144491/ASCO-Offers-Glimpse-Of-LAG-3-Inhibitors-Potential-Opportunities--And-Limitations

2021 ASCO ANNUAL MEETING

# Relatlimab (RELA) + nivolumab (NIVO) versus NIVO in first-line advanced melanoma: primary phase 3 results from **RELA**TIVITY-047 (CA224-047)

Evan J. Lipson,[1] Hussein A. Tawbi,[2] Dirk Schadendorf,[3] Paolo A. Ascierto,[4] Luis Matamala,[5] Erika Castillo Gutiérrez,[6] Piotr Rutkowski,[7] Helen J. Gogas,[8] Christopher D. Lao,[9] Juliana Janoski De Menezes,[10] Stéphane Dalle,[11] Ana Arance,[12] Jean-Jacques Grob,[13] Shivani Srivastava,[14] Mena Abaskharoun,[14] Katy L. Simonsen,[14] Bin Li,[14] Georgina V. Long,[a,15] F. Stephen Hodi[a,16]

[1]Bloomberg Kimmel Institute for Cancer Immunotherapy, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA; [2]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]University Hospital Essen, Essen, Germany; [4]Istituto Nazionale Tumori Fondazione "G. Pascale", Napoli, Italy; [5]Instituto Oncologico Fundacion Arturo Lopez Perez, Santiago, Chile; [6]FAICIC Clinical Research, Veracruz, Mexico; [7]Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [8]National and Kapodistrian University of Athens, Athens, Greece; [9]University of Michigan, Ann Arbor, MI, USA; [10]Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil; [11]Hospices Civils de Lyon, Cancer Research Center of Lyon, Pierre-Bénite, France; [12]Hospital Clinic Barcelona, Barcelona, Spain; [13]Aix-Marseille University, CHU Timone, Marseille, France; [14]Bristol Myers Squibb, Princeton, NJ, USA; [15]Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, Australia; [16]Dana-Farber Cancer Institute, Boston, MA, USA [a]Co-senior author

# Study design

- **RELATIVITY-047** is a global, randomized, double-blind, phase 2/3 study

**Key eligibility criteria**

- Previously untreated unresectable or metastatic melanoma[a]
- ECOG PS 0–1

**Stratification factors**

- LAG-3[b] — Analytically validated IHC assay
- PD-L1[c] — Agilent/Dako 28-8 pharmDx
- *BRAF*
- AJCC v8 M stage

N = 714

R 1:1

- RELA 160 mg + NIVO 480 mg fixed-dose combination (FDC) IV Q4W
- NIVO 480 mg IV Q4W

**Primary endpoint**

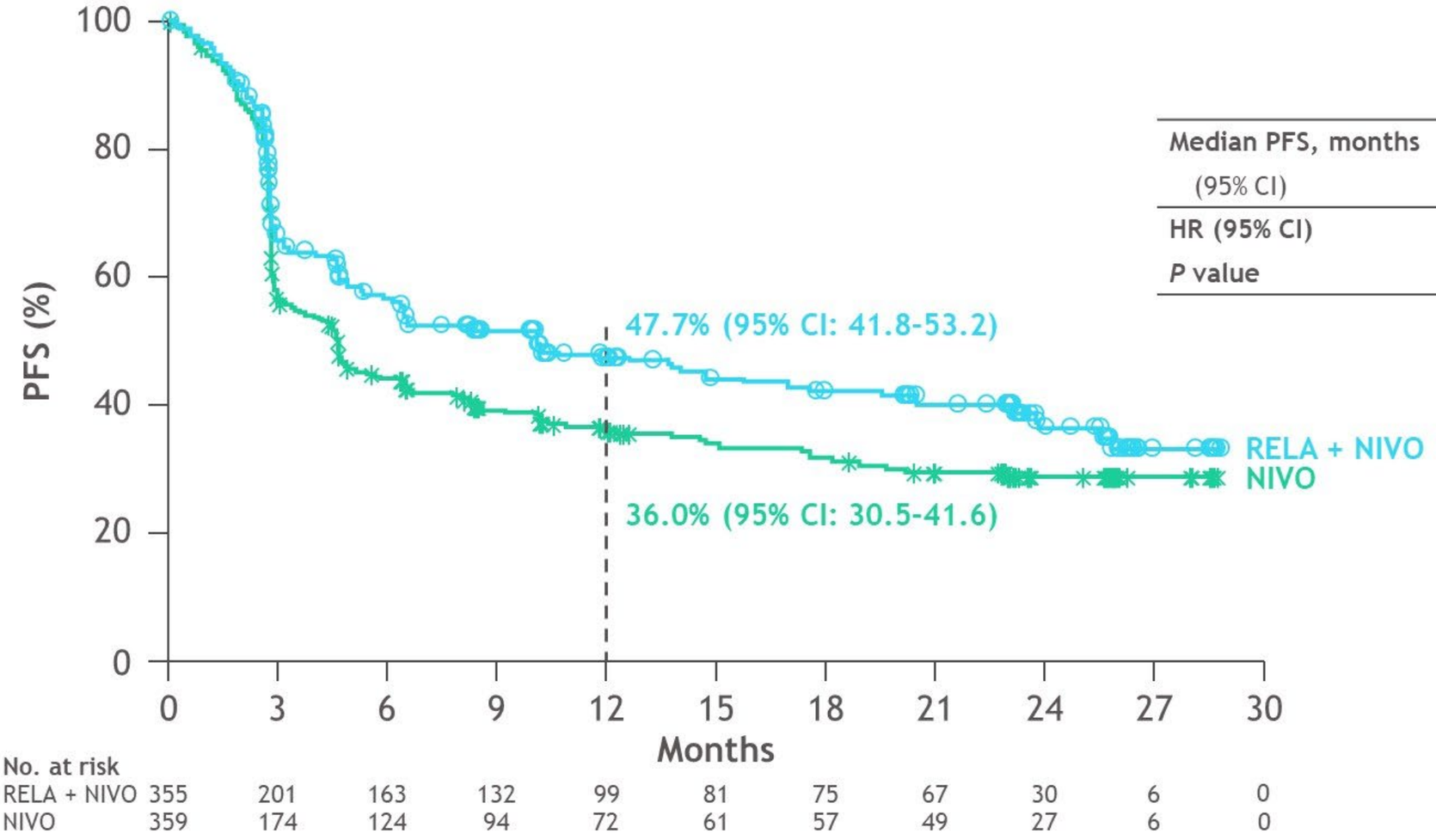
- PFS by BICR[d]

**Secondary endpoints**

- OS
- ORR by BICR[d]

AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; CTLA-4, cytotoxic T lymphocyte antigen-4; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; IV, intravenous; ORR, overall response rate; Q4W, every 4 weeks; R, randomization.
ClinicalTrials.gov: NCT03470922; Lipson E, et al. Poster presentation at ESMO Congress; October 19-23, 2018; Munich, Germany. Abstract 1302TiP.
[a]Prior adjuvant/neoadjuvant treatment permitted (anti-PD-1 or anti-CTLA-4 permitted if at least 6 months between the last dose and recurrence; interferon therapy permitted if the last dose was at least 6 weeks before randomization); [b]LAG-3 expression on immune cells was determined using an analytically validated IHC assay (LabCorp); [c]PD-L1 expression on tumor cells was determined using the validated Agilent/Dako PD-L1 IHC 28-8 pharmDx test; [d]First tumor assessment (RECIST v1.1) performed 12 weeks after randomization, every 8 weeks up to 52 weeks, and then every 12 weeks. Database lock date: March 9, 2021.

# RELATIVITY 047 demonstrated superior PFS benefit by BICR for RELA + NIVO FDC vs NIVO




| | RELA + NIVO (n = 355) | NIVO (n = 359) |
|---|---|---|
| Median PFS, months | 10.12 | 4.63 |
| (95% CI) | (6.37-15.74) | (3.38-5.62) |
| HR (95% CI) | 0.75 (0.62-0.92) | |
| *P* value | 0.0055 | |

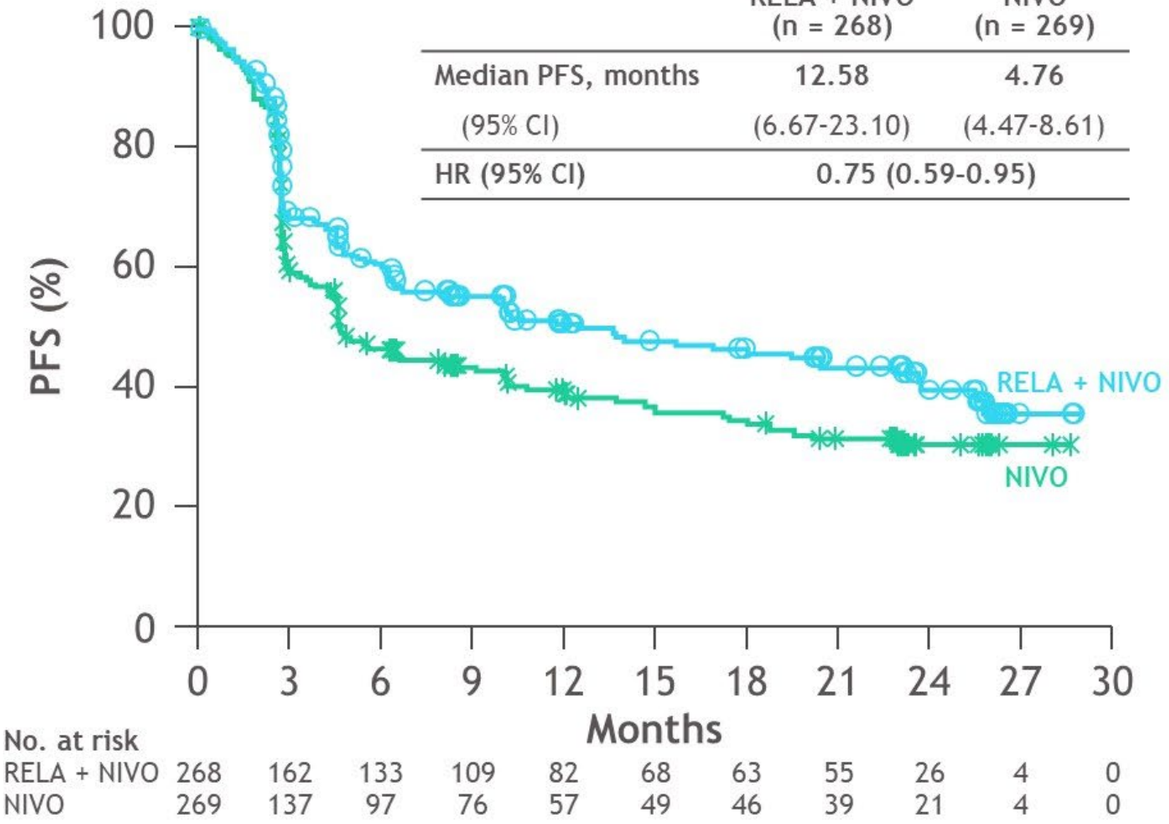
CI, confidence interval; HR, hazard ratio.
All randomized patients. Statistical model for HR and *P* value: stratified Cox proportional hazard model and stratified log-rank test. Stratified by LAG-3 (≥ 1% vs < 1%), *BRAF* (mutation positive vs mutation wild-type), AJCC M stage (M0/M1any[0] vs M1any[1]). PD-L1 was removed from stratification because it led to subgroups with < 10 patients.

# PFS by LAG-3 expression

- PFS benefit favored RELA + NIVO FDC regardless of LAG-3 expression status

## LAG-3 expression ≥ 1%

| | RELA + NIVO (n = 268) | NIVO (n = 269) |
|---|---|---|
| Median PFS, months | 12.58 | 4.76 |
| (95% CI) | (6.67-23.10) | (4.47-8.61) |
| HR (95% CI) | 0.75 (0.59-0.95) | |

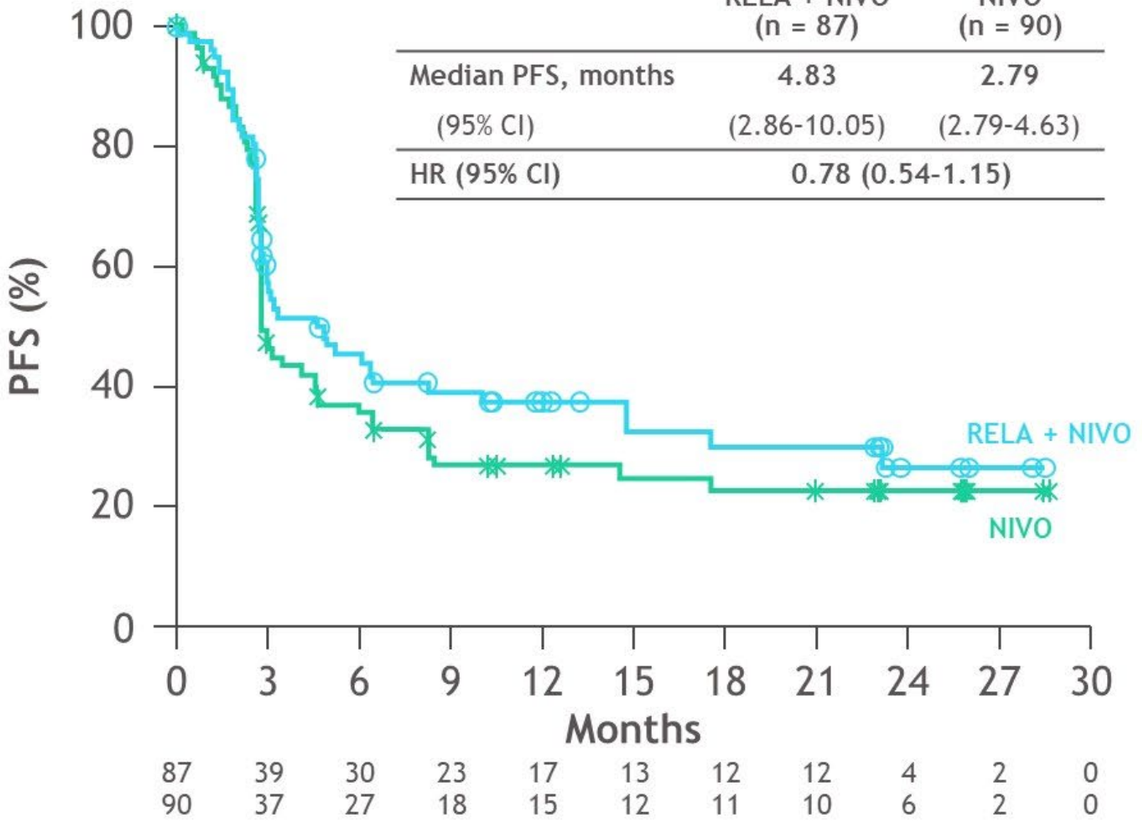



No. at risk

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| RELA + NIVO | 268 | 162 | 133 | 109 | 82 | 68 | 63 | 55 | 26 | 4 | 0 |
| NIVO | 269 | 137 | 97 | 76 | 57 | 49 | 46 | 39 | 21 | 4 | 0 |

## LAG-3 expression < 1%

| | RELA + NIVO (n = 87) | NIVO (n = 90) |
|---|---|---|
| Median PFS, months | 4.83 | 2.79 |
| (95% CI) | (2.86-10.05) | (2.79-4.63) |
| HR (95% CI) | 0.78 (0.54-1.15) | |




| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 87 | 39 | 30 | 23 | 17 | 13 | 12 | 12 | 4 | 2 | 0 |
| | 90 | 37 | 27 | 18 | 15 | 12 | 11 | 10 | 6 | 2 | 0 |

Statistical model for HR: unstratified Cox proportional hazard model.

# Benchmarking Relativity-047 Data

*Similar mPFS with lower toxicity*

| Cross-trial comparison in 1st-line melanoma | | | |
|---|---|---|---|
| **Regimen** | Opdivo | Opdivo + Yervoy | Opdivo + relatlimab |
| **Study** | Checkmate-066 | Checkmate-067 | Relativity-047 |
| **mPFS** | 5.1mth | 11.5mth | 10.1mth |
| **12-mth PFS** | 43.0% | 50.0% | 47.7% |
| **ORR** | 42% (20% CR) | 58% (22% CR) | Not given |
| **TRAE** | 74.3% | 96.0% | 81.1% |
| **Gr3-4 TRAE** | 11.7% | 59.0% | 18.9% |
| *Source: Asco, NEJM & prescribing information.* | | | |

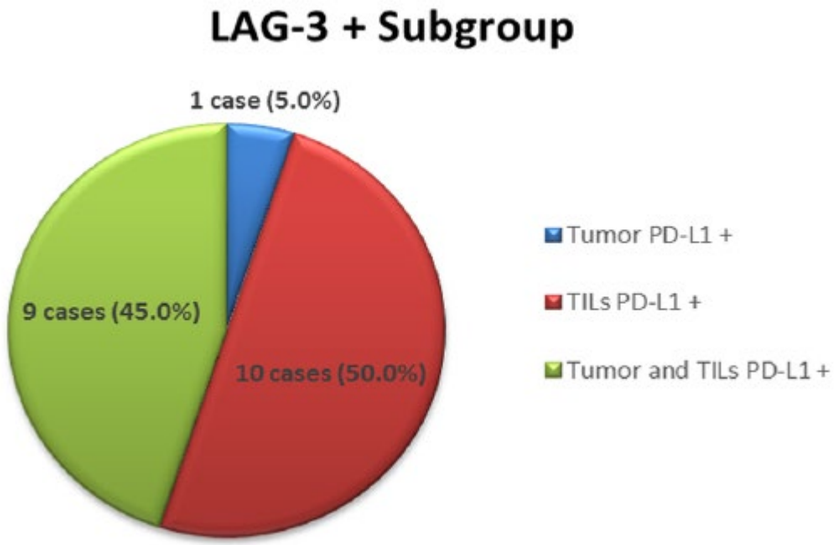


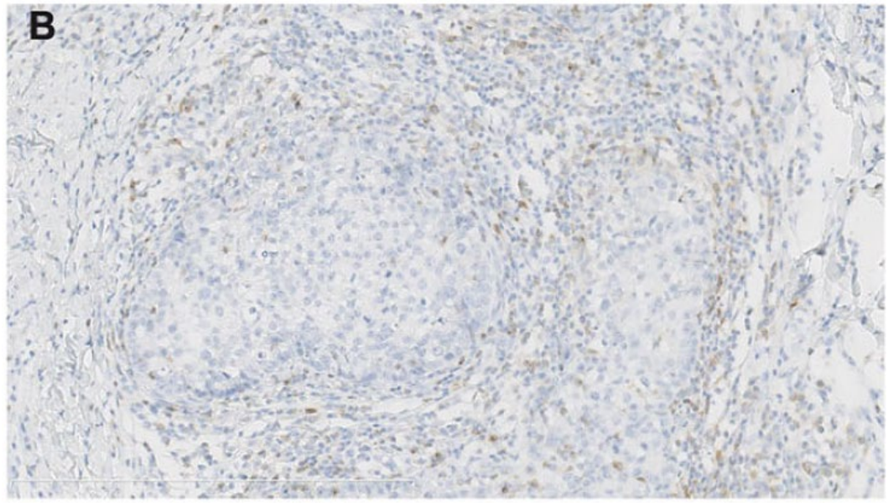
https://https://www.evaluate.com/vantage/articles/events/conferences/asco-2021-bristols-lag3-case-replacement-yervoy-And-Limitations

# LAG-3 Immunohistochemistry

*TNBC Study: Intact Mismatch Repair and Partial Co-Expression of PD-L1 and LAG-3*

- **LAG-3 (clone D2G40, dilution 1:150; Cell Signaling Technology, MA, USA)**
- **LAG-3 defined as positive when there were intra tumoral and peri-tumor stromal lymphocytes with any immunoreactivity in ≥1% of the entire tumoral area.**
- **20 LAG-3+ cases (27.0%, 20/74), all of which were PD-L1+**
- **Co-expression of PD-L1 and LAG-3 was noted in 46.5% (20/43) of the PD-L1+ population**





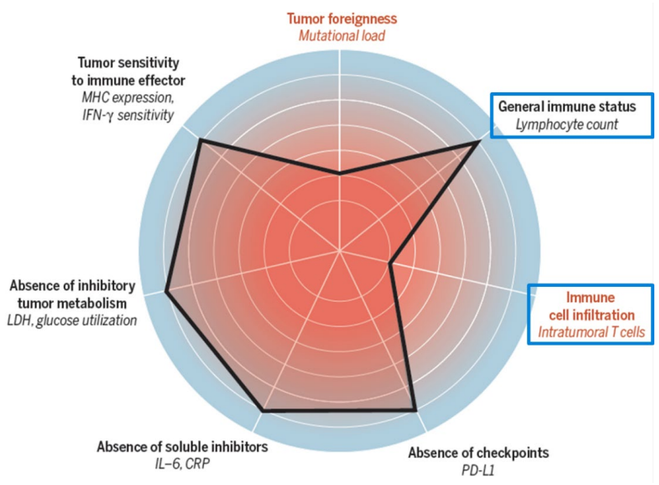



Wu et al. Triple-Negative Breast Cancer: Intact Mismatch Repair and Partial Co-Expression of PD-L1 and LAG-3, Frontier Immunology 24 Feb 2021

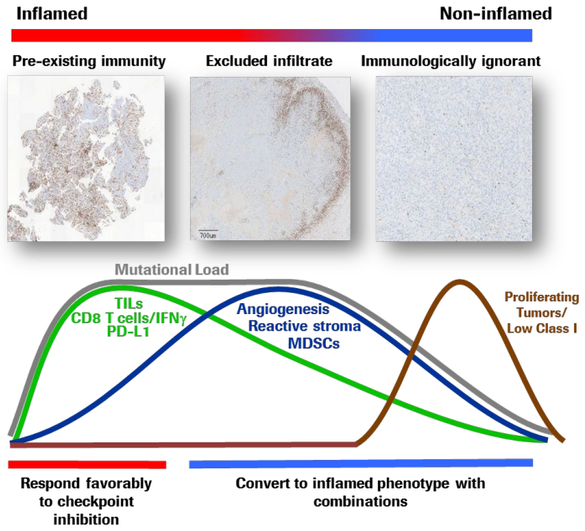
# The Need for More Accurate Predictive Biomarkers

*Multi-modal solution integrating biologic and AI-based insights*

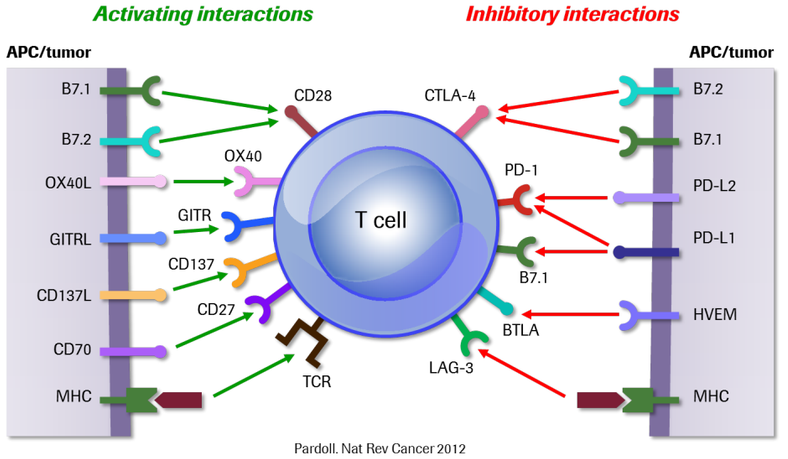
## Immune Responsiveness Factors




## Tumor Immune Infiltration Status

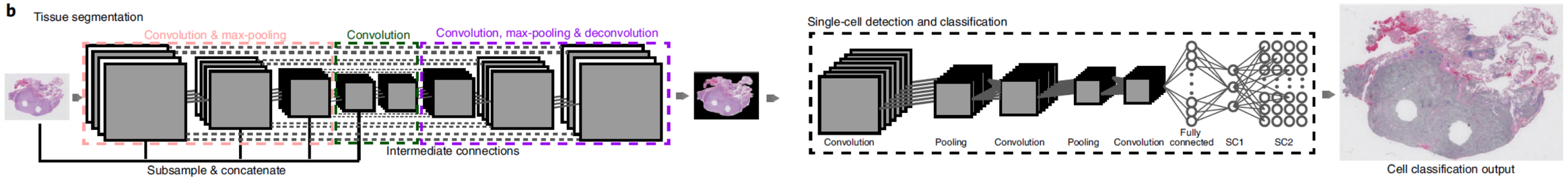



## Immune Checkpoint Regulation Status

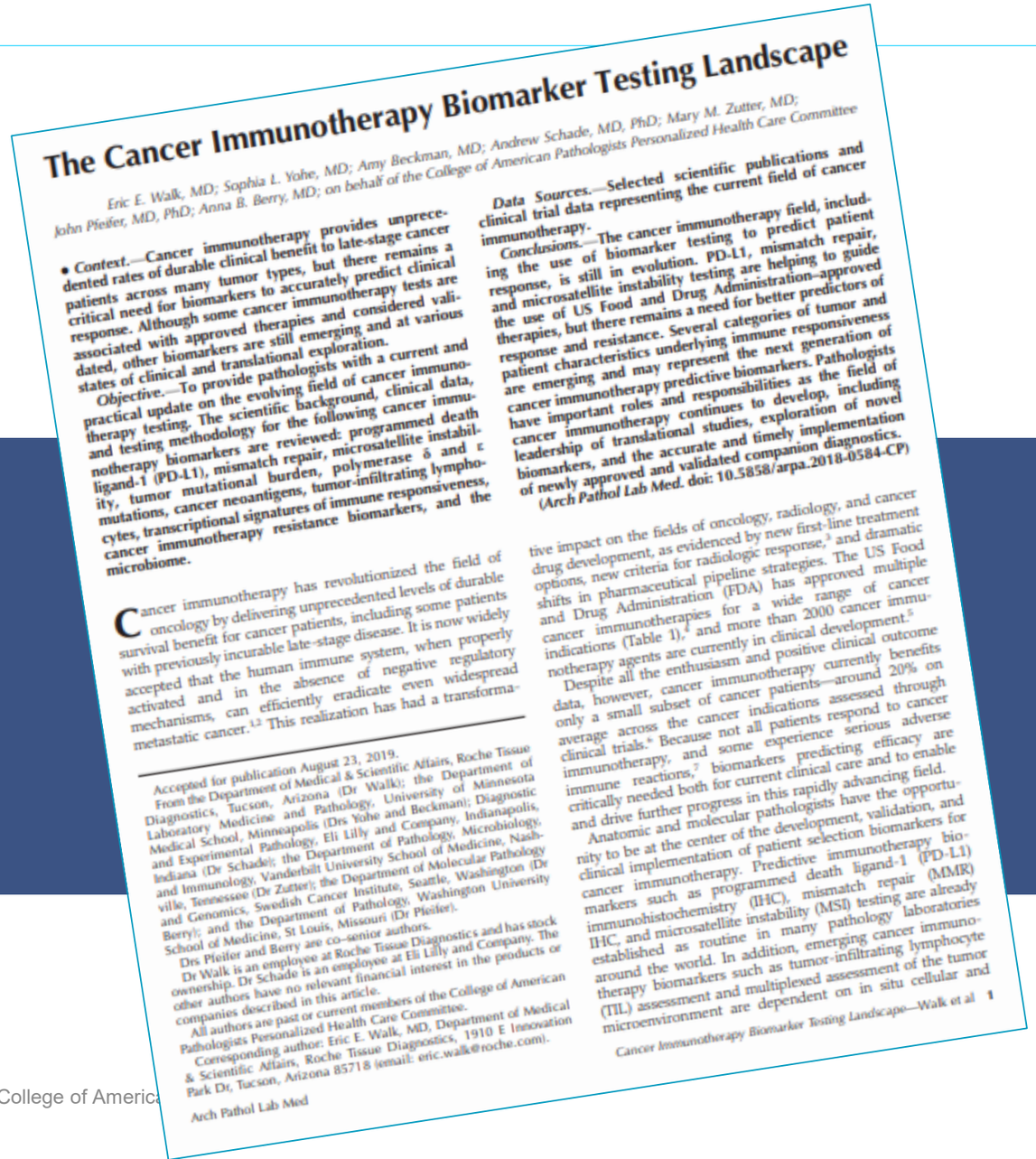



Pardoll. Nat Rev Cancer 2012

## Digital Pathology + Deep Learning



# CAP Personalized Healthcare Committee



## The Cancer Immunotherapy Biomarker Testing Landscape

*Eric E. Walk, MD; Sophia L. Yohe, MD; Amy Beckman, MD; Andrew Schade, MD, PhD; Mary M. Zutter, MD; John Pfeifer, MD, PhD; Anna B. Berry, MD; on behalf of the College of American Pathologists Personalized Health Care Committee*

• **Context.**—Cancer immunotherapy provides unprecedented rates of durable clinical benefit to late-stage cancer patients across many tumor types, but there remains a critical need for biomarkers to accurately predict clinical response. Although some cancer immunotherapy tests are associated with approved therapies and considered validated, other biomarkers are still emerging and at various states of clinical and translational exploration.

**Objective.**—To provide pathologists with a current and practical update on the evolving field of cancer immunotherapy testing. The scientific background, clinical data, and testing methodology for the following cancer immunotherapy biomarkers are reviewed: programmed death ligand-1 (PD-L1), mismatch repair, microsatellite instability, tumor mutational burden, polymerase δ and ε mutations, cancer neoantigens, tumor-infiltrating lymphocytes, transcriptional signatures of immune responsiveness, cancer immunotherapy resistance biomarkers, and the microbiome.

**Data Sources.**—Selected scientific publications and clinical trial data representing the current field of cancer immunotherapy.

**Conclusions.**—The cancer immunotherapy field, including the use of biomarker testing to predict patient response, is still in evolution. PD-L1, mismatch repair, and microsatellite instability testing are helping to guide the use of US Food and Drug Administration–approved therapies, but there remains a need for better predictors of response and resistance. Several categories of tumor and patient characteristics underlying immune responsiveness are emerging and may represent the next generation of cancer immunotherapy predictive biomarkers. Pathologists have important roles and responsibilities as the field of cancer immunotherapy continues to develop, including leadership of translational studies, exploration of novel biomarkers, and the accurate and timely implementation of newly approved and validated companion diagnostics.

(*Arch Pathol Lab Med.* doi: 10.5858/arpa.2018-0584-CP)

Cancer immunotherapy has revolutionized the field of oncology by delivering unprecedented levels of durable survival benefit for cancer patients, including some patients with previously incurable late-stage disease. It is now widely accepted that the human immune system, when properly activated and in the absence of negative regulatory mechanisms, can efficiently eradicate even widespread metastatic cancer.[1,2] This realization has had a transformative impact on the fields of oncology, radiology, and cancer drug development, as evidenced by new first-line treatment options, new criteria for radiologic response,[3] and dramatic shifts in pharmaceutical pipeline strategies. The US Food and Drug Administration (FDA) has approved multiple cancer immunotherapies for a wide range of cancer indications (Table 1),[4] and more than 2000 cancer immunotherapy agents are currently in clinical development.[5]

Despite all the enthusiasm and positive clinical outcome data, however, cancer immunotherapy currently benefits only a small subset of cancer patients—around 20% on average across the cancer indications assessed through clinical trials.[6] Because not all patients respond to cancer immunotherapy, and some experience serious adverse immune reactions,[7] biomarkers predicting efficacy are critically needed both for current clinical care and to enable and drive further progress in this rapidly advancing field.

Anatomic and molecular pathologists have the opportunity to be at the center of the development, validation, and clinical implementation of patient selection biomarkers for cancer immunotherapy. Predictive immunotherapy biomarkers such as programmed death ligand-1 (PD-L1) immunohistochemistry (IHC), mismatch repair (MMR) IHC, and microsatellite instability (MSI) testing are already established as routine in many pathology laboratories around the world. In addition, emerging cancer immunotherapy biomarkers such as tumor-infiltrating lymphocyte (TIL) assessment and multiplexed assessment of the tumor microenvironment are dependent on in situ cellular and

Accepted for publication August 23, 2019.

From the Department of Medical & Scientific Affairs, Roche Tissue Diagnostics, Tucson, Arizona (Dr Walk); the Department of Laboratory Medicine and Pathology, University of Minnesota Medical School, Minneapolis (Drs Yohe and Beckman); Diagnostic and Experimental Pathology, Eli Lilly and Company, Indianapolis, Indiana (Dr Schade); the Department of Pathology, Microbiology, and Immunology, Vanderbilt University School of Medicine, Nashville, Tennessee (Dr Zutter); the Department of Molecular Pathology and Genomics, Swedish Cancer Institute, Seattle, Washington (Dr Berry); and the Department of Pathology, Washington University School of Medicine, St Louis, Missouri (Dr Pfeifer).

Drs Pfeifer and Berry are co–senior authors.

Dr Walk is an employee at Roche Tissue Diagnostics and has stock ownership. Dr Schade is an employee at Eli Lilly and Company. The other authors have no relevant financial interest in the products or companies described in this article.

All authors are past or current members of the College of American Pathologists Personalized Health Care Committee.

Corresponding author: Eric E. Walk, MD, Department of Medical & Scientific Affairs, Roche Tissue Diagnostics, 1910 E Innovation Park Dr, Tucson, Arizona 85718 (email: eric.walk@roche.com).



COLLEGE of AMERICAN PATHOLOGISTS

ARCHIVES of Pathology & Laboratory Medicine

Educational resource for pathologists and oncologists on the current standard of care and emerging trends in immuno-oncology testing

**Walk E**, Yohe S, Schade A, et al. The Cancer Immunotherapy Biomarker Testing Landscape. Arch Pathol Lab Med. 2020 Jun;144(6):706-724.

# CAP Personalized Healthcare Committee: Precision Medicine Webpage

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Member Resources | Advocacy | Laboratory Improvement | Learning | Protocols and

Home > Member Resources > Articles > Cancer Immunotherapy Biomarker Testing – What Pathologists Need to Know

## Cancer Immunotherapy Biomarker Testing – What Pathologists Need to Know

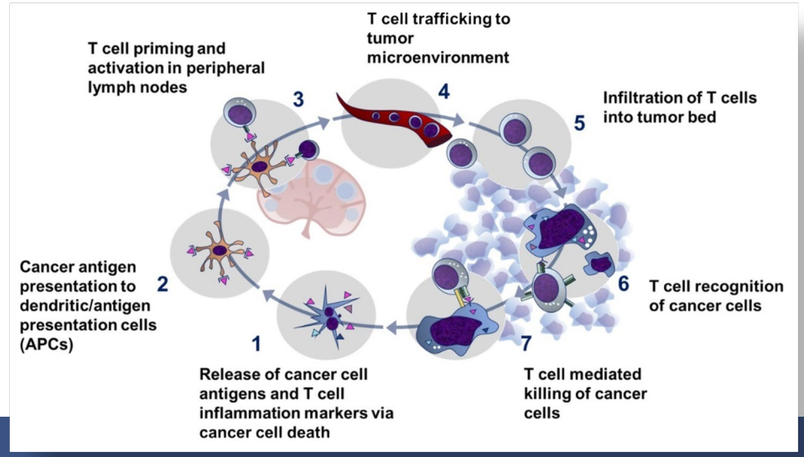
Cancer immunotherapy has revolutionized the field of oncology by delivering unprecedented levels of durable survival benefit for cancer patients, including some patients with previously incurable late-stage disease.

Anatomic and molecular pathologists have the opportunity to be at the center of the development, validation and clinical implementation of critically needed cancer immunotherapy biomarkers. Predictive immunotherapy biomarkers such as programmed death ligand-1 (PD-L1) immunohistochemistry (IHC), mismatch repair (MMR) IHC and microsatellite instability (MSI) testing are already established as routine testing in many pathology laboratories around the world, with other biomarkers and technologies still in the exploratory phase.

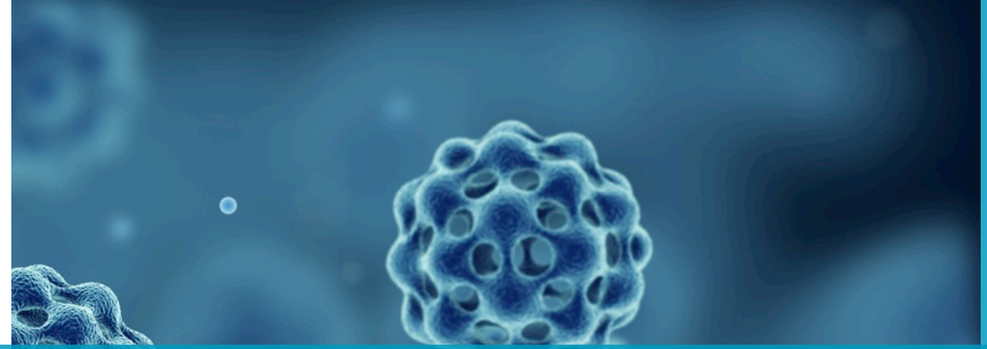
Clear guidelines for cancer immunotherapy testing are not currently available and the field is evolving rapidly in response to new clinical and translational data.

The intent of this webpage is to briefly summarize those cancer immunotherapy biomarkers that are in routine use as a resource for individualized test selection in clinical pathology practice.

For a more complete review of this field, please refer to the recently published article ***The Cancer Immunotherapy Biomarker Testing Landscape' (Walk et. al Arch Pathol Lab Med-Vol 144, June 2020)[1].***

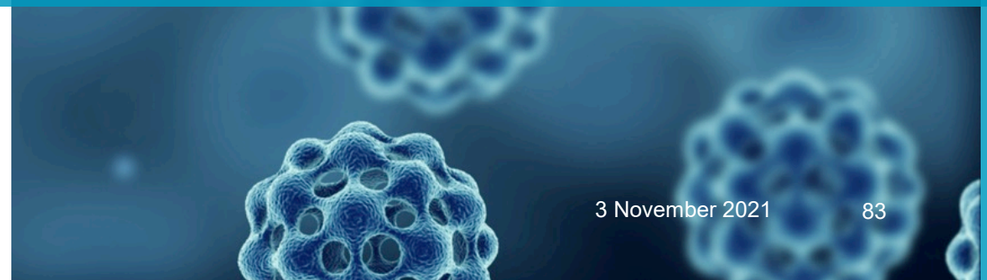



Brief, relevant articles by CAP members that enable the reader to gain a better understanding of a particular area of precision medicine.



# Thank You!

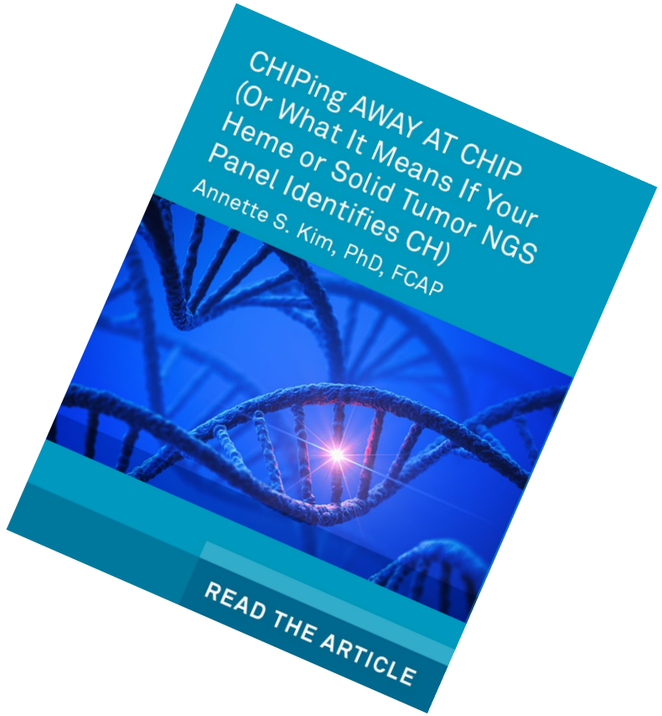
# Questions & Answers



# CAP's Precision Medicine Webpage

- **The webpage includes brief, relevant articles by CAP members that enable the reader to gain a better understanding of a particular area of precision medicine.**
  - **Examples include pharmacogenetics, immune response genes, and the latest in the molecular drivers of cancer.**
  - **Access them [www.cap.org](http://www.cap.org) >**

    **Member Resources > Precision Medicine**



# CAP's Pathology Resource Guide: Precision Medicine

- **The CAP has created the Pathology Resource Guides to assist pathologists in understanding key emerging technologies.**
  - **Printed guides are now available for members ($39) and non-members ($69)**
  - **The digital copy of the Resource Guides are a complimentary member benefit**
  - **Access them [www.cap.org](http://www.cap.org) > Resources and Publications**

# THANK YOU!

**Thank you for attending our webinar,**

**“Cancer Immunotherapy: Progress and Challenges on the Journey to Cure Cancer”**

**by Eric Walk MD, FCAP**

**For comments about this webinar or suggestions for upcoming webinars, please contact phcwebinars@cap.org.**

**NOTE: There is no CME/CE credit available for today’s free webinar. The PDF of the presentation will be sent out in a week.**

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