Tumor Mutation Burden:
Current Data and Approvals

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Disclosures

- Consulting Fees: AbbVie, Aduro BioTech Inc., Alkermes, AstraZeneca, DebioPharm, eFFECTOR Therapeutics, F. Hoffman-La Roche Ltd., Genentech Inc., IBM Watson, Infinity Pharmaceuticals, Jackson Laboratory, Kolon Life Science, Lengo Therapeutics, OrigiMed, PACT Pharma, Parexel International, Pfizer Inc., Samsung Bioepis, Seattle Genetics Inc., Tallac Therapeutics, Tyra Biosciences, Xencor, Zymeworks, Black Diamond, Eisai, Immunomedics, Inflection Biosciences, Karyopharm Therapeutics, Loxo Oncology, Mersana Therapeutics, OnCusp Therapeutics, Puma Biotechnology Inc., Seattle Genetics, Silverback Therapeutics, Spectrum Pharmaceuticals, Zentalis
- Fees for Non CE Services: Chugai Biopharmaceuticals, Mayo Clinic, Rutgers Cancer Institute of New Jersey
- Contracted Research: Aileron Therapeutics, Inc. AstraZeneca, Bayer Healthcare Pharmaceutical, Calithera Biosciences Inc., Curis Inc., CytomX Therapeutics Inc., Daiichi Sankyo Co. Ltd., Debiopharm International, eFFECTOR Therapeutics, Genentech Inc., Guardant Health Inc., Klus Pharma, Takeda Pharmaceutical, Novartis, Puma Biotechnology Inc., Taiho Pharmaceutical Co.

I will be discussing non-FDA approved indications during my presentation.
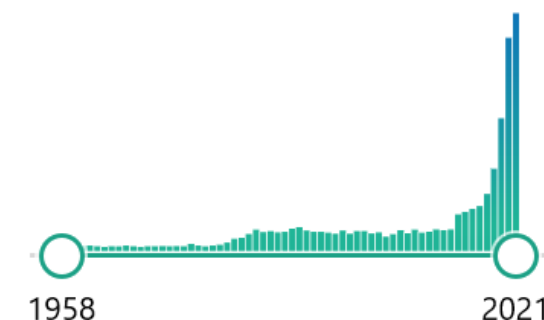
Tumor Mutation Burden (TMB)

- Number of somatic mutations per megabase of interrogated genomic sequence

- Predictive biomarker potential for the identification of patients with cancer likely to respond to immune checkpoint inhibitors
  - Many of the tumors that had early CPI approvals have higher TMB

TMB: An Active Area of Study
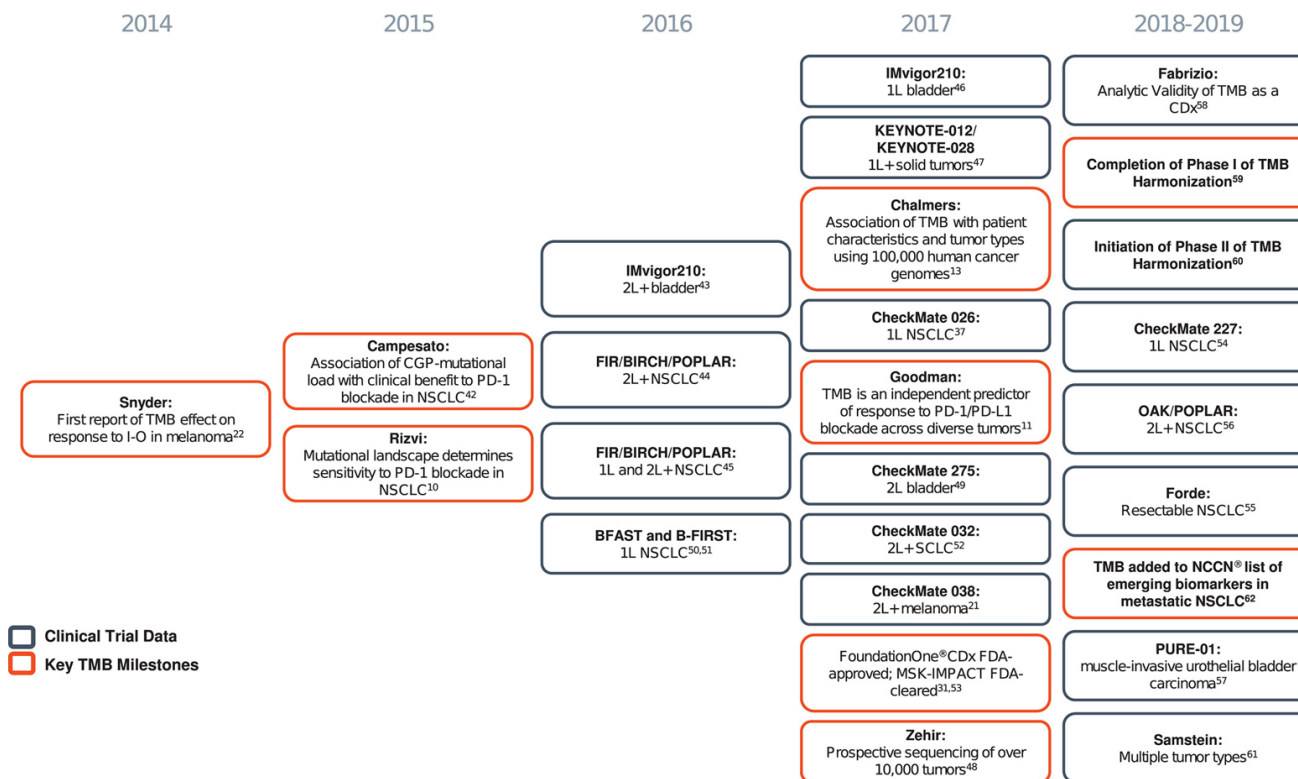
Klempner et al, The Oncologist, 2019

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

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

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Drug Approvals and Databases

Resources for Information | Approved Drugs

Content current as of:
06/17/2020

Regulated Product(s)
Drugs
Prescription Drugs

On June 16, 2020, the Food and Drug Administration granted accelerated approval to pembrolizumab (KEYTRUDA, Merck & Co., Inc.) for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

Today, the FDA also approved the FoundationOneCDx assay (Foundation Medicine, Inc.) as a companion diagnostic for pembrolizumab.

Efficacy was investigated in a prospectively-planned retrospective analysis of 10 cohorts of patients with various previously treated unresectable or metastatic TMB-H solid tumors enrolled in a multicenter, non-randomized, open-label trial, KEYNOTE-158 (NCT02628067). Patients received pembrolizumab 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression.

The main efficacy outcome measures were overall response rate (ORR) and duration of response (DoR) in patients who have received at least one dose of pembrolizumab as assessed by blinded independent central review according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

A total of 102 patients (13%) had tumors identified as TMB-H, defined as TMB ≥10 mut/Mb. The ORR for these patients was 29% (95% CI: 21,39), with a 4% complete response rate and 25% partial response rate. The median DoR was not reached, with 57% of patients having response durations ≥12 months and 50% of patients having response durations ≥24 months.
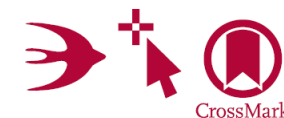
Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study

Aurélien Marabelle, Marwan Fakih, Juanita Lopez, Manisha Shah, Ronnie Shapira-Frommer, Kazuhiko Nakagawa, Hyun Cheol Chung, Hedy L Kindler, Jose A Lopez-Martin, Wilson H Miller Jr, Antoine Italiano, Steven Kao, Sarina A Piha-Paul, Jean-Pierre Delord, Robert R McWilliams, David A Fabrizio, Deepti Aurora-Garg, Lei Xu, Fan Jin, Kevin Norwood, Yung-Jue Bang

Summary

Background Tumour mutational burden (TMB) has been retrospectively correlated with response to immune

KEYNOTE-158

- Multi-cohort, open-label, non-randomized, phase 2 KEYNOTE-158 study
- Patients enrolled from 81 academic and community-based institutions across 21 countries
- Eligible tumor types were anal, biliary, cervical, endometrial, mesothelioma, neuroendocrine, salivary, small-cell lung, thyroid, and vulvar
- Participants were given pembrolizumab 200 mg intravenously every 3 weeks
- Tissue TMB (tTMB) was assessed in formalin-fixed paraffin-embedded tumour samples using the FoundationOne CDx assay (Foundation Medicine, Cambridge, MA, USA)
- The prespecified definition of tTMB-high status was at least 10 mutations per megabase

Marabelle et al, Lancet Oncol, 2020

KEYNOTE-158 Objective response assessed by independent central review in the efficacy population

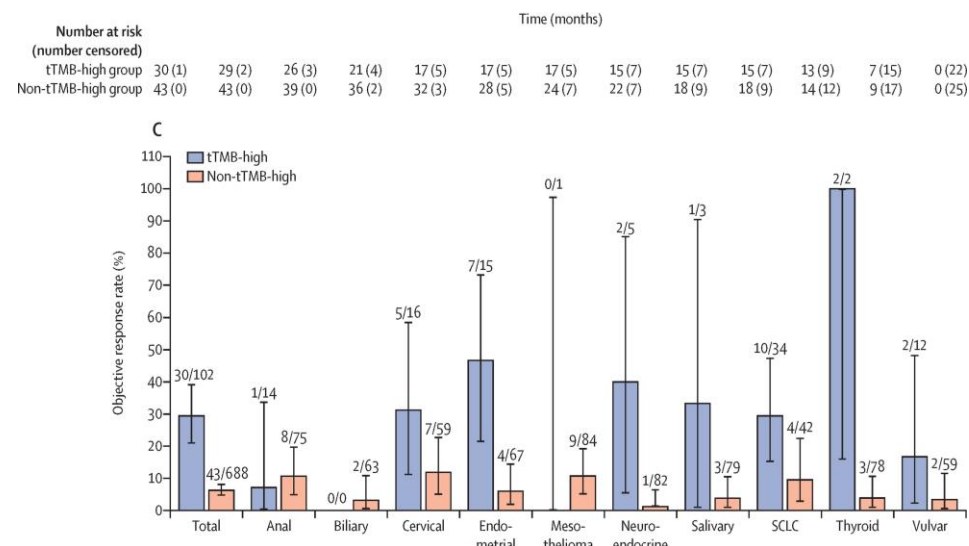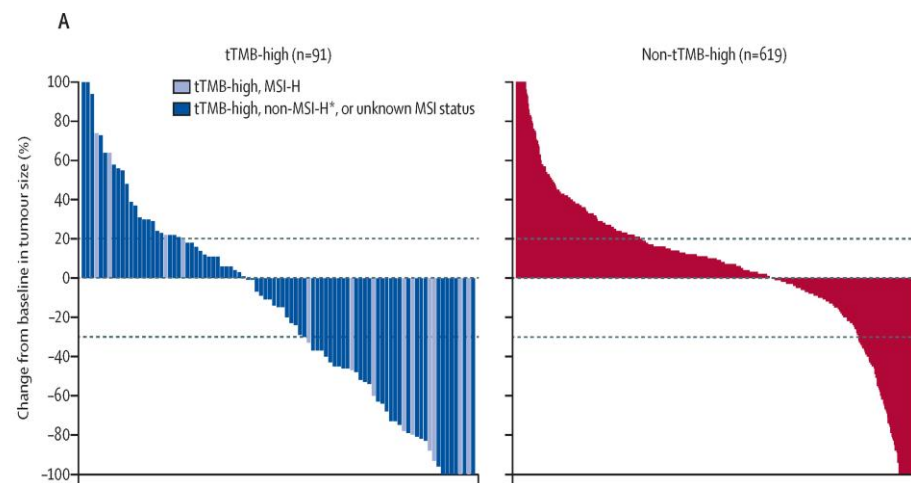|		tTMB-high (n=102)	tTMB-high (excluding MSI-H; n=81)*	Non-tTMB-high (n=688)
Best response				
	Complete response	4 (4%)	3 (4%)	11 (2%)
	Partial response	26 (25%)	20 (25%)	32 (5%)
	Stable disease	14 (14%)	11 (14%)	227 (33%)
	Non-complete response or non-progressive disease[†]	0	0	3 (<1%)
	Progressive disease	48 (47%)	38 (47%)	349 (51%)
	Not evaluable[‡]	1 (1%)	1 (1%)	13 (2%)
	Not assessed[§]	9 (9%)	8 (10%)	53 (8%)
Objective response rate		29% (21–39)	28% (19–40)	6% (5–8)

Data are n (%) or % (95% CI). MSI-H=high microsatellite instability. RECIST=Response Evaluation Criteria in Solid Tumors. tTMB-high=high tissue tumour mutational burden.

Marabelle et al, Lancet Oncol, 2020

KEYNOTE-158 Objective response assessed by independent central review in the efficacy population

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Marabelle et al, Lancet Oncol, 2020

KEYNOTE-158 Objective response assessed by independent central review in the efficacy population

Marabelle et al, Lancet Oncol, 2020

KEYNOTE- 158: PFS and OS

Marabelle et al, Lancet Oncol, 2020

- TMB score was not associated with PD-L1 combined positive score, either in the overall efficacy population (ρ=0·18) or in patients with a response (ρ=0·07) or without a response (ρ=0·15)
  - tTMB predicted clinical outcomes with pembrolizumab monotherapy across the tumour types included in this study, irrespective of PD-L1 expression

- Excluding 14 participants with MSI-H status (all of whom were in the tTMB-high group) and seven participants with missing MSI status from the analysis of objective response, 23 (28%; 95% CI 19–40) of 81 participants with tTMB-high status had an objective response
  - MSI-H status did not account for all of the increased benefit in the tTMB-high subgroup

Efficacy of atezolizumab in the treatment of solid tumors with high tumor mutational burden (TMB): A MyPathway study cohort

John Hainsworth*,[1,2] Claire F. Friedman*,[3,4] Razelle Kurzrock,[5] David R. Spigel,[1,2] Howard Burris,[1,2] Christopher J. Sweeney,[6] Funda Meric-Bernstam,[7] Yong Wang,[8] Jonathan Levy,[8] David S. Shames,[8] Katja Schulze,[8] Arisha Patel,[8] Charles Swanton[9,10]

*Co-lead authors.

- 121 patients with advanced solid tumors with TMB ≥10 mut/Mb by any CLIA assay
- Atezolizumab 1200 mg q3w

Hainsworth, Friedman et al, AACR 2021
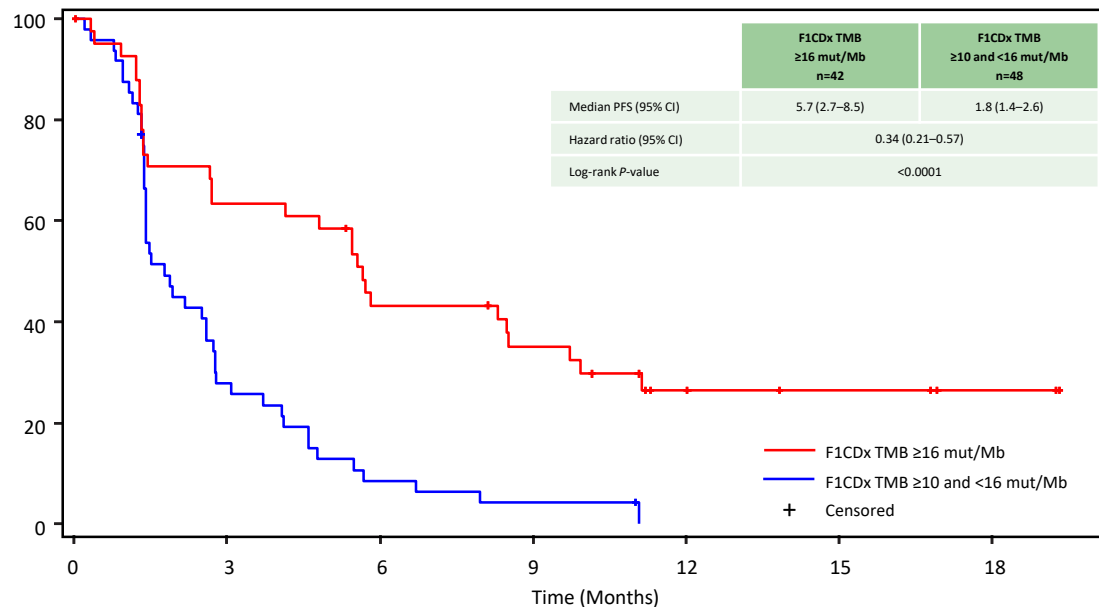
Primary and Secondary Clinical Outcomes

Clinical outcome	F1CDx TMB ≥16 mut/Mb n=42	F1CDx TMB ≥10 and <16 mut/Mb n=48
Confirmed objective response rate[a], n (%) 95% CI	16 (38.1) 23.6–54.4 3 CR[b], 13 PR	1 (2.1) 0.1–11.1 1 PR
Disease control rate[c], n (%) 95% CI	26 (61.9) 45.6–76.4	11 (22.9) 12.0–37.3
Duration of confirmed response, median months 95% CI	Not reached	Not reached
Progression-free survival, median months 95% CI	5.7 2.7–8.5	1.8 1.4–2.6
Overall survival, median months 95% CI	19.8 11.9–NE	11.4 5.3–15.7

[a]Includes patients with confirmed CR or PR. [b]Patients with CR had biliary, colon, and head and neck cancers. [c]Includes patients with CR, PR, or stable disease >4 months.
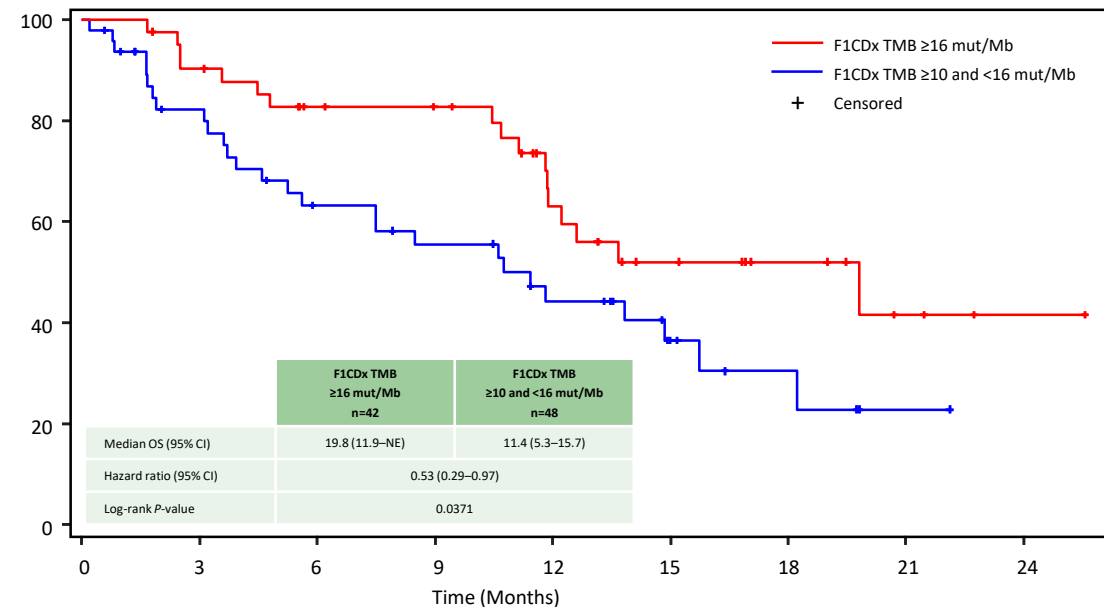CI, confidence interval; CR, complete response; NE, not evaluable; PR, partial response.

Hainsworth, Friedman et al, AACR 2021

Progression-Free and Overall Survival

Progression-free survival

	F1CDx TMB ≥16 mut/Mb n=42	F1CDx TMB ≥10 and <16 mut/Mb n=48
Median PFS (95% CI)	5.7 (2.7–8.5)	1.8 (1.4–2.6)
Hazard ratio (95% CI)	0.34 (0.21–0.57)	
Log-rank P-value	<0.0001	

Patients remaining at risk

TMB ≥16 mut/Mb	42	26	17	13	6	4	2
TMB ≥10 and <16 mut/Mb	48	13	4	2	0	0	0

Overall survival

	F1CDx TMB ≥16 mut/Mb n=42	F1CDx TMB ≥10 and <16 mut/Mb n=48
Median OS (95% CI)	19.8 (11.9–NE)	11.4 (5.3–15.7)
Hazard ratio (95% CI)	0.53 (0.29–0.97)	
Log-rank P-value	0.0371	

Patients remaining at risk

TMB ≥16 mut/Mb	42	37	30	28	18	11	7	3	1
TMB ≥10 and <16 mut/Mb	48	35	25	21	15	7	4	1	0

- Median follow-up was 11.7 months in patients with F1CDx TMB ≥16 mut/Mb and 7.5 months in patients with F1CDx TMB ≥10 and <16 mut/Mb

Hainsworth, Friedman et al, AACR 2021

Clinical Outcomes by MSI Status
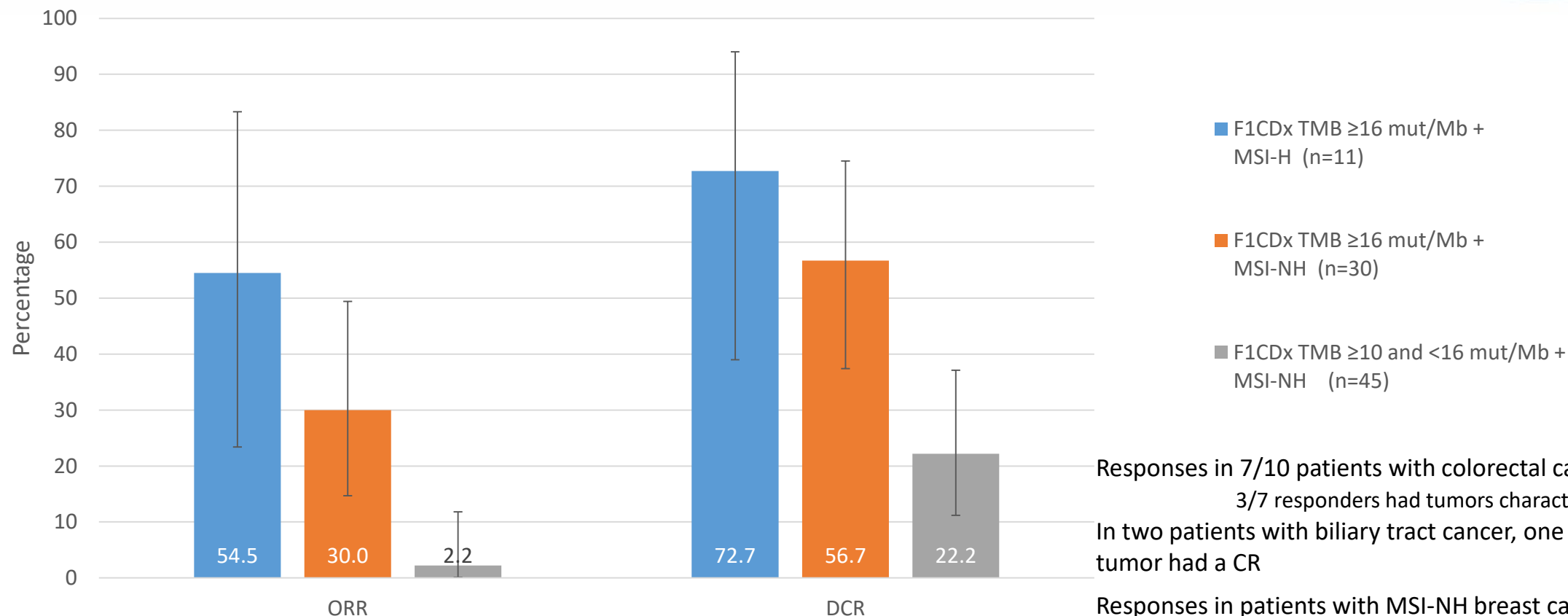
Hainsworth, Friedman et al, AACR 2021

Exploratory Clinical Outcomes

- In patients with a local non-F1CDx TMB assay and subsequent central F1CDx TMB testing, overall agreement for TMB subgroups (<16 mut/Mb or ≥16 mut/Mb) was 74.4% (29/39 patients)

- No confirmed responses were observed among:
  - Patients with TMB <10 mut/Mb by F1CDx (n=17)
  - Patients with TMB ≥16 mut/Mb by any CLIA assay and TMB <16 mut/Mb by F1CDx (n=9)

- ORR was higher in patients with TMB ≥16 mut/Mb by any CLIA test than those with TMB ≥10 and <16 mut/Mb

	Any CLIA test ≥16 mut/Mb n=42	Any CLIA test ≥10 and <16 mut/Mb n=48
Confirmed objective response rate, n (%) 95% CI	16 (28.6) 17.3–42.2 3 CR, 13 PR	2 (3.1) 0.4–10.8 2 PR

Hainsworth, Friedman et al, AACR 2021

TMB and combined anti-PD-1/CTLA-4 blockade

TMB and ipi/nivo in Small-Cell Lung Cancer
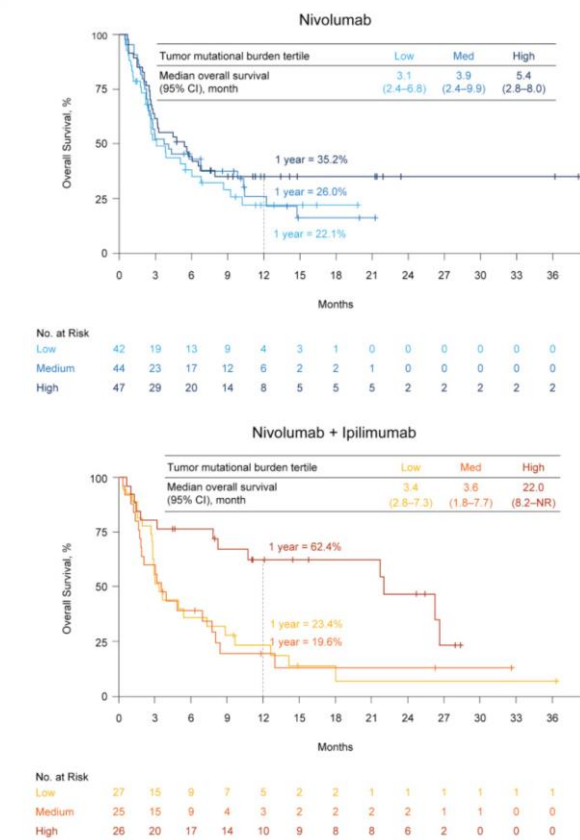
Hellman Cancer Cell 2018

MYSTIC: TMB and durva/treme in NSCLC
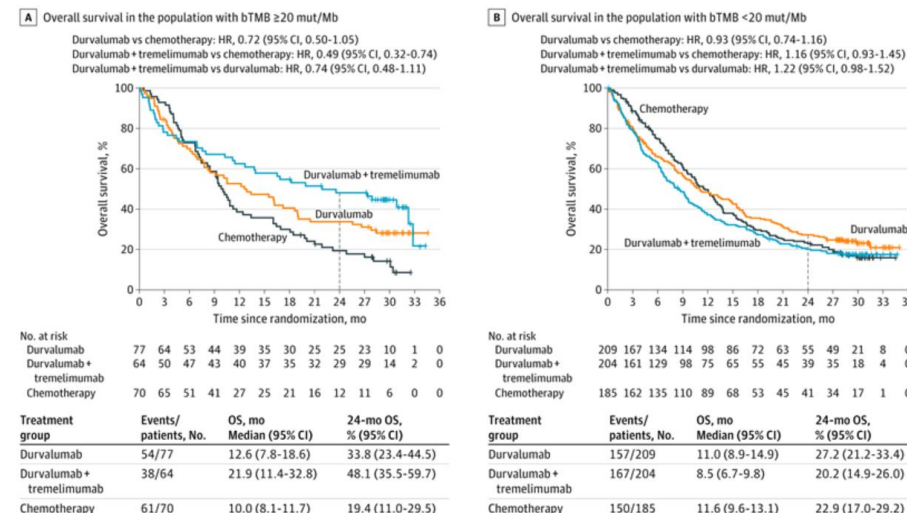
- bTMB ≥20 mut/Mb associated with improved OS for durvalumab plus tremelimumab vs chemotherapy

median, 21.9 months [95% CI, 11.4-32.8] vs 10.0 months [95% CI, 8.1-11.7]; unadjusted HR, 0.49; 95% CI, 0.32-0.74)

- No improvement in OS for durvalumab plus tremelimumab vs chemotherapy in patients with bTMB <20 mut/Mb

Rizvi et al, JAMA Oncology, 2020

TMB and combined anti-PD-1/CTLA-4 blockade

Clinical outcome and TMB analysis of CA209-538
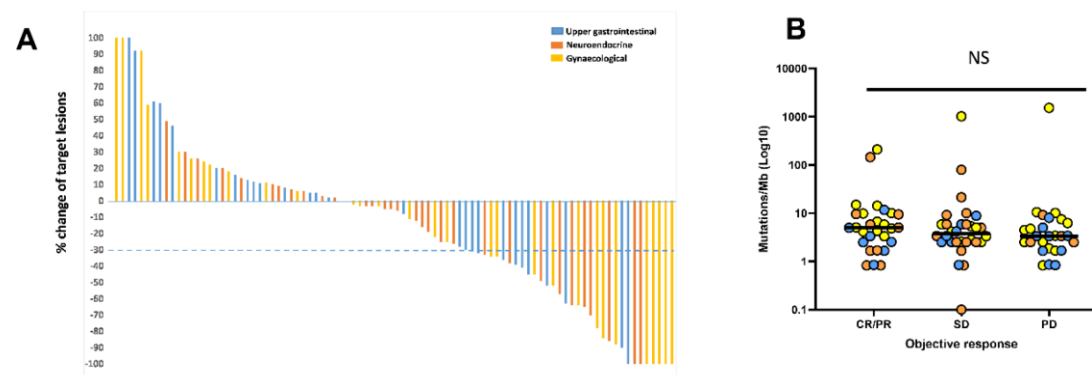
The ORR of TMB[high] patients without MSI-H tumors was 36% versus 31% respectively, with the majority of responders (79%) having non-TMB[high] tumors

Klein et al Cancer Cell 2021

TMB remains controversial

ESMO
GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

ANNALS OF ONCOLOGY
driving innovation in oncology

ORIGINAL ARTICLE

High tumor mutation burden fails to predict immune checkpoint blockade response across all cancer types

D. J. McGrail[1*], P. G. Pilié[2], N. U. Rashid[3,4], L. Voorwerk[5], M. Slagter[6,7,8], M. Kok[5,9], E. Jonasch[2], M. Khasraw[10], A. B. Heimberger[11], B. Lim[12], N. T. Ueno[12], J. K. Litton[12], R. Ferrarotto[13], J. T. Chang[14,15], S. L. Moulder[12] & S.-Y. Lin[1*]

McGrail et al, Ann Onc, 2021

TMB as Predictor of Response and OS on CPI

- The TMB-H biomarker is predicated on the concept that increased mutational load will correspond with more immunogenic neoantigens

- Many cancer types, such as breast and prostate cancers, do not exhibit a positive correlation between CD8 T-cell infiltration and neoantigen load

- In cancer types where CD8 T-cell levels positively correlated with neoantigen load, such as melanoma, lung, and bladder cancers, TMB-H tumors exhibited a 39.8% ORR to ICB [95% confidence interval (CI) 34.9-44.8], which was significantly higher than that observed in low TMB (TMB-L) tumors [odds ratio (OR) ¼ 4.1, 95% CI 2.9-5.8, P < 2 1016].

- In cancer types that showed no relationship between CD8 T-cell levels and neoantigen load, such as breast cancer, prostate cancer, and glioma, TMB-H tumors failed to achieve a 20% ORR (ORR ¼15.3%, 95% CI 9.2-23.4, P ¼ 0.95), and exhibited a significantly lower ORR relative to TMB-L tumors (OR ¼0.46, 95% CI 0.24-0.88, P ¼ 0.02)

McGrail et al, Ann Onc, 2021

Friends of Cancer Research
# TMB Harmonization Project

- In silico assessment of variation in TMB quantification across diagnostic platforms

- Eleven laboratories used WES data from The Cancer Genome Atlas Multi-Center Mutation calling in 32 cancer types and calculated TMB from the subset of the exome restricted to the genes covered by their targeted panel using their own bioinformatics pipeline (panel TMB)

- A reference TMB value was calculated from the entire exome using a uniform bioinformatics pipeline all members agreed on (WES TMB)

Merino et al, J Immunother Cancer, 2020

# Panel TMB vs WES TMB for each of the 11 participating laboratories
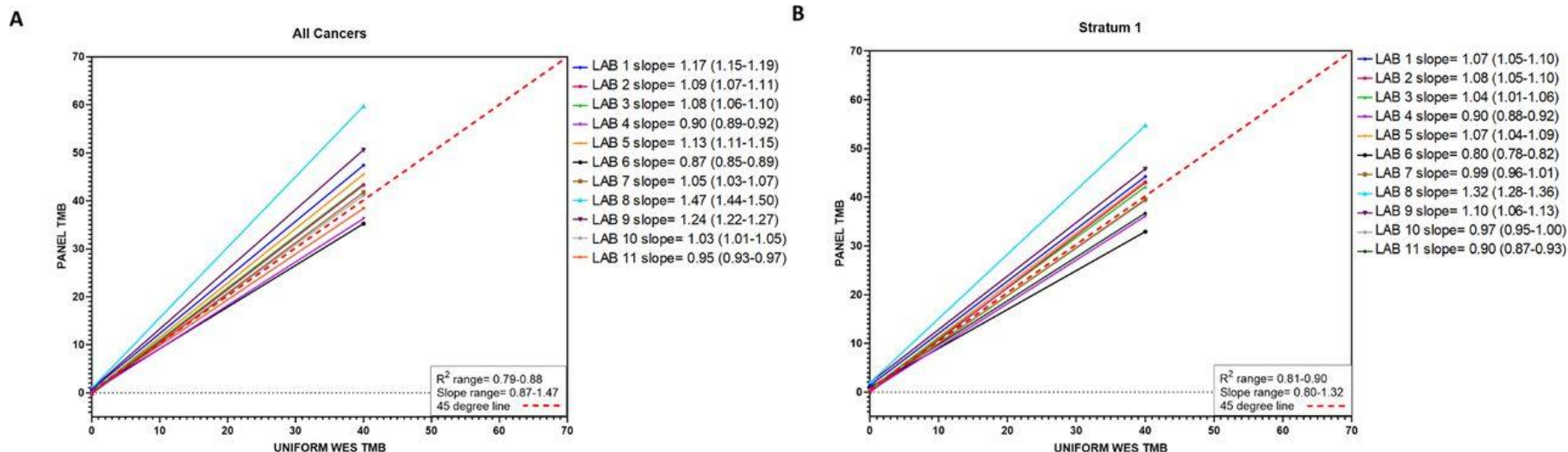
- Panel TMB values were strongly correlated with WES TMB across laboratories
- Study results demonstrated that variability within and between panel TMB values increases as the WES TMB values increase.

- A limitation of analyzing all cancer types together is the variable distribution of TMB across different cancer types, with some cancer types displaying large dynamic ranges of TMB values up to several hundred mutations per Mb and others with very limited distributions with very few samples reaching 20 mutations per Mb (see online supplementary figure 3). To account for this limitation, cancer types were categorized into strata by their distribution of WES TMB values. Stratum 1 (n=1563 samples with <40 mut/Mb) had samples with a good distribution of WES TMB values covering 0–40 mut/Mb, : bladder urothelial carcinoma (BLCA, n=195), colon adenocarcinoma (COAD, n=128), head and neck squamous cell carcinoma (HNSC, n=232), lung adenocarcinoma (LUAD, n=228), lung squamous cell carcinoma (LUSC, n=228), skin cutaneous melanoma (SKCM, n=166), stomach adenocarcinoma (STAD, n=189) and uterine corpus endometrial carcinoma (UCEC, n=197).

Merino et al, J Immunother Cancer, 2020

Estimated regression lines for panel TMB as a function of WES TMB for eight cancer types
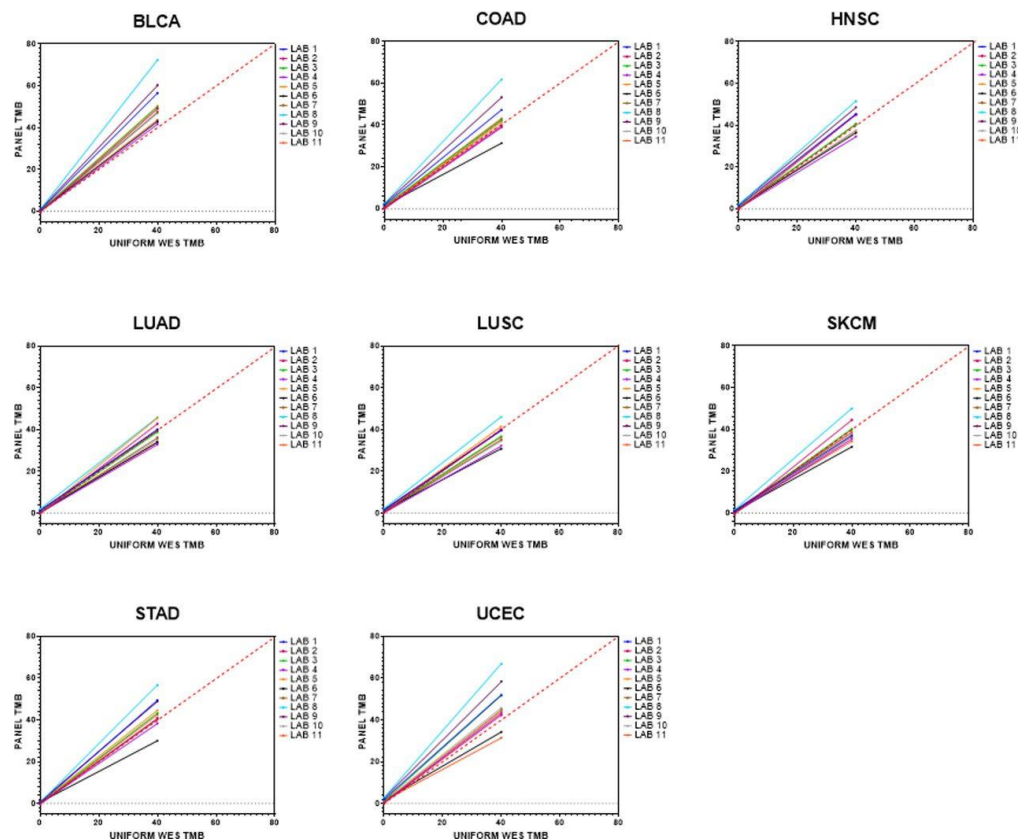
Certain cancer types, such as uterine, bladder and colon cancers exhibited greater variability in panel TMB values, compared with lung and head and neck cancers

Merino et al, J Immunother Cancer, 2020

95% prediction intervals for panel TMB estimated at discreet WES TMB values across laboratories
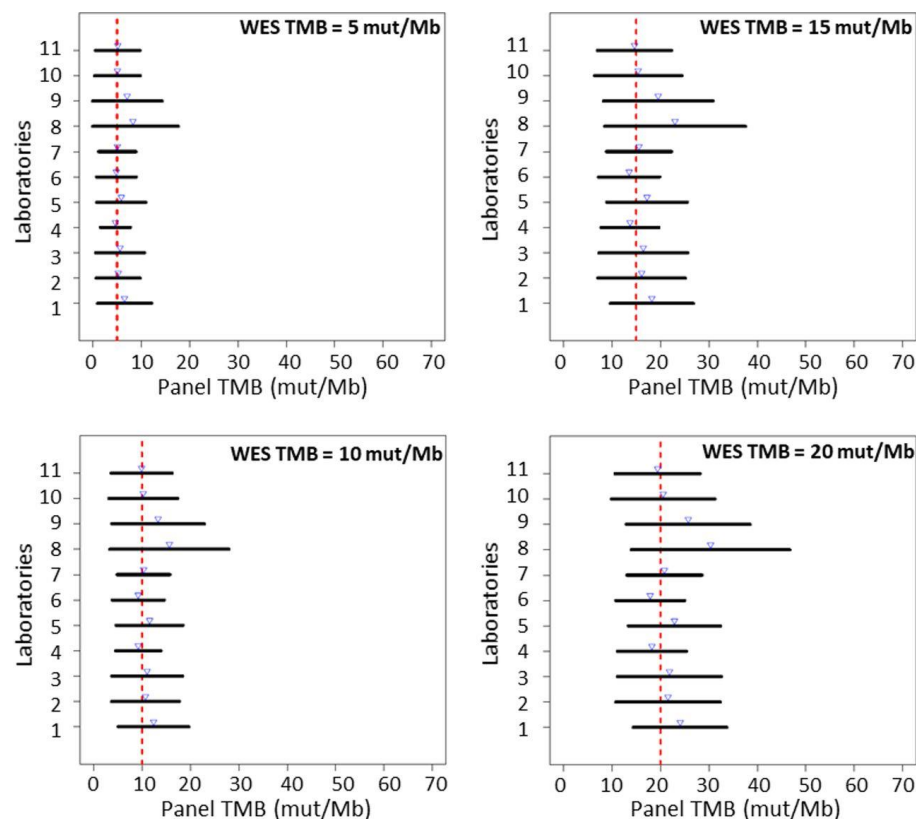
Some laboratories had consistently tighter (narrower) prediction intervals, while others demonstrated more variability (wider intervals)

Prediction intervals became tighter with decreasing WES TMB value, indicating greater variability in panel TMB at larger WES TMB values

The prediction intervals observed for each participating laboratory were generally similar, with laboratories demonstrating intervals that spanned as small as ±4.7 mut/Mb or as large as ±12.3 mut/Mb when the WES TMB was 10 mut/Mb

Merino et al, J Immunother Cancer, 2020

Harmonization of TMB Values

- Please refer to Merino et al for consensus recommendations for the standardization of analytical validation studies of targeted NGS panels that estimate TMB

- A few highlights:

- Ensure reporting consistency: TMB should be reported in mutations/megabase (mut/Mb)

- Analytical validation studies for TMB estimation should be standardized to include assessment of analytical accuracy, precision and sensitivity

- Consistency across panels could be ensured through alignment of panel TMB values to WES-derived universal reference standard

Summary

- TMB-H is approved as a tumor-agnostic biomarker for one CPI already

- There remains several areas of controversy:
  - Is TMB-H is equally predictive across tumor types?
  - Is 10 mut/Mb is the optimum cut-off?
  - Should cut-offs with vary CPI?
  - Cut-off may vary by assay
  - Further data especially needed for bTMB

Conclusions

- There is enough data to:
  - Perform genomic testing in patients with metastatic cancer that are candidates for immunotherapy with NGS assays that can report TMB
  - Consider CPI in TMB-H patients, beyond diseases with disease-specific CPI approval- taking into account extent of TMB increase, other therapy options, suitability

- TMB is just a piece of the puzzle- There are diseases like RCC where CPI are active but TMB is low

- Need for education on TMB and role of genomic testing as well as assay interpretation

Questions/comments/collaborations

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