# *INTERPRETATION OF PD1 , MSI ,TMB IN NSCLC*

*6TH ANNUAL INTERNATIONAL BREAST CANCER CONFERENCE & PRECISION ONCOLOGY 2022*
*JAIPUR*

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# Key Question

1.What if one uses non companion assay ie complimentary assay – validity and concordance ?

2.Is there phenotypic drift with disease progression/ impact of chemotherapy – repeat biopsy and retest ?

3.Why ICI work even in PDL1 negative NSCLC and do not work even in strong PD 1 positive patients ?

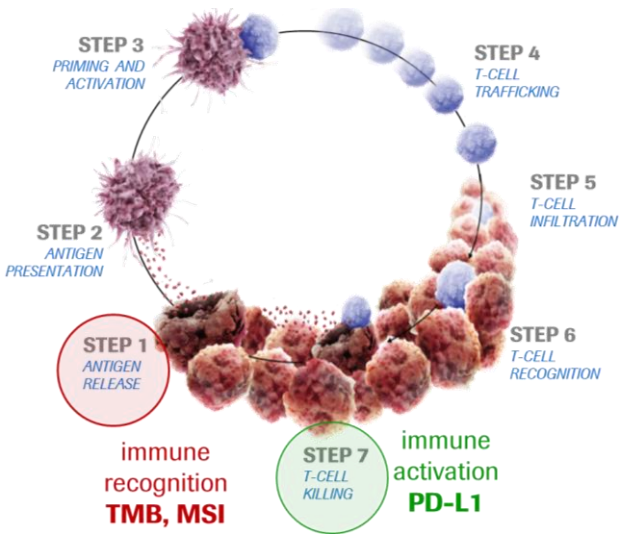
4.Can we use TMB / MSI alone to decide treatment plan ?

5. What's the way forward – ideal biomarker ??

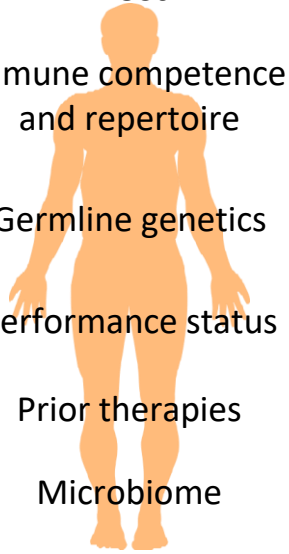
# Prediction of response to CIT will require integrated analyses of the complex interplay of tumour and host immune factors

CIT predictive biomarkers are fundamentally different from the driver oncogene biomarkers identified for molecularly targeted therapies: continuous rather than categorical (binary), spatially and temporally variable, and influenced by multiple complex interactions with host-related factors rather than a single, dominant determinant (e.g. *EGFR*m)

**Tumour**




**Host**



Immune competence and repertoire

Germline genetics

Performance status

Prior therapies

Microbiome

CIT predictive BMs in the tumour microenvironment are related to key steps of cancer immunity cycle

Adapted from Chen and Mellman. Immunity 2013

# A. PD1/PDL1

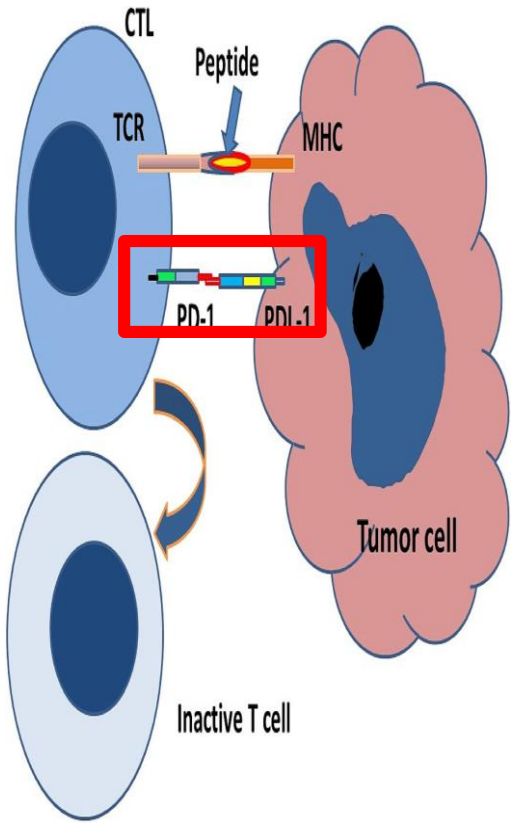



**Fig. 5** Engagement of PD-L1 on the tumor cell with PD-1 on the ATC along with co-stimulation provided by T-cell receptor and MHC results in inactivation of the lymphocyte

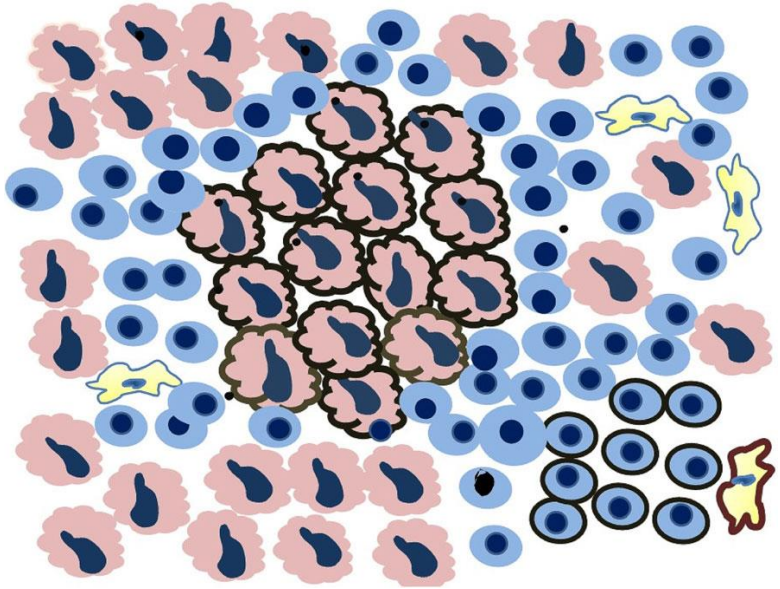


**Fig. 9** Schematic drawing of a tumor with PD-L1 staining. There are 37 tumor cells, 14 of which are depicting membrane staining (middle part of the drawing). In addition, 10 of the tumor immune cells, including one macrophage, are positive for PD-L1 (lower right-hand corner). Based on this, tumor positive score (TPS) and combined positive score (CPS) can be calculated.

$$\mathrm{TPS} = \frac{(\mathrm{No.positvetumorcells})14}{(\mathrm{No.viabletumorcells})37} \times 100 = 37.8$$

$$\mathrm{CPS} = \frac{(\mathrm{No.allpositvecells})24}{(\mathrm{No.viabletumorcells})37} \times 100 = 64.8$$

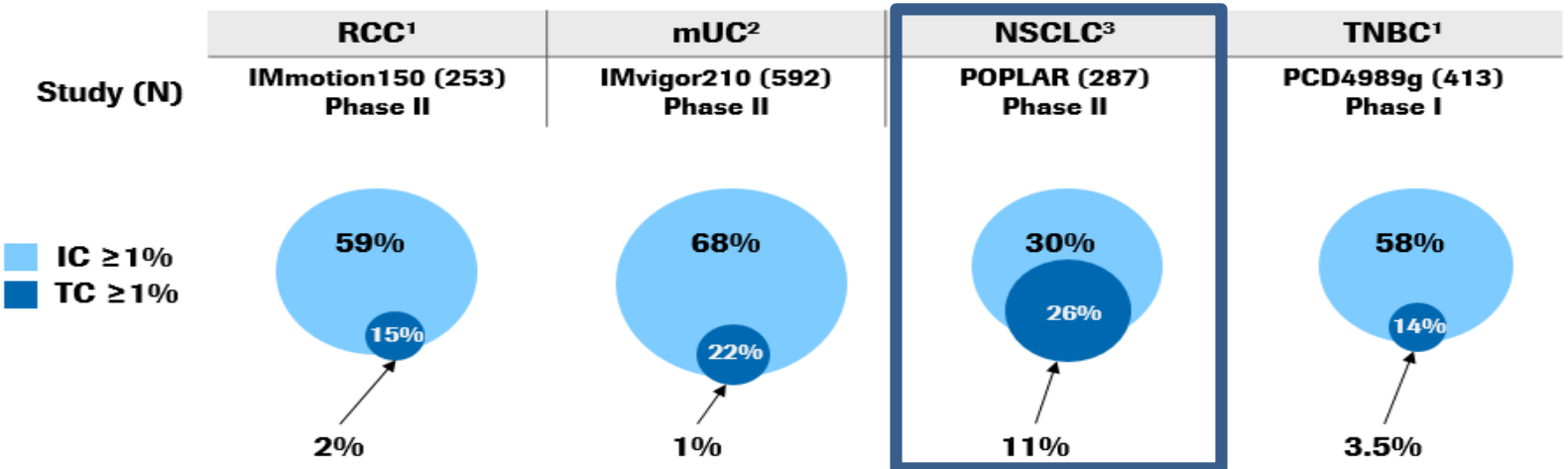
## Biology

- Programmed death-ligand 1 (PD-L1) is physiologically expressed by immune, endothelial, and other cell types in an inflammatory microenvironment. It binds to its receptors, PD-1 and B7.1, on the surface of T cells and acts as a checkpoint to down-modulate ongoing host immune responses in peripheral tissues
- In tumours, PD-L1 is expressed by multiple cell types within the tumour microenvironment, including cancer cells (TC) as well as tumour-infiltrating immune cells (IC) (including lymphocytes, macrophages, and dendritic cells). PD-L1 can turn off effector T cells, and is regulated by adaptive (e.g. IFNg-induced) or constitutive (e.g. oncogene-driven) mechanisms

## Alterations in NSCLC

- PD-L1 expression occurs on TCs and/or ICs, with less overlap than in other tumour types
- Intratumoural heterogeneity can be temporal (dynamic expression over time) and geographical (inter- and intra-lesional)

## PD-L1 expression on TC or IC across tumour types




1. Roche data on file; 2. Rosenberg et al. ECC 2015; 3. Fehrenbacher et al. Lancet 2016

# Basics of PDL1 testing ( Companion vs complimentary )

4 antibodies

22 C3

28—8

SP 263

SP 142

2 platforms

Dako

Ventana

**Table 1** Details of FDA-approved immune checkpoint inhibitors and corresponding antibodies for immunohistochemical staining

| | Year | Drug | Target protein | Antibody | Threshold % | Cell type | Therapy type |
|---|---|---|---|---|---|---|---|
| NSCLC | 2015 | Pembrolizumab | PD-1 | 22C3 | 50 | TC | 2nd line |
| NSCLC | 2016 | Pembrolizumab | PD-1 | 22C3 | 1 | TC | 2nd line |
| NSCLC | 2016 | Pembrolizumab | PD-1 | 22C3 | 5 | TC | 1st line |
| NSCLC (Metastatic) | 2020 | Atezolizumab. | PD-L1 | SP142 | TC:50<br>IC: 10 | IC+TC | 1st line |
| NSCLC (metastatic) | 2020 | Nivolumab + ipilimumab | PD-L1 | 28-8 | 1 | TC | 1st line |

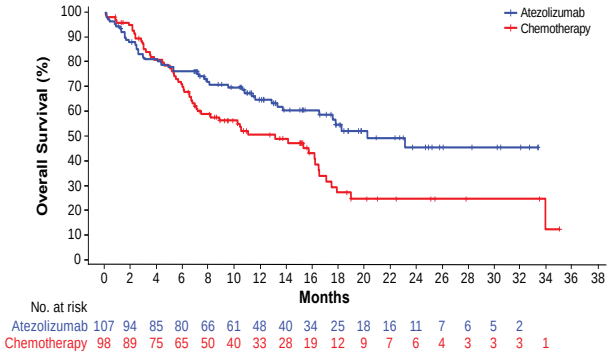
# PD-L1

## Predictive/prognostic

- Depending on the indication, PD-L1 is a companion Dx (CDx, patient selection) or has complementary status (informative)
- Prognostic implications can be dependent on the tumour type and/or setting

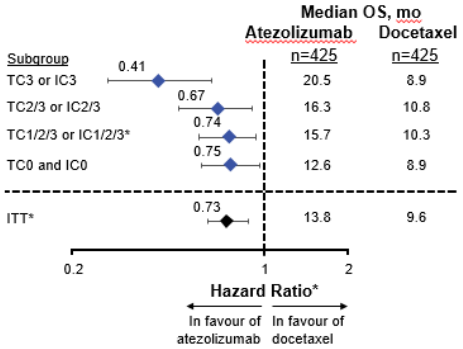
## Companion

IMpower110, 1L NSCLC, SP142




## Complementary

OAK, 2L NSCLC, SP142




## Prevalence

- Percentage of PD-L1+ tumours depends on the clinical setting, histology, and Dx assay used (including its scoring algorithm [TC and/or IC] and cut-off value)
- In 1L metastatic NSCLC, PD-L1 has ~30% prevalence with ≥50% tumour proportion score (TPS, membrane staining only on TC) with 22C3 assay

Barlesi et al. ESMO 2016 (Abs LBA44); Rittmeyer et al. Lancet 2017

# PD-L1

## Dx methods

- Several commercial assays have been co-developed as CDx in clinical trials with different anti-PD-(L)1 drugs
- Challenges exist due to differences in analytical performance and scoring algorithms, including defined positivity cut-off values within a biological continuum. Several analytical concordance studies have been conducted

## Guidelines

PD-L1 expression testing by IHC is recommended for all patients with newly diagnosed advanced NSCLC:

Positive results required (CDx, on label) for:

- pembrolizumab monotherapy in 1L or 2L+
- atezolizumab monotherapy in 1L
- nivolumab/ipilimumab in 1L
- durvalumab in stage III

Informative (complementary) in 2L+ for nivolumab and atezolizumab

Based on analytical comparison studies, other commercial assays may be valid alternatives

# PD-L1 IHC tests independently developed and clinically validated in clinical trials of PD-(L)1 inhibitors

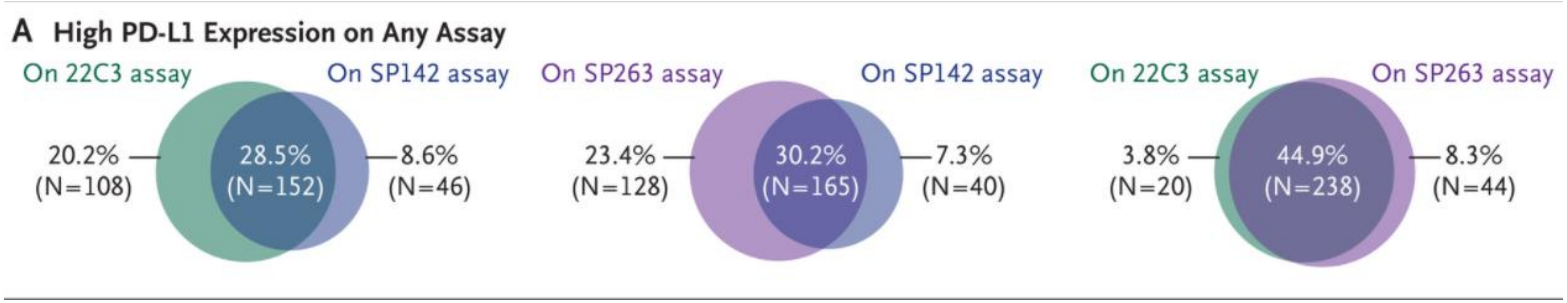
- The PD-L1 (22C3) IHC test was first to receive FDA premarketing approval (PMA) and was introduced as a companion diagnostic, whereas the other assays were initially complementary diagnostics for drugs approved in NSCLC irrespective of PD-L1 status

| Assay | Agilent/Dako PD-L1 IHC (22C3) pharmDx[3] | Agilent/Dako PD-L1 IHC (28-8) pharmDx[4] | VENTANA PD-L1 IHC (SP142) assay[1] | VENTANA PD-L1 IHC (SP263) assay[2]* |
|---|---|---|---|---|
| **Primary diagnostic assay for:** | KEYTRUDA (pembrolizumab) | OPDIVO (nivolumab) | TECENTRIQ (atezolizumab) | IMFINZI (durvalumab) |
| **Current PD-L1 IHC assay intended uses** | **Pembrolizumab**<br>• 1L monotherapy: ≥50% TPS (EMA) or ≥1% (FDA)<br>• 2L monotherapy: ≥1% TPS | **Durvalumab**<br>• Post chemoradiation: ≥1% TC (EMA only – FDA is PD-L1 all-comers)<br>**Nivolumab**<br>• 1L combination with ipilimumab (Yervoy): ≥1% TC (FDA) | **Atezolizumab**<br>• 1L monotherapy: '≥50% TC or ≥10% IC'‡ (FDA)<br>*Complementary diagnostic for the following*<br>• 2L monotherapy: '≥50% TC or ≥10% IC'‡<br>• 1L combination with bevacizumab (Avastin) + chemotherapy: '≥1% TC or ≥1% IC'§ | **Pembrolizumab**<br>• 1L monotherapy: ≥50% TC<br>• 2L monotherapy: ≥1% TC<br>**Nivolumab**<br>*SP263 is only intended as a complementary diagnostic for nivolumab in NSCLC*<br>• 2L monotherapy: ≥1%, ≥5% or ≥10% TC<br>**Durvalumab**<br>• Post chemoradiation (EMA only): ≥1% TC |
| **Cell types scored in NSCLC** | TC | TC | TC and IC | TC |

PMA, premarketing approval. *The EMA label for SP263 enables its use as a diagnostic for nivolumab, pembrolizumab or durvalumab;
‡'≥50% TC or ≥10% IC' = TC3 or IC3; §'≥1% TC or ≥1% IC' = TC1/2/3 or IC1/2/3

1. Vennapusa et al. Appl Immunohistochem Mol Morphol 2019
2. Rebelatto et al. Diagn Pathol 2016; 3. Dolled-Filhart et al. Arch Pathol Lab Med 2016
4. Phillips et al. Appl Immunohistochem Mol Morphol 2015

# IMpower 110:
# *SP142 / 22C3 / SP263 concordance*



THE LANCET Oncology

Articles

# Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB–IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial

*Mary O'Brien*, Luis Paz-Ares*, Sandrine Marreaud, Urania Dafni, Kersti Oselin, Libor Havel, Emilio Esteban, Dolores Isla, Alex Martinez-Marti, Martin Faehling, Masahiro Tsuboi, Jong-Seok Lee, Kazuhiko Nakagawa, Jing Yang, Ayman Samkari, Steven M Keller, Murielle Mauer, Nitish Jha, Rolf Stahel, Benjamin Besse†, Solange Peters†, on behalf of the EORTC-1416-LCG/ETOP 8-15 – PEARLS/KEYNOTE-091 Investigators‡*

## Summary

**Background** Pembrolizumab is a standard-of-care for advanced non-small-cell lung cancer (NSCLC). We assessed pembrolizumab as adjuvant therapy for completely resected stage IB–IIIA NSCLC.

**Methods** In this randomised, triple-blind, phase 3 trial (PEARLS/KEYNOTE-091), patients were recruited from 196 medical centres in 29 countries. Eligible patients were aged 18 years or older, with completely resected, pathologically confirmed stage IB (tumours of ≥4 cm in diameter), II, or IIIA NSCLC per the American Joint Committee on Cancer staging system (7th edition) of any histology or PD-L1 expression level, and an Eastern Cooperative Oncology Group performance status of 0 or 1; adjuvant chemotherapy was to be considered for stage IB

*Lancet Oncol* 2022

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*Contributed equally

†Contributed equally

‡Listed in the appendix (pp 2–6)

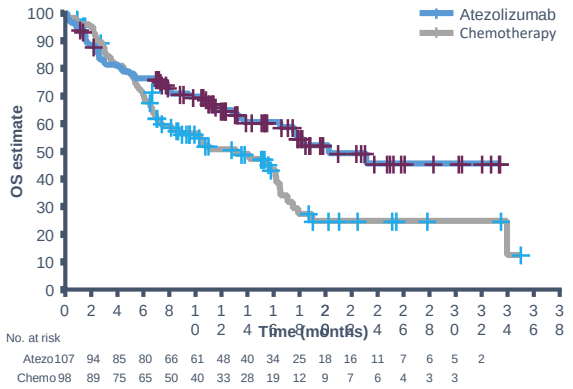
# Summary and Conclusions

- Baseline characteristics
  - Generally balanced between treatment arms in overall and PD-L1 TPS ≥50% populations
  - Generally similar between overall and PD-L1 TPS ≥50% populations
- Adverse event profile generally similar between overall and PD-L1 TPS ≥50% populations
- As expected, median and long-term DFS estimates numerically improved in PD-L1 TPS ≥50% population compared with TPS 1-49% and <1% populations in pembrolizumab arm
  - Unexpectedly, similar findings also seen in placebo arm
- Lack of statistically significant DFS benefit for pembrolizumab in PD-L1 TPS ≥50% population at IA2 likely results from placebo overperformance in this population
  - DFS in the TPS ≥50% population will be tested again at the next IA
- **Overall, data from PEARLS/KEYNOTE-091 support the benefit of pembrolizumab for participants with completely resected stage IB-IIIA NSCLC and, if recommended, prior adjuvant chemotherapy, regardless of PD-L1 expression**

# OS benefit in PD-L1 high subgroup for atezolizumab over chemotherapy was maintained with 22C3 and SP263

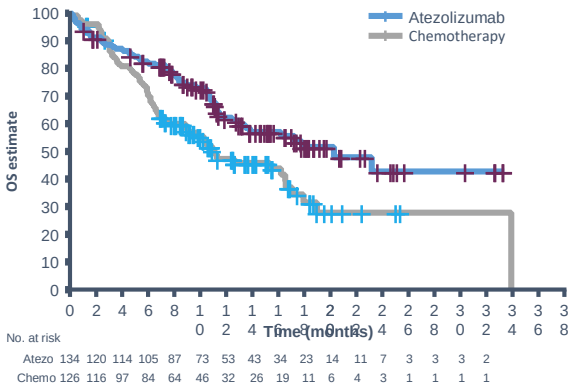
**Additional pre-specified PD-L1 biomarker analyses were performed using the Dako 22C3 PD-L1 IHC assay (exploratory endpoint) and VENTANA SP263 PD-L1 IHC assay (secondary endpoint) within the SP142 TC1/2/3 or IC1/2/3 WT population**

## SP142 (TC3 or IC3-WT)*



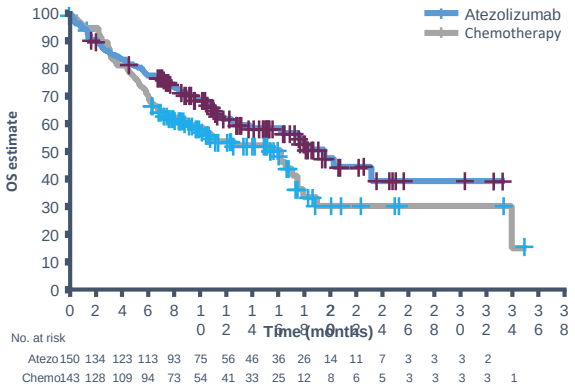

| | Atezo (n=107) | Chemo (n=98) |
|---|---|---|
| mOS, mo | 20.2 | 13.1 |
| HR (95% CI)‡ | 0.59 (0.40, 0.89) | |

## 22C3 BEP-WT (TPS ≥50%)*




| | Atezo (n=134) | Chemo (n=126) |
|---|---|---|
| mOS, mo | 20.2 | 11.0 |
| HR (95% CI)§ | 0.60 (0.41, 0.86) | |

## SP263 BEP-WT (TC ≥50%)*




| | Atezo (n=150) | Chemo (n=143) |
|---|---|---|
| mOS, mo | 19.5 | 16.1 |
| HR (95% CI)§ | 0.71 (0.50, 1.00) | |

*SP142 TC1/2/3 or IC1/2/3-WT (n=554); 22C3 BEP-WT (n=534); SP263 BEP-WT (n=546)
‡Stratified. §Unstratified

Herbst, et al. N Engl J Med 2020

Roche is now using the SP263 assay for newly initiated lung cancer trials and, moving forward, SP263 is our PD-L1 assay of choice lung cancer to best harmonise the testing landscape.

# Challenges in using PD-L1 as a biomarker

PD-L1 expression may be missed in **small biopsy specimens**, e.g. needle biopsies

**PD-L1 expression in tumour samples collected months or years before might not accurately reflect PD-L1 status** at treatment initiation; therapies given after biopsy, may alter PD-L1 expression

Antibodies used for PD-L1 detection have **different affinities and specificities**

PD-L1 expression among multiple tumour lesions from individual patients can **vary over time and by anatomical site**

PD-L1 epitopes detected by some antibodies are **potentially unstable** with prolonged specimen fixation or inadequate tissue handling before fixation

PD-L1 can be expressed by **multiple cell types** within the tumour microenvironment, which poses challenges for scoring and interpretation

Topalian SL. Nat Rev Cancer 2016

National Comprehensive Cancer Network®

# NCCN Guidelines Version 3.2022
# Non-Small Cell Lung Cancer

## ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 0–1)

No contraindications to PD-1 or PD-L1 inhibitors[d]

**Preferred**

- Pembrolizumab/carboplatin/pemetrexed (category 1)[1,2,e]
- Pembrolizumab/cisplatin/pemetrexed (category 1)[2,e]

**Other Recommended**

- Atezolizumab/carboplatin/paclitaxel/bevacizumab[e] (category 1)[3,f,g,h,i]
- Atezolizumab/carboplatin/albumin-bound paclitaxel[4,e]
- Nivolumab/ipilimumab[5,d]
- Nivolumab/ipilimumab/pemetrexed/(carboplatin or cisplatin) (category 1)[6,e]

## SQUAMOUS CELL CARCINOMA (PS 0–1)

No contraindications to PD-1 or PD-L1 inhibitors[d]

**Preferred**

- Pembrolizumab/carboplatin/paclitaxel (category 1)[34,e]
- Pembrolizumab/carboplatin/albumin-bound paclitaxel (category 1)[34,e]

**Other recommended**

- Nivolumab/ipilimumab[5,e]
- Nivolumab/ipilimumab/paclitaxel/carboplatin (category 1)[6,e]

- Atezolizumab 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks for up to 1 year[12]
  - Atezolizumab for patients with completely resected stage IIB–IIIA or high risk stage IIA PD-L1 ≥1% NSCLC who received previous adjuvant chemotherapy.

**PD-L1 ≥1%**

- **First-line therapy[d]**
  - **Pembrolizumab[42-44]**
  - **(Carboplatin or cisplatin)/pemetrexed/ pembrolizumab (nonsquamous)[45,46]**
  - **Carboplatin/paclitaxel/bevacizumab[c]/ atezolizumab (nonsquamous)[47]**
  - **Carboplatin/(paclitaxel or albumin-bound paclitaxel)/pembrolizumab (squamous)[48]**
  - **Carboplatin/albumin-bound paclitaxel/ atezolizumab (nonsquamous)[48]**
  - **Nivolumab/ipilimumab[49]**
  - **Nivolumab/ipilimumab/pemetrexed/ (carboplatin or cisplatin) (nonsquamous)[50]**
  - **Nivolumab/ipilimumab/paclitaxel/carboplatin (squamous)[50]**

**PD-L1 ≥50% (in addition to above)**

- **First-line therapy[d]**
  - **Atezolizumab[51]**
  - **Cemiplimab-rwlc[52]**

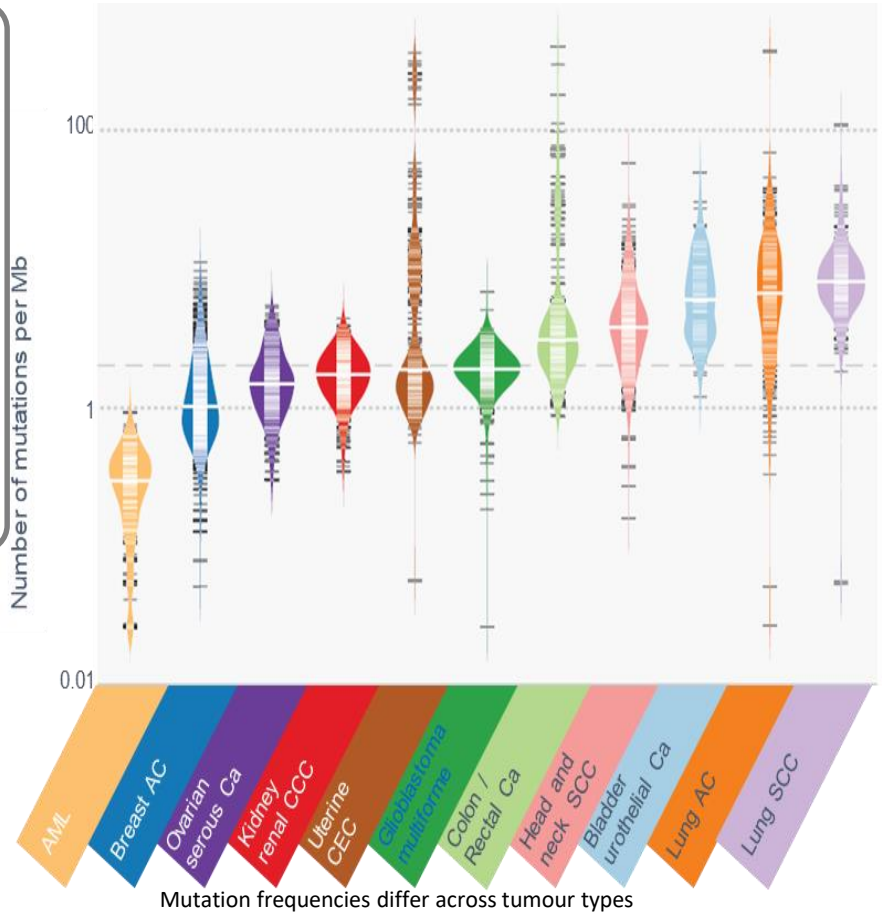
# B.TMB

## Biology

- Mutations (nonsynonymous) in coding sequences of the tumour genome (e.g. caused by DNA repair defects in MMR-deficient tumours and carcinogens) can result in abnormal proteins, presented as neo-antigens potentially recognised and targeted by the immune system
- Tumour mutational burden (TMB) is an accurate proxy for neo-antigen load translated into neo-antigen diversity
- Higher TMB is associated with higher levels of predicted neoantigens and response to CIT

## Alterations in NSCLC

- NSCLC and SCLC are often tobacco carcinogen-associated and have among the highest prevalence of somatic mutations/TMB in human tumours
- TMB is highly variable between and within subtypes (NSQ has TMB-low subsets, particularly in never-smokers/oncogene-driven, while in SQ TMB has a more homogenous distribution of TMB-H)
- MMR-D/MSI-H NSCLC is a very rare subset of TMB-H (<0.5%)



Mutation frequencies differ across tumour types

high TMB levels will correlate with high neoantigen levels that will activate an antitumor immune response

ature 2013

# TMB

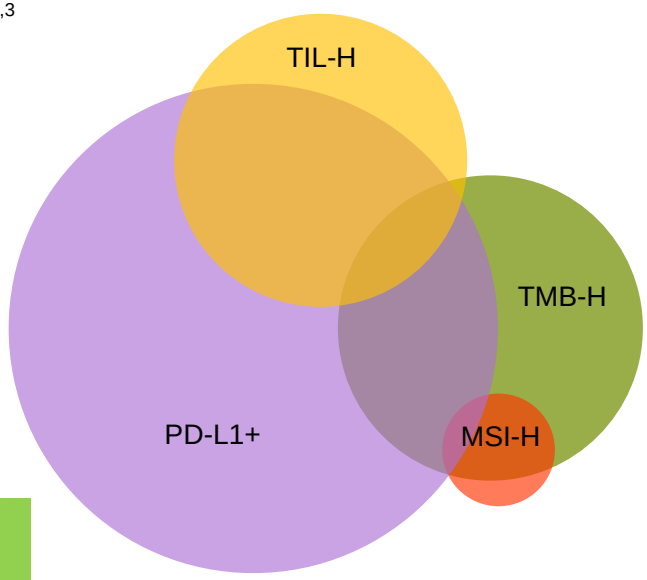
## Predictive/prognostic

- TMB-H is associated with improved response (ORR, PFS, and OS) with CIT in multiple cancer types, including NSCLC
- Ongoing prospective validation of bTMB as predictor for atezolizumab monotherapy efficacy in 1L NSCLC

## Prevalence

- Mutation load differs across tumour types[1]
- Prevalence depends on cut-off value and methodology; TMB-H identifies a population that is distinct from PD-L1 IHC-positive patients

**Tumour mutational burden (TMB)** acts as a proxy for neoantigen load to allow more informed immunotherapy use; a blood-based TMB measurement is in progress for when tissue cannot be obtained[2,3]




TMB levels are typically high in patients with NSCLC who are smokers or former smokers.

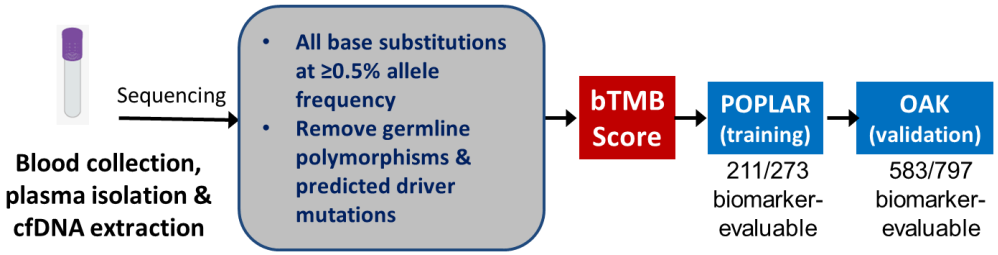
Low TMB is more commonly detected in never smokers.3

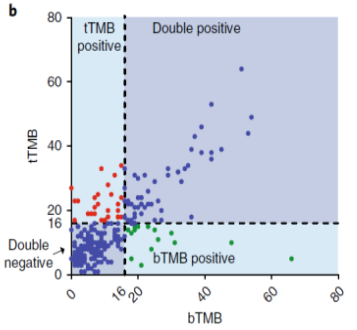
andoth et al. Nature 2013; 2. Foundation Medicine website. FoundationOne CDx. able at: https://www.foundationmedicine.com/genomic-testing/foundation-one-cdx otember 2018); 3. Foundation Medicine Press Release. Blood TMB. Available at: http://investors.foundationmedicine.com/news-releases/news-release-details/foundation-medicine-publishes-new-data-nature-medicine (Accessed October 2018)

AML: acute myeloid leukaemia; CCC: clear cell carcinoma; CEC: corpus endometrial carcinoma; Mb: megabase

# bTMB associated with atezolizumab efficacy in retrospective analyses in 2L+ NSCLC

**bTMB Computational Methodology and Study Design**



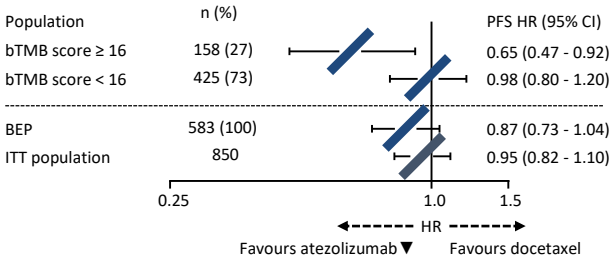



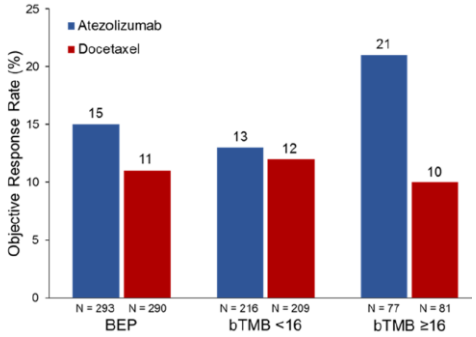

Spearman rank correlation = 0.64 (95% CI: 0.56–071)

| Metric | Performance |
|---|---|
| PPA | 64% (95% CI: 54–74%) |
| NPA | 88% (95% CI: 83–92%) |

**OAK study**

**Second-line or later atezolizumab▼**
PFS in bTMB score-high vs low subgroups




- TMB measured in blood correlates with TMB measured in tumour tissue
  (using FMI tests)
- Enrichment of PFS benefit was observed in the bTMB ≥16 subgroup, while OS was consistent between the ≥16 and <16 subgroups

Gandara et al. Nat Med 2018

# Association Between Tissue TMB and Clinical Outcomes with Pembrolizumab Monotherapy in PD-L1-Positive Advanced NSCLC in the KEYNOTE-010 and 042 Trials

Roy S. Herbst[1], Gilberto Lopes[2], Dariusz M. Kowalski[3], Makoto Nishio[4]; Yi-long Wu[5], Gilberto de Castro Jr[6], Paul Baas[7], Dong-Wan Kim[8], Matthew A. Gubens[9], Razvan Cristescu[10], Deepti Aurora-Garg[10], Andrew Albright[10], Mark Ayers[10], Andrey Loboda[10], Jared Lunceford[10], Julie Kobie[10], Gregory Lubiniecki[10], M. Catherine Pietanza[10], Bilal Piperdi[10], Tony SK Mok[11]

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TMB does not identify patients who will respond to chemotherapy; therefore, TMB has limited value for assessing combination immunotherapy plus chemotherapy regimens

019

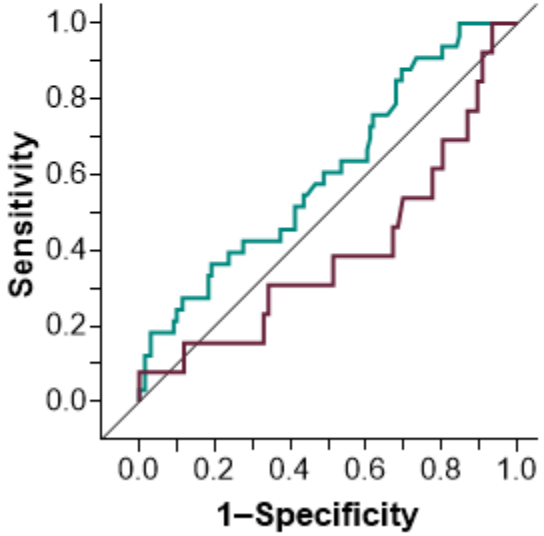
| Nominal *P* Value[b] | Pembro (n = 164) | Chemo (n = 89) |
|---|---|---|
| OS | 0.006 (one-sided) | 0.410 (two-sided) |
| PFS | 0.001 (one-sided) | 0.579 (two-sided) |
| ORR | 0.009 (one-sided) | 0.330 (two-sided) |

tTMB was associated with outcomes for pembro as a continuous variable but not with chemo based on α = 0.05 significance level and AUROC analysis

[a]All patients were PD-L1-positive (TPS ≥1%). [b]Wald test. *P* values are one-sided for pembro as the a priori hypothesis was that tTMB was positively associated with improved outcomes of pembro. *P* values are two-sided for placebo because there was no a priori hypothesis regarding the direction of the association between tTMB and outcomes of chemo. TMB was assessed as a continuous, $\log_{10}$-transformed variable.
Data cutoff date: Mar 16, 2018.

**ROC Curves of ORR for tTMB**

| | AUROC (95% CI) |
|---|---|
| Pembro | 0.61 (0.50-0.71) |
| Chemo | 0.40 (0.21-0.58) |



TMB is also not an ideal immune biomarker because some patients with low TMB levels respond to immunotherapy and others with high levels do not respond to immunotherapy

2019

# (KEYNOTE-042[a])

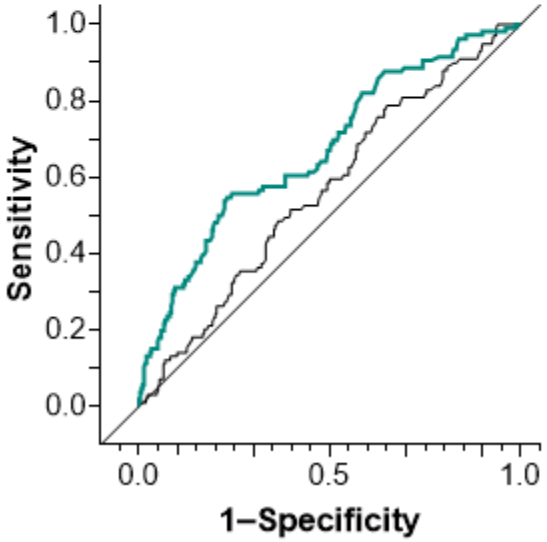
| Nominal *P* Value[b] | Pembro (n = 414) | Chemo (n = 379) |
|---|---|---|
| OS | <0.001 (one-sided) | 0.060 (two-sided)[c] |
| PFS | <0.001 (one-sided) | 0.174 (two-sided)[c] |
| ORR | <0.001 (one-sided) | 0.035 (two-sided) |

tTMB was associated with outcomes for pembro as a continuous variable but not chemo in general, based on α = 0.05 significance level and AUROC

[a]All patients were PD-L1-positive (TPS ≥1%). [b]Wald test. *P* values are one-sided for pembro as the a priori hypothesis was that tTMB was positively associated with improved outcomes of pembro. *P* values are two-sided for placebo as there was no a priori hypothesis regarding the direction of association between tTMB and outcomes of chemo. TMB was assessed as a continuous, $\log_{10}$-transformed variable. [c]tTMB showed negative directions of association with OS and PFS in the chemo arm.
Data cutoff date: Sep 4, 2018.

## ROC Curves of ORR for tTMB

| | AUROC (95% CI) |
|---|---|
| Pembro | 0.67 (0.61-0.73) |
| Chemo | 0.57 (0.50-0.63) |



high TMB levels do not correlate with PD-L1 expression levels in patients with NSCLC.

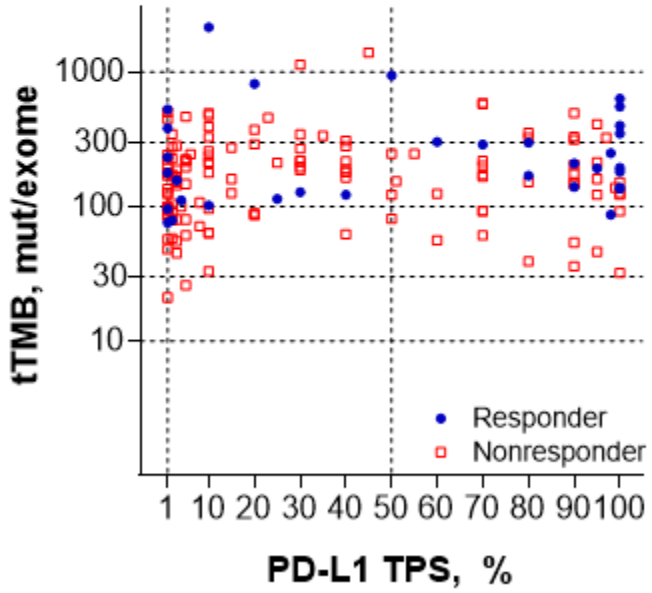
2019

# Relationship Between tTMB and PD-L1 (KEYNOTE-010[a])

## Pembro

**No association between tTMB and PD-L1**

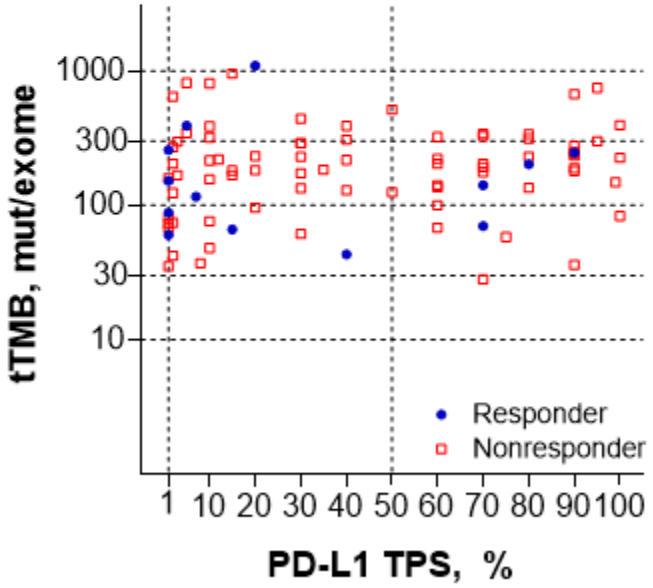
**r = 0.16**




## Chemo

**No association between tTMB and PD-L1**

**r = 0.18**




[a]All patients were PD-L1-positive (TPS ≥1%). tTMB was graphed on a $\log_{10}$ scale. PD-L1 TPS was graphed on a linear scale.
Data cutoff date: Mar 16, 2018.

# TMB

- *1) lack of agreement on the definition of a cut off for designating high TMB levels;*

- *2) lack of standardization of TMB measurements across laboratories.*

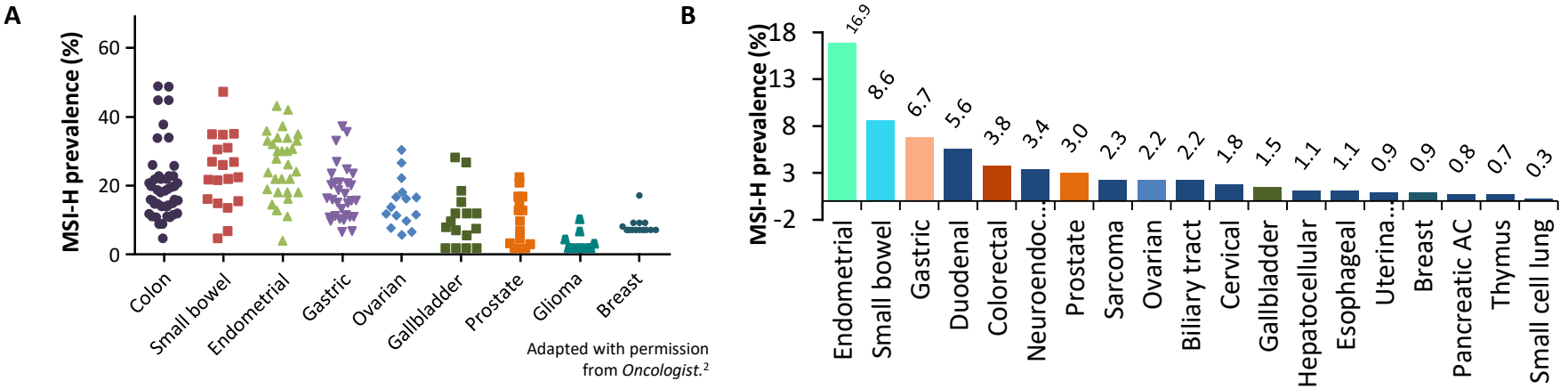
- *3)Guidelines do not recommend measurement of TMB levels before deciding whether to use nivolumab plus ipilimumab regimens or to use other ICIs, such as pembrolizumab.*

# C.MSI-H/dMMR

- MSI-H, indicative of dMMR, is found across several tumor types[1–4]
- MSI-H is highly prevalent in Lynch syndrome–associated tumor types, such as endometrial (17%–30%), colon (16%–20%), and gastric cancers (7%–20%), but is rarely present in lung malignancies and melanoma (both < 1%)[1,3,4]
  - Among endometrial cancers, rates of MSI-H range from 40%–50% in endometrioid tumors to 2% in serous and clear-cell tumors[2]
  - Among gastric cancers, the incidence of MSI-H differs between eastern (8%–10%) and western nations (16%–25%)[5]



**MSI-H prevalence across tumor types reported by (A) Lee et al.[2] and (B) Akagi et al.[4,a]**




Adapted with permission from *Oncologist*.[2]

[a]Data shown for Akagi et al. only includes tumor types with > 100 samples available for analysis; among tumor types with < 100 samples available, MSI-H prevalence was highest in the following tumor types: upper urinary tract (16.7%), adrenal gland (11.5%), and testis (9.1%). AC, adenocarcinoma; dMMR, deficient mismatch repair; MSI-H, microsatellite instability-high.

1. Cortes-Ciriano I et al. *Nat Commun* 2017;8:15180. 2. Lee V et al. *Oncologist* 2016;21:1200–1211. 3. Bonneville R et al. *JCO Precis Oncol* 2017. doi: 10.1200/PO.17.00073. 4. Akagi K et al. *Cancer Sci* 2021;112:1105–1113. 5. An JY et al. *Int J Cancer* 2012;131:505–511.

# Conclusion

1.PD1/ PD L1 : imperfect though most validated biomarker with limitation and evolution

2.TMB: some data to support biological rationale, but less validation compared with PDL 1

3.MSI : Highly uncommon in NSCLC and < 0.5 %
SCLC- rarely used as predictive biomarker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