Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

The Future of MSI/TMB

Mohamed E. Salem, MD

Associate Professor

Levine Cancer Institute, Charlotte, NC

Disclosures

- Consulting Fees: Taiho Oncology, Astrazeneca, Daiichi Sankyo, Bristol Myers Squibb, Merk, Pfizer, QED Therapeutics, Novartis, Exelixis
- I will not be discussing non-FDA approved indications during my presentation.

2016

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Magazine > Features

ASCO Names Immunotherapy as Cancer Advance of the Year

Feb 04, 2016

***2016 Clinical Cancer Advances* report reviews the year's top research accomplishments**

No recent cancer discovery has been more transformative than immunotherapy. Its ability to prolong life for people with advanced melanoma and lung cancer, and results presented or published in the past year showing that it can slow the growth of many other cancers, makes cancer immunotherapy ASCO's Advance of the Year. This standout achievement was announced as part of *Clinical Cancer Advances 2016: ASCO's Report on Progress Against Cancer*.

2017

Immunotherapy 2.0 Named Advance of the Year in ASCO's Report

Society for Immunotherapy of Cancer

ASCO sp

Clinical Cancer Advances 2021: ASCO's Repo on Progress Against Cancer

EXECUTIVE SUMMARY (CONTINUED)

cancer has lagged. Molecular profiling has helped change the outlook for patients with GI cancer by identifying the molecular and genetic signatures that allow oncologists to deliver treatments that are highly specific to a tumor. For these reasons, ASCO has identified molecular profiling driving progress in GI cancer as the 2021 Advance of the Year. This selection recognizes the treatment advances made possible by molecular testing for patients with GI cancers.

Society for Immunotherapy of Cancer

FDA Approved Therapy Based on Molecular Characteristics

- *K(RAS)-Wild type*
- *BRAF^{V600E}*
- NTRAK
- *HER2-Neu*
- MSI-High/dMMR
- TMB-High
- *KRAS-G12C*

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Recent FDA Approvals

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Advances in Cancer Immunotherapy™

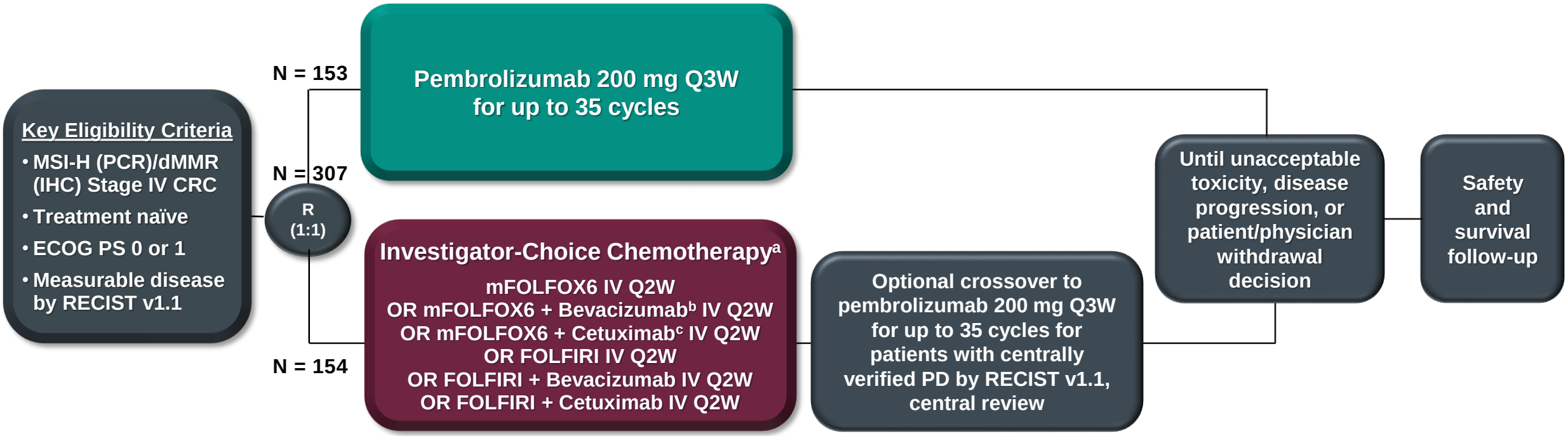
Drug(s)	Date	Indication
Pembrolizumab	June 29, 2020	1st line treatment of MSI-H/dMMR colorectal cancer
Nivolumab	July 31, 2017	Refractory MSI-H/ MMR-D CRC
Nivo + Ipi	July 11, 2018	
Pembrolizumab	May 23, 2017	

Pembrolizumab Versus Chemotherapy for Microsatellite Instability-High/Mismatch Repair Deficient Metastatic Colorectal Cancer: The Phase 3 KEYNOTE-177 Study

Thierry André,[1] Kai-Keen Shiu,[2] Tae Won Kim,[3] Benny Vittrup Jensen,[4] Lars Henrik Jensen,[5] Cornelis Punt,[6] Denis Smith,[7] Rocio Garcia-Carbonero,[8] Manuel Benavides,[9] Peter Gibbs,[10] Christelle de la Fouchardiere,[11] Fernando Rivera,[12] Elena Elez,[13] Johanna Bendell,[14] Dung T. Le,[15] Takayuki Yoshino,[16] Ping Yang,[17] Mohammed Farooqui,[18] Patricia Marinello,[18] and Luis A. Diaz Jr[19]

[1]Sorbonne Université and Hôpital Saint Antoine, Paris, France; [2]University College Hospital, NHS Foundation Trust, London, United Kingdom; [3]Asan Medical Center, University of Ulsan, Seoul, Republic of Korea; [4]Herlev and Gentofte Hospital, Herlev, Denmark; [5]University Hospital of Southern Denmark, Vejle, Denmark; [6]Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, Netherlands; [7]Bordeaux University Hospital, Bordeaux, France; [8]Hospital Universitario 12 de Octubre, Imas12, CNIO, UCM, Madrid, Spain; [9]Hospital Regional Universitario de Malaga, Malaga, Spain; [10]Western Health, St Albans, Australia; [11]Léon Bérard Center, Lyon, France; [12]Hospital Universitario Marques de Valdecilla, IDIVAL, Santander, Spain; [13]Vall d'Hebron Institute of Oncology, Barcelona, Spain; [14]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [15]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [16]National Cancer Center Hospital East, Kashiwa, Japan; [17]MSD China, Beijing, China; [18]Merck & Co., Inc. Kenilworth, NJ, USA; [19]Memorial Sloan Kettering Cancer Center, New York, NY, USA

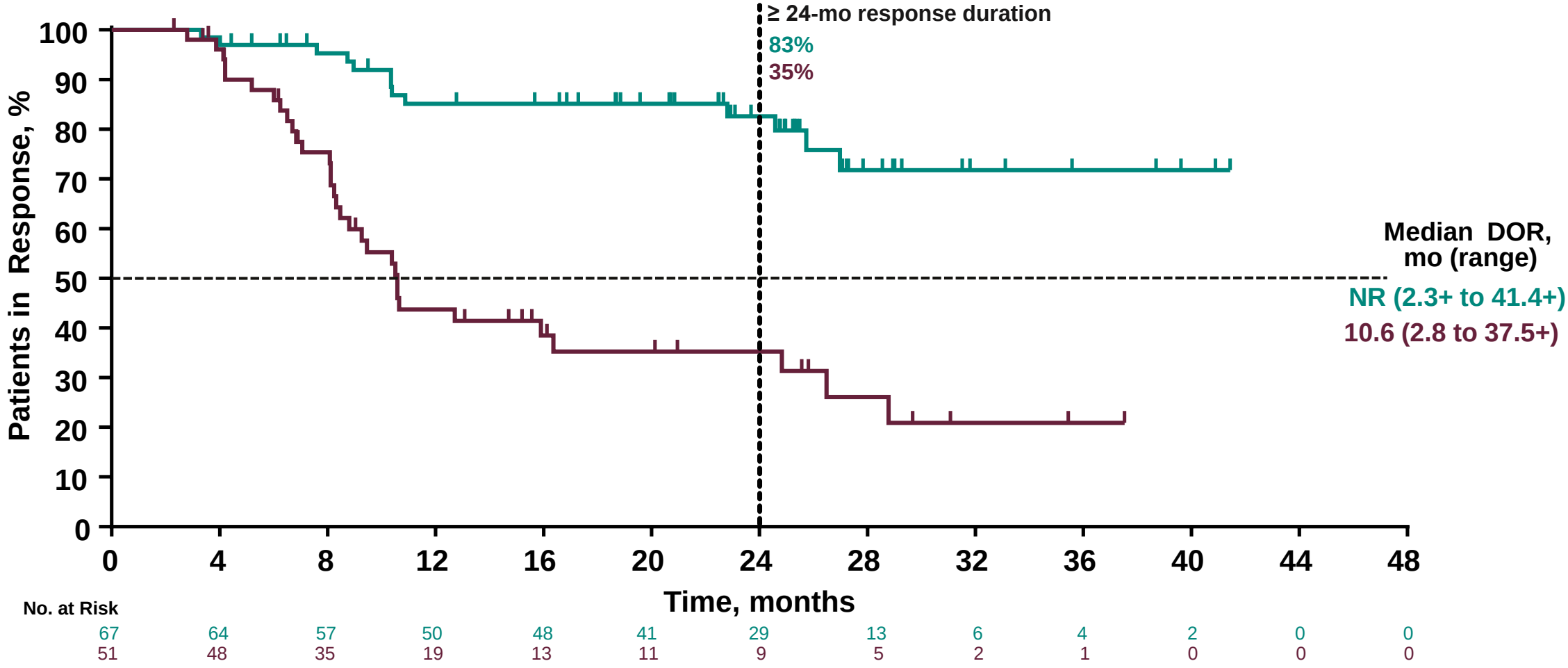
KEYNOTE-177 Study Design
(NCT02563002)



- Dual-Primary endpoints: PFS per RECIST v1.1, BICR; OS
- Secondary endpoints: ORR per RECIST v1.1 by BICR, PFS2, HRQoL, safety
- Tumor response assessed at week 9 and Q9W thereafter per RECIST v1.1 by BICR

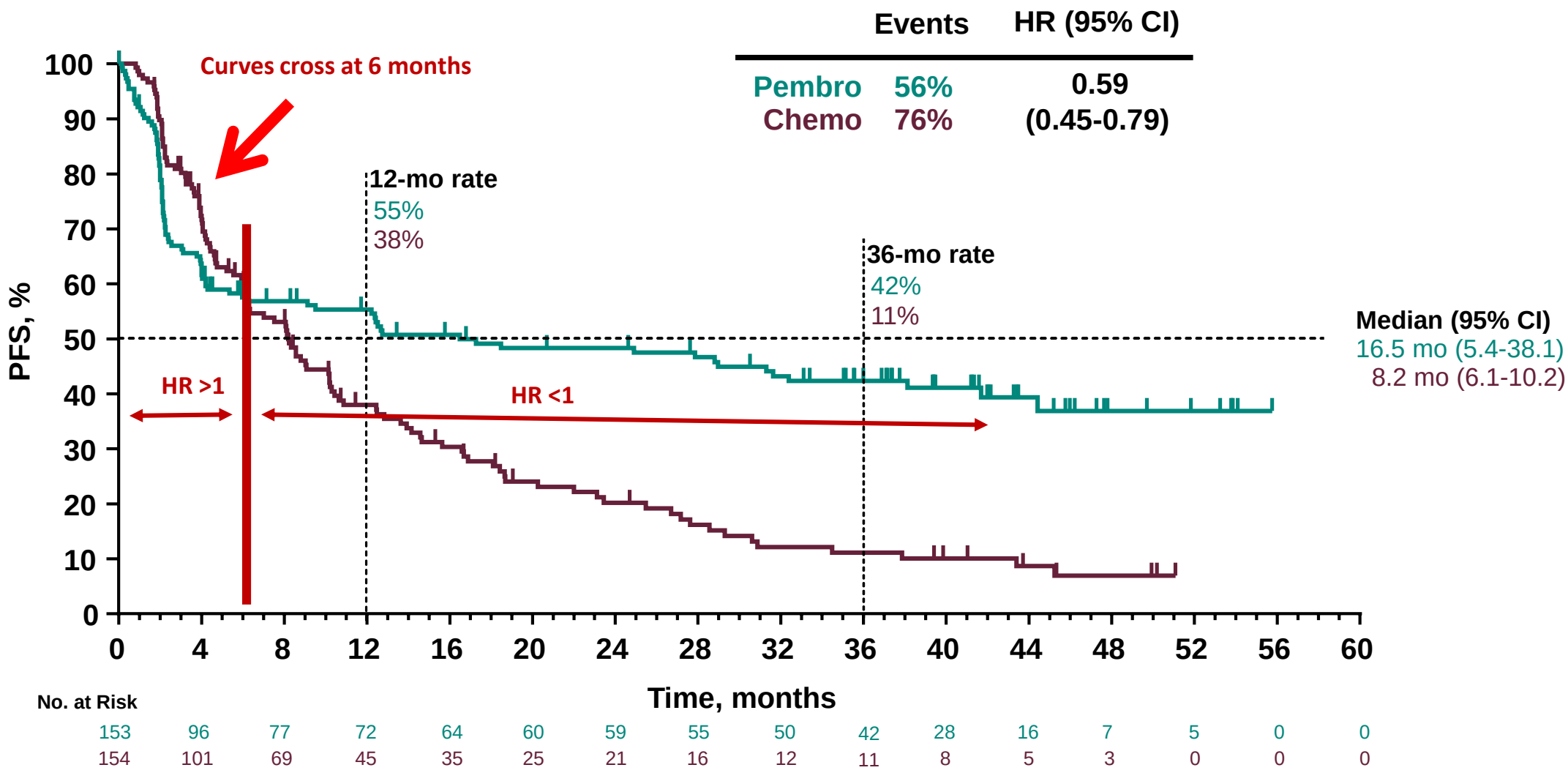
[a]Chosen before randomization; [b]Bevacizumab 5 mg/kg IV; [c]Cetuximab 400 mg/m2 over 2 hours then 250 mg/mg^2 IV over 1 hour weekly.
BICR, blinded independent central review; IHC: immunohistochemistry with hMLH1, hMSH2, hMSH6, PMS2; PCR: polymerase chain reaction; PFS, progression-free survival; OS: overall survival; ORR: overall response rate; Q9W: every 9 weeks.

Duration of Response



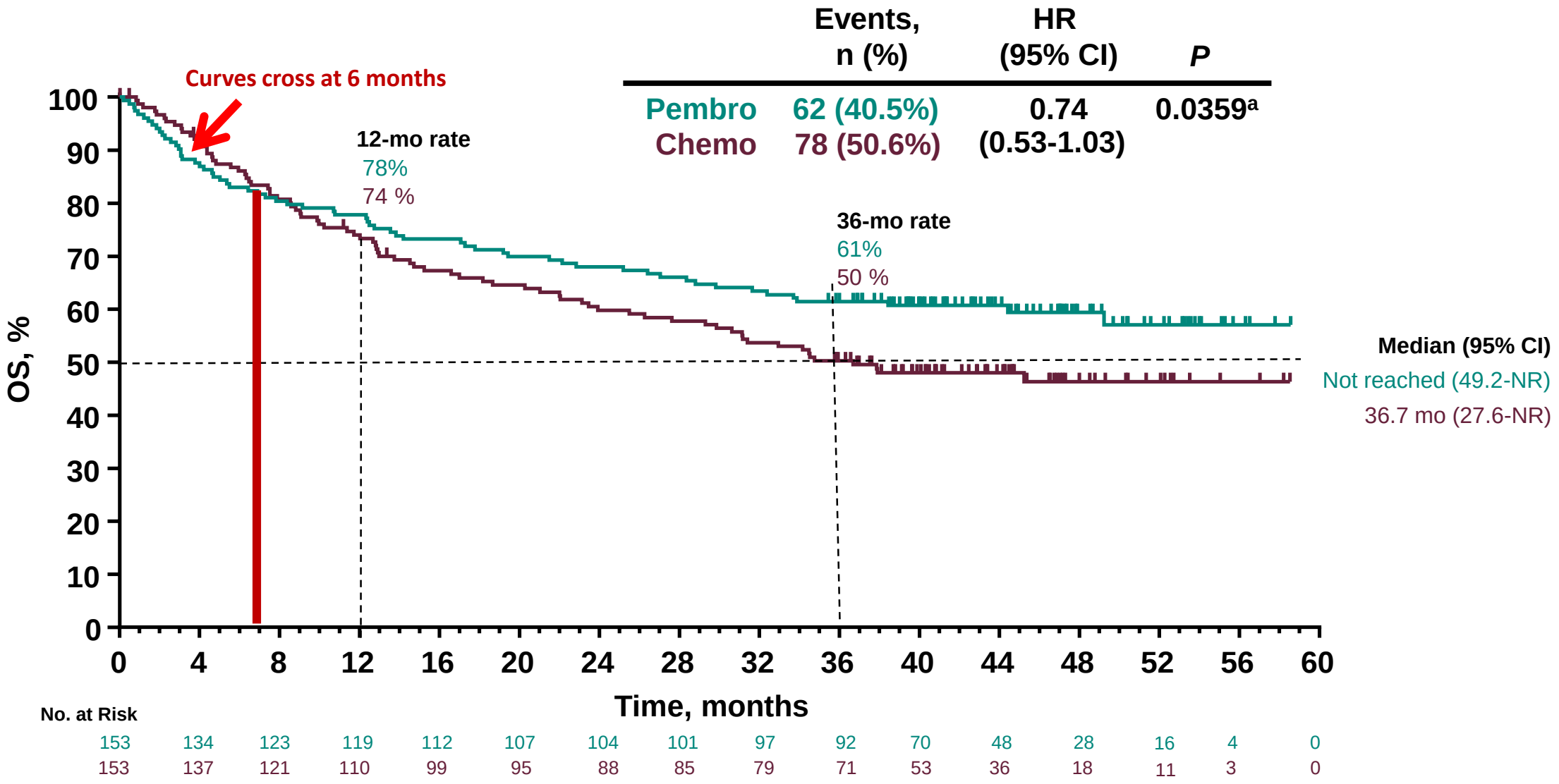
Duration of Response assessed per RECIST v1.1 by BICR; Data cut-off: 19Feb2020.

Progression-Free Survival



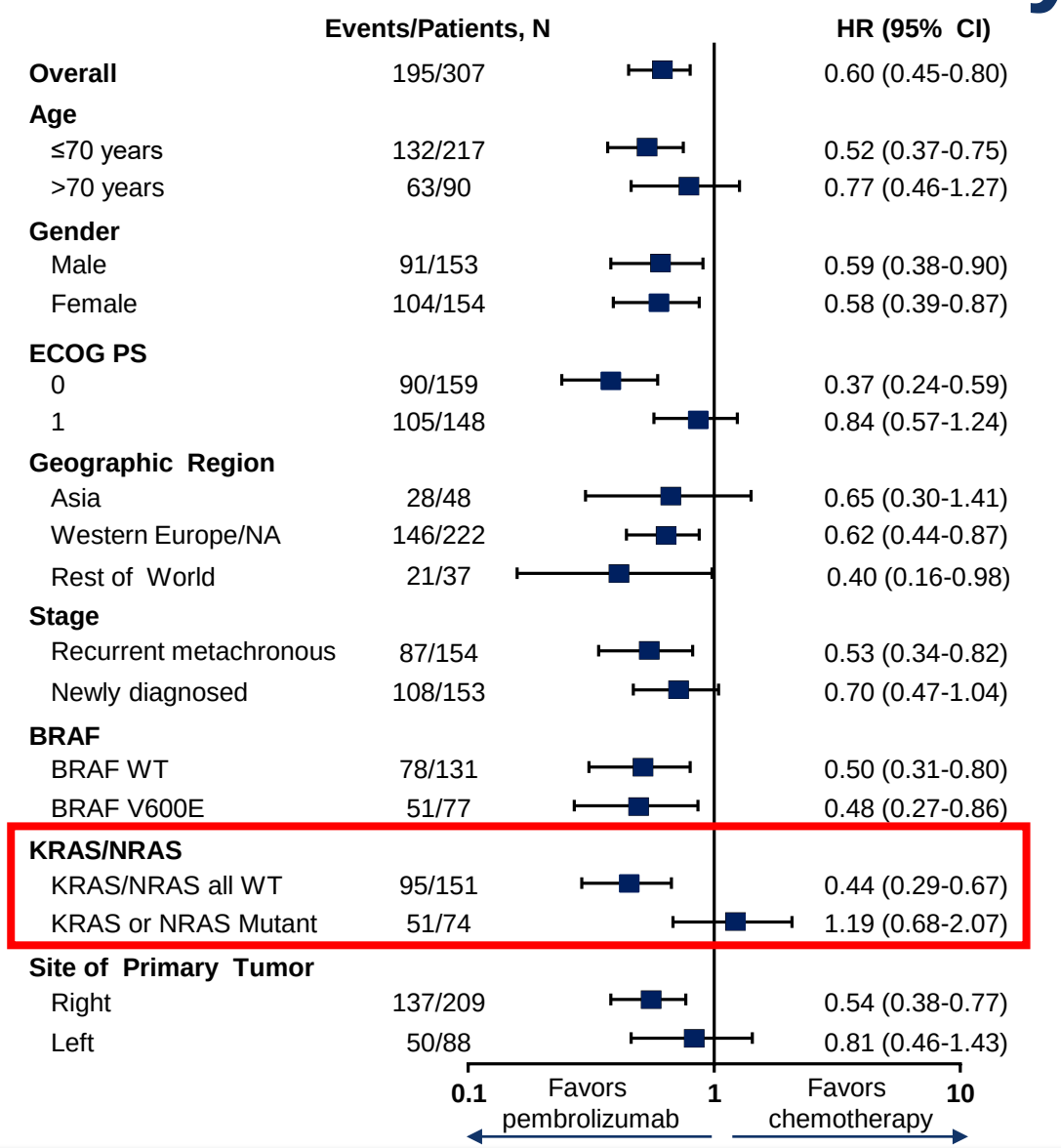
Data cut-off: 19Feb2021.

Overall Survival



[a]**Pembrolizumab was not superior to chemotherapy for OS as one-sided α > 0.0246. Pre-specified sensitivity analyses to adjust for crossover effect by rank-preserving structure failure time model and inverse probability of censoring weighting showed OS HRs of 0.66 (95% CI 0.42-1.04) and 0.77 (95% CI 0.44-1.38).** Data cut-off: 19Feb2021.

Progression-Free Survival in Key Subgroups



NA, North America; Data cut-off: 19Feb2020.

Antitumor Response

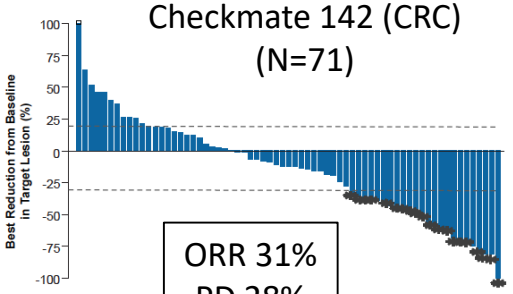
	Pembrolizumab N = 153	Chemotherapy N = 154
ORR, n (%)	**69 (45.1)[a]**	**51 (33.1)**
Best Overall Response, n (%)		
Complete response	20 (13.1)[b]	6 (3.9)
Partial response	49 (32.0)[c]	45 (29.2)
Stable disease	30 (19.6)	65 (42.2)
Disease control rate (CR+PR+SD)	99 (64.7)	116 (75.3)
Progressive disease	45 (29.4)	19 (12.3)
Not evaluable	3 (2.0)	2 (1.3)
No assessment	6 (3.9)	17 (11.0)
Median duration or response (range), mo	NR (2.3+ to 53.5+)	10.6 (2.8 to 48.3+)
≥ 24 months response duration, %	83.5	33.6

[a]ORR 43.8%; [b]CR rate 11.1%; [c]PR rate 32.7% at IA2 (data cut-off 19Feb2020).
Data cut-off: 19Feb2021.

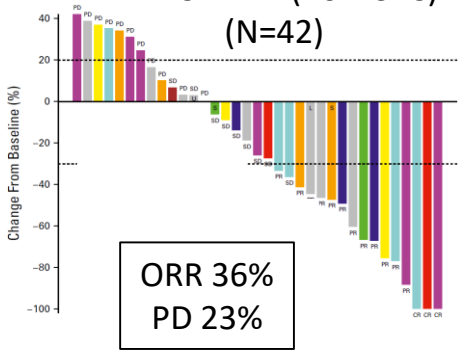
Pembrolizumab and Nivolumab in dMMR/MSI-H Cancers

Nivolumab

Checkmate 142 (CRC)
(N=71)

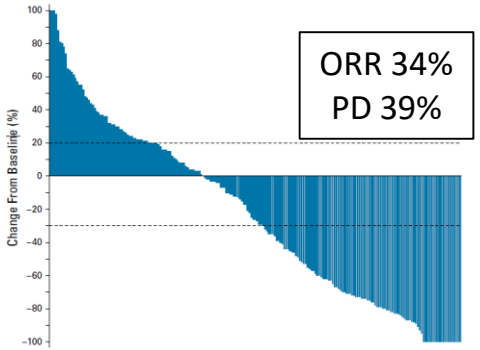


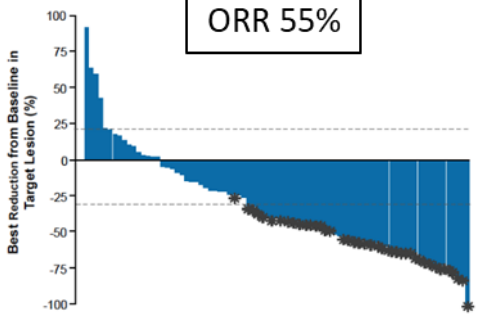
MATCH Z1D (non-CRC)
(N=42)



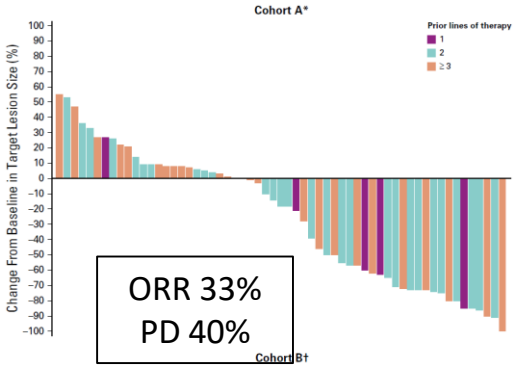
Pembrolizumab

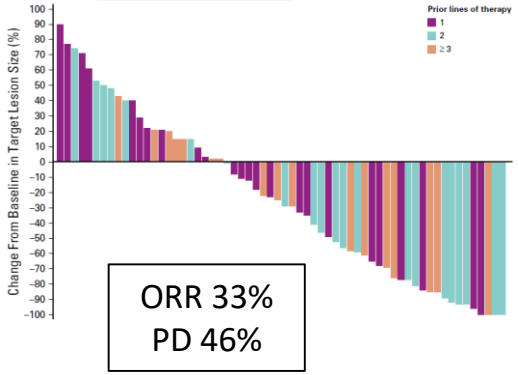
Keynote 158 (non-CRC)
(N=233)





Keynote 164 (CRC)
(N=124)





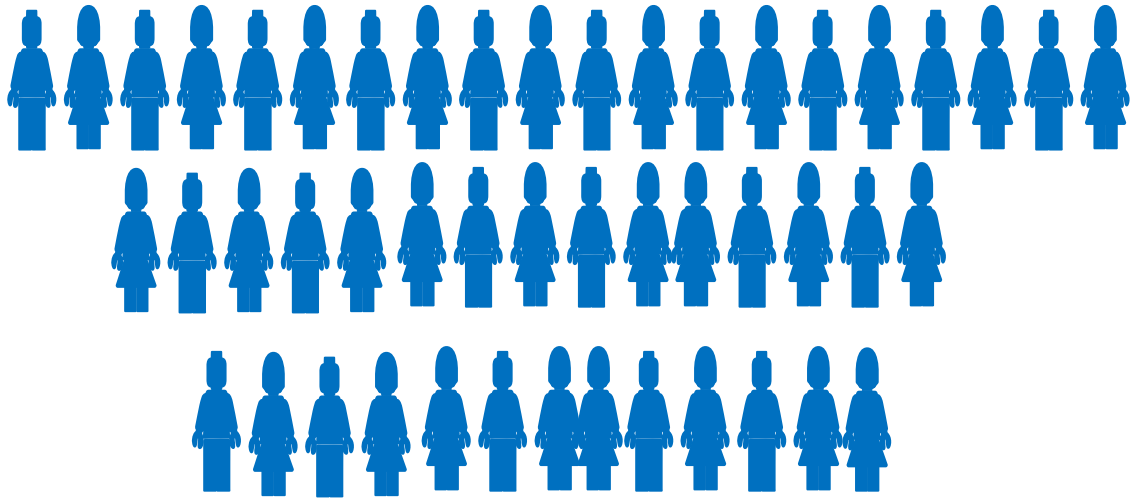
Nivo/Ipi

Overman M, et al. *Lancet Onc*. 2017; Lee JW, et al. *JCO*. 2020; Marabelle A, et al. *JCO*. 2019; Azad S, et al. *JCO*. 2019.

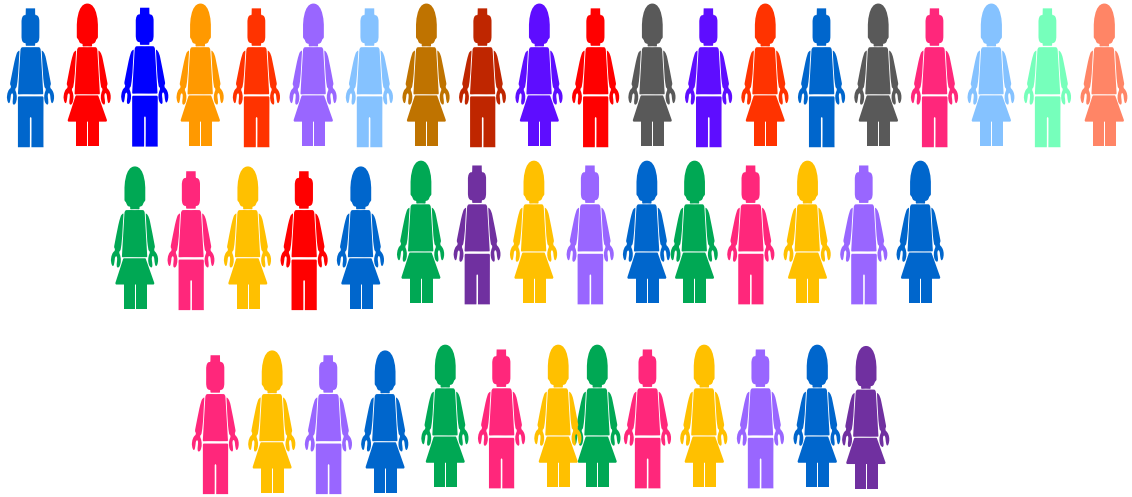
Slide curtesy of Dr. H. lenz

Are all MSI-High/dMMR tumors created equal?

MSI-H/dMMR Tumors are One Disease



MSI-H/dMMR Tumors are NOT One Disease



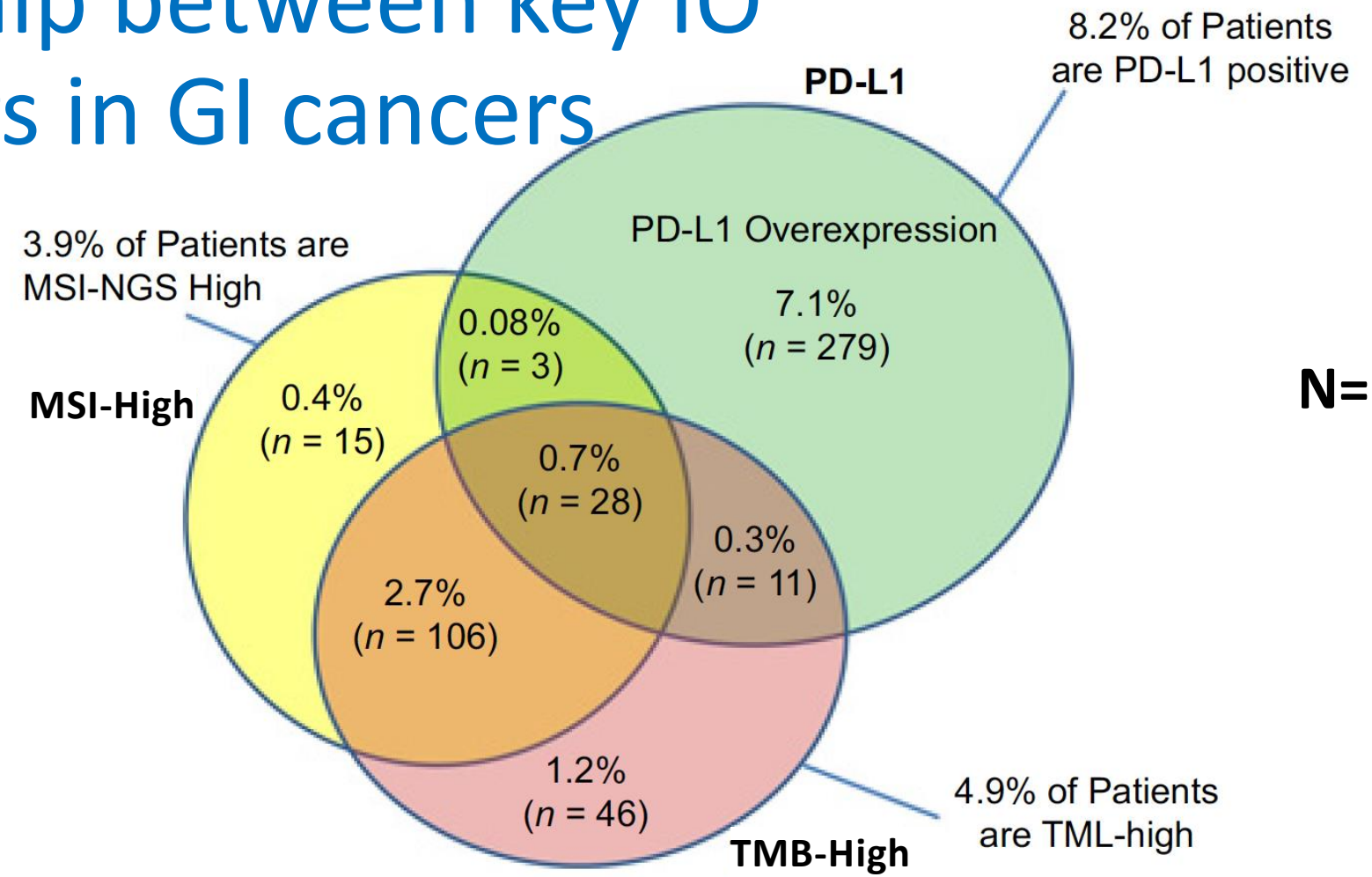
Genomics

Molecular Cancer Research

Landscape of Tumor Mutation Load, Mismatch Repair Deficiency, and PD-L1 Expression in a Large Patient Cohort of Gastrointestinal Cancers

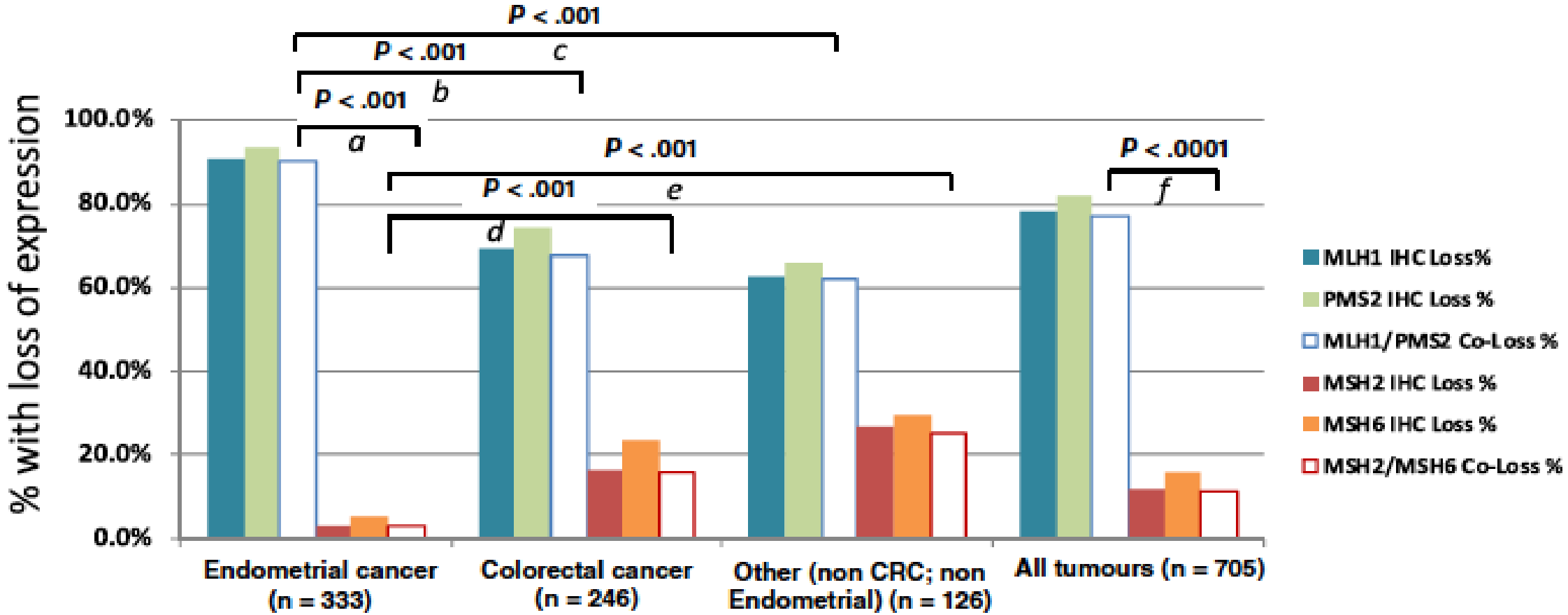
Mohamed E. Salem[1], Alberto Puccini[2], Axel Grothey[3], Derek Raghavan[1], Richard M. Goldberg[4], Joanne Xiu[5], W. Michael Korn[5], Benjamin A. Weinberg[6], Jimmy J. Hwang[1], Anthony F. Shields[7], John L. Marshall[6], Philip A. Philip[7], and Heinz-Josef Lenz[2]

Relationship between key IO biomarkers in GI cancers



N=3,896 pts

Salem et al. Mol Cancer Res 2018



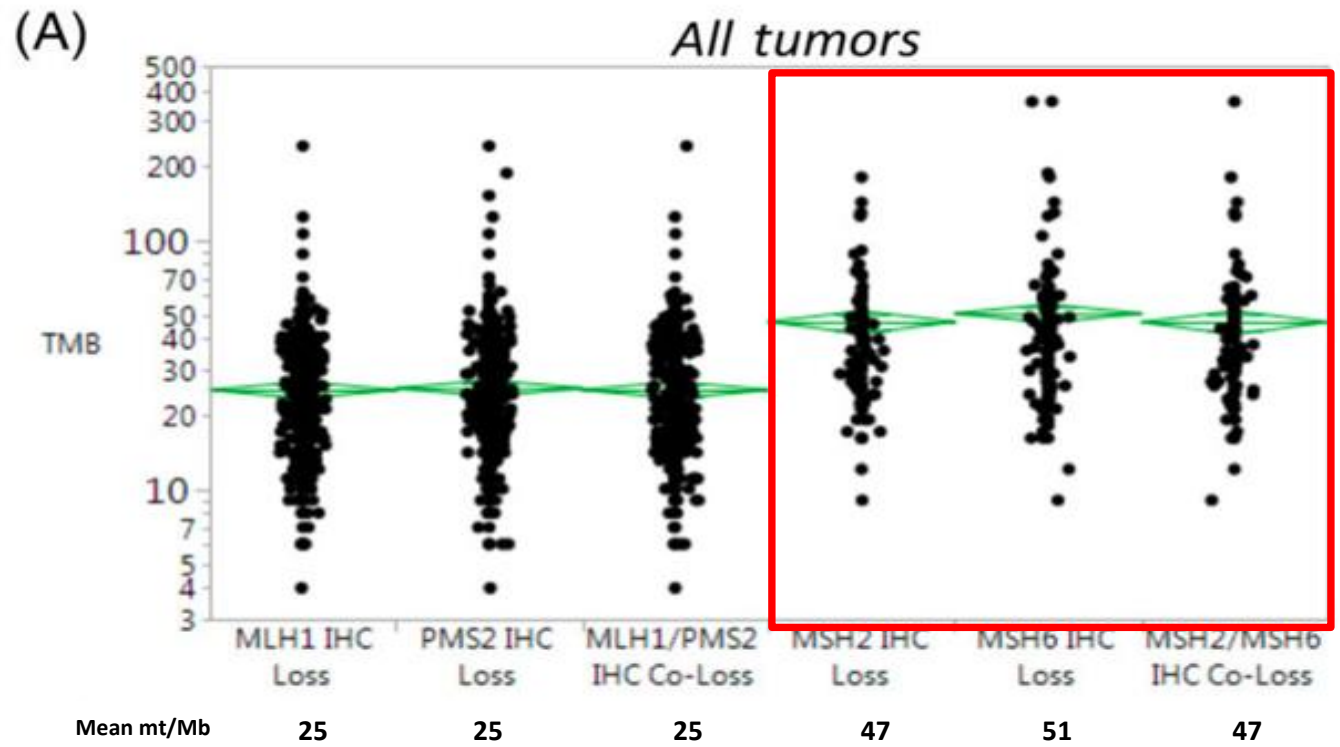
In MSI-H IHC tested tumors, loss of co-expression of MLH1/PMS2 was more common (77.2%) than loss of MSH2/MSH6 (11.5%), P < .0001

Salem et al. *Int J Cancer*. 2020

IJC International Journal of Cancer

Tumor Markers And Signatures

Relationship between MLH1, PMS2, MSH2 and MSH6 gene-specific alterations and tumor mutational burden in 1057 microsatellite instability-high solid tumors



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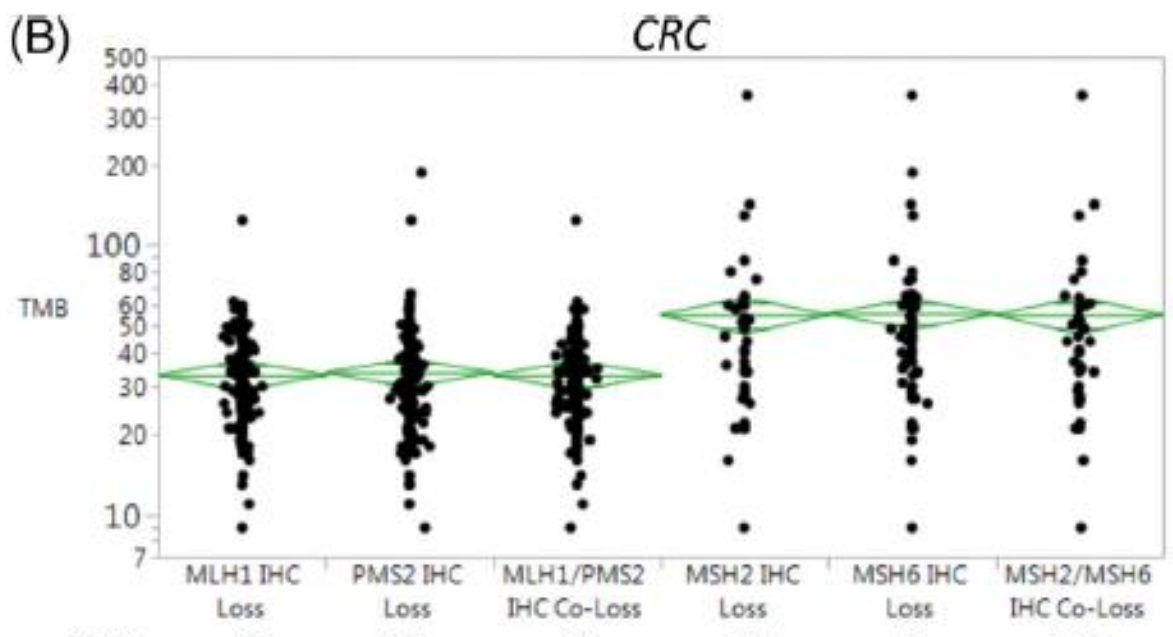
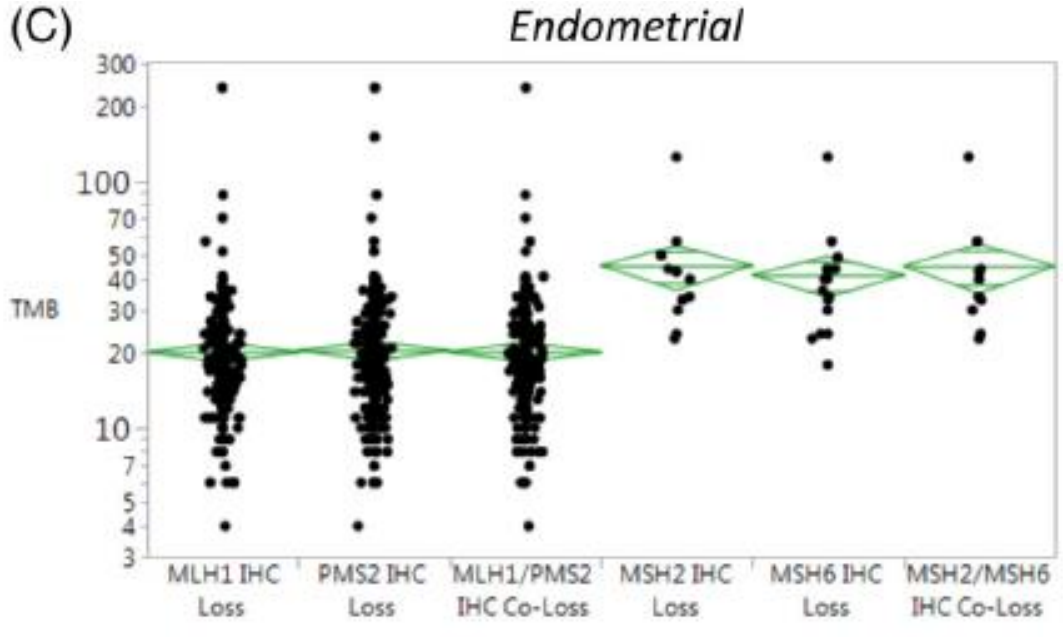
Salem et al. *Int J Cancer*. 2020

TMB in MSI-H tumors varied by histology



Mean mt/Mb	33	34	33	55	56	55



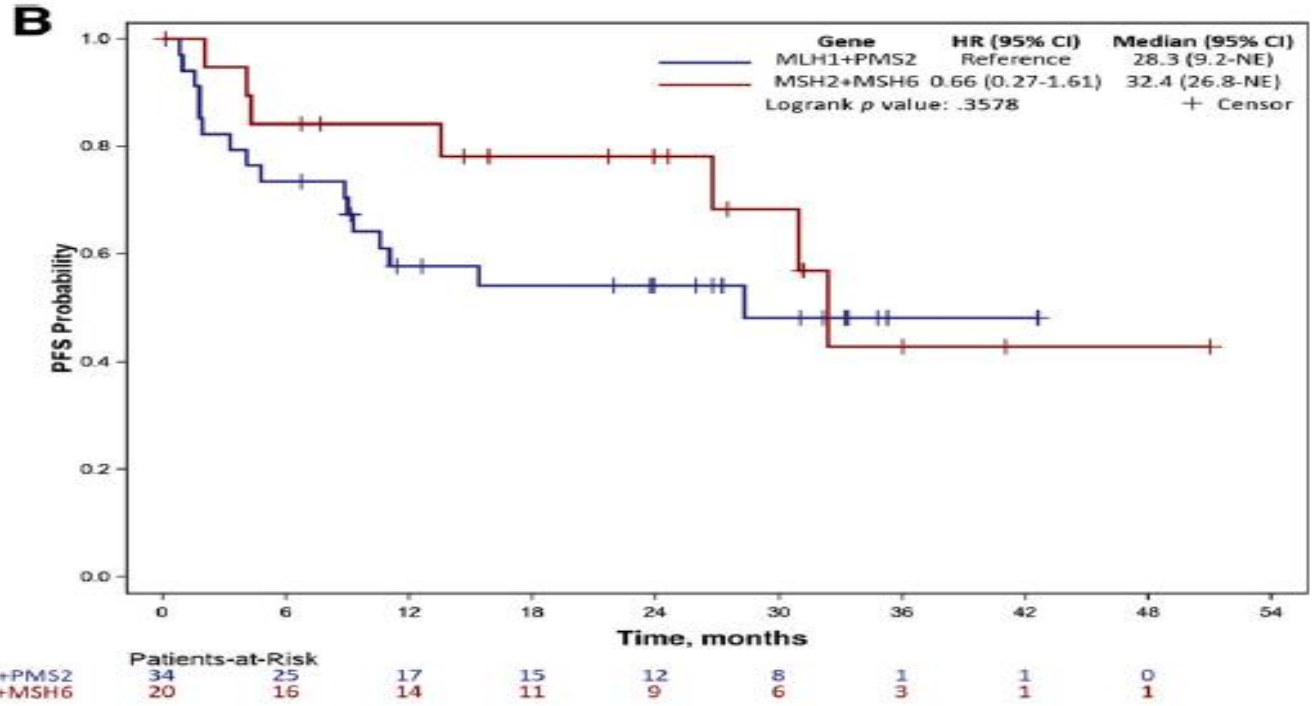
Mean mt/Mb	20	21	20	46	42	45

CRC

Endometrial

Salem et al. *Int J Cancer*. 2020

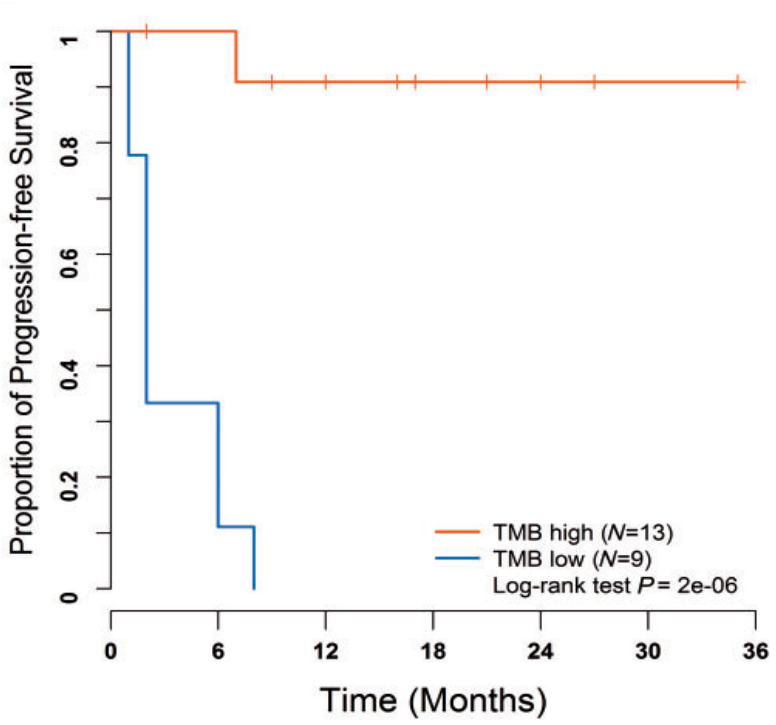
Mismatch Repair (MMR) Gene Alteration and BRAF V600E Mutation Are Potential Predictive Biomarkers of Immune Checkpoint Inhibitors in MMR-Deficient Colorectal Cancer

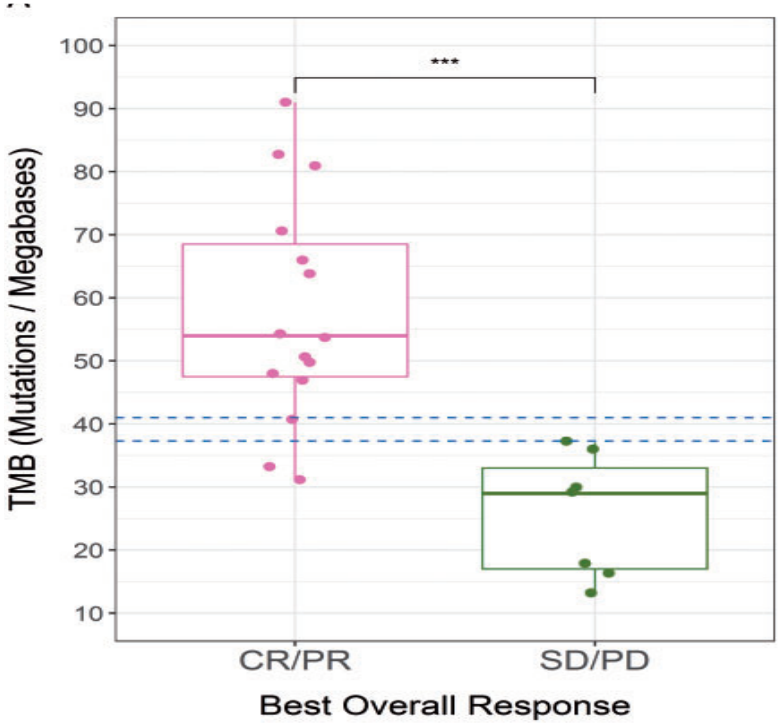


Sahin, Goyal, Pumpalova et al.

TMB as an IO Response Predictor in MSI H

- 22 pts treated with PD1 based therapy
- Optimal TMB cut-point: 37-41 mut/Mb
  - PR/CR vs SD/PD p=0.0003 (p=0.088 for MSI score)
- (foundation medicine 37.4 mut/Mb = 35th percentile)





Schrock et la. AoO 2019

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original reports

First-Line Nivolumab Plus Low-Dose Ipilimumab for Microsatellite Instability-High/ Mismatch Repair-Deficient Metastatic Colorectal Cancer: The Phase II CheckMate 142 Study

Heinz-Josef Lenz, MD[1]; Eric Van Cutsem, MD, PhD[2]; Maria Luisa Limon, MD[3]; Ka Yeung Mark Wong, PhD[4]; Alain Hendlisz, MD, PhD[5]; Massimo Aglietta, MD, PhD[6]; Pilar García-Alfonso, MD[7]; Bart Neyns, MD, PhD[8]; Gabriele Luppi, MD[9]; Dana B. Cardin, MD[10]; Tomislav Dragovich, MD, PhD[11]; Usman Shah, MD[12]; Sandzhar Abdullaev, MD, PhD[13]; Joseph Gricar, MS[13]; Jean-Marie Ledeine, MS[13]; Michael James Overman, MD[14]; and Sara Lonardi, MD[15]

CheckMate 142 NIVO3 + IPI1 1L cohort study design

- CheckMate 142 is an ongoing, multicohort, nonrandomized phase 2 trial evaluating the efficacy and safety of NIVO-based therapies in patients with mCRC[a]

- Histologically confirmed metastatic or recurrent CRC
- MSI-H/dMMR per local laboratory
- No prior treatment for metastatic disease

→ NIVO3 Q2W + IPI1 Q6W[b]

Primary endpoint:

- ORR per investigator assessment (RECIST v1.1)

Other key endpoints:

- ORR per BICR, DCR,[c] DOR, PFS, OS, and safety

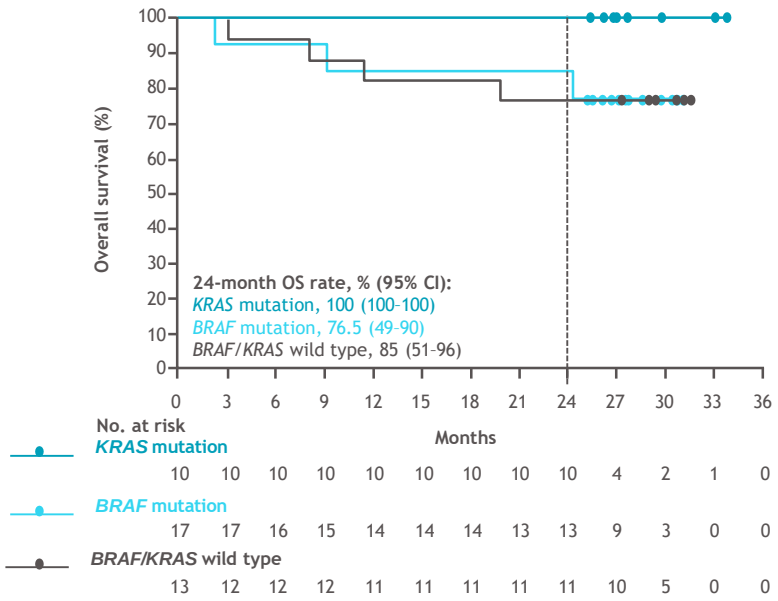
- At data cutoff (October 2019), the median duration of follow-up was 29.0 months (range, 24.2–33.7)[d]

[a]ClinicalTrials.gov number, NCT02060188. [b]Until disease progression or discontinuation in patients receiving study therapy beyond progression, discontinuation due to toxicity, withdrawal of consent, or the study end. [c]Patients with CR, PR, or SD for ≥ 12 weeks divided by the number of treated patients. [d]Median follow-up was defined as time from first dose to data cutoff. BICR, blinded independent central review; CR, complete response; CRC, colorectal cancer; DCR, disease control rate; DOR, duration of response; NIVO3, nivolumab 3 mg/kg; IPI1, ipilimumab 1 mg/kg; PR, partial response; SD, stable disease.

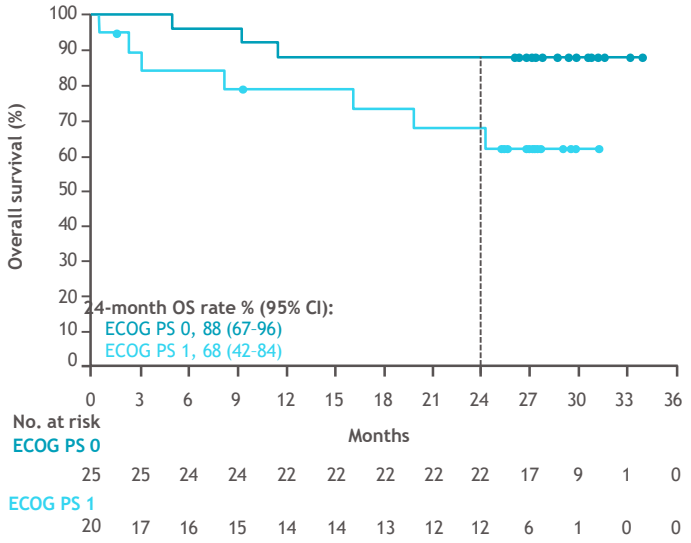
Overall survival by subgroup[a]

- In the overall population, median OS was **not reached** (95% CI, NE) and the 24-month OS rate was **79%** (95% CI, 64.1-88.7)

Mutation status[b]



ECOG PS



OS in other key subgroups

	24-mo rate, % (95% CI)
Age, years	
< 65 (n = 22)	85 (61-95)
≥ 65 (n = 23)	74 (51-87)
Initial diagnosis stage[c]	
II-III (n = 28)	77 (56.5-89)
IV (n = 17)	82 (55-94)
Primary tumor location[d]	
Left-sided (n = 15)	67 (37.5-85)
Right-sided (n = 26)	84 (63-94)

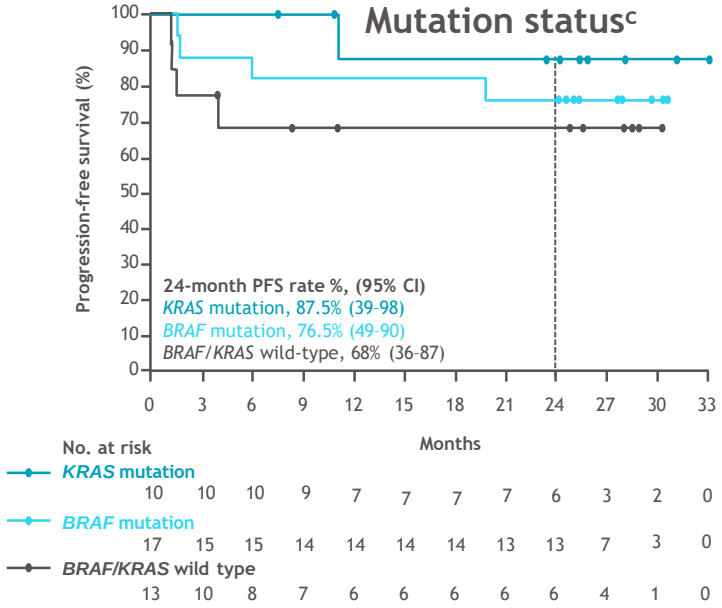
- OS benefit was observed with NIVO3 + IPI1 across all evaluated subgroups and consistent with that of the overall population
- Median OS was not reached in any evaluated subgroup

[a]Median follow-up, 29.0 months. [b]Excluded 5 pts with unknown mutation status. [c]All patients had stage IV disease at study entry. [d]Excluded 4 patients with uncategorized primary tumor location. mo, months; NE, not estimable.

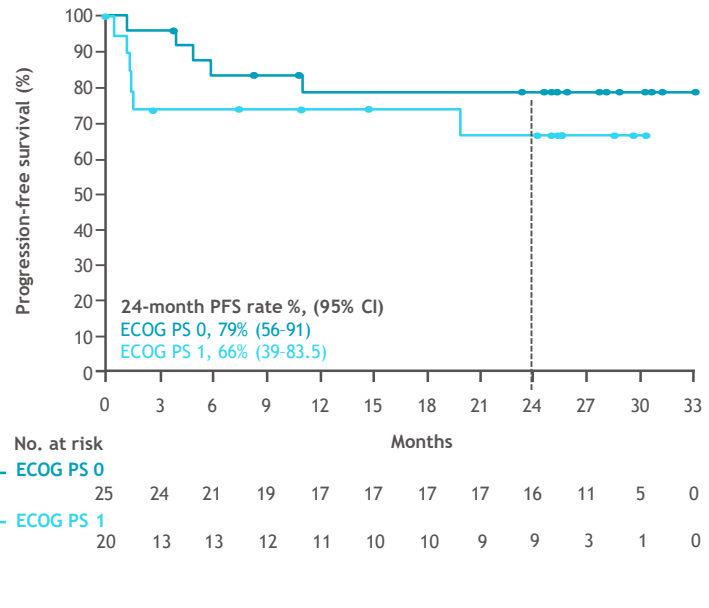
Progression-free survival by subgroup[a,b]

- In the overall population, median PFS was **not reached** (95% CI, NE), and the 24-month PFS rate was **74%** (95% CI, 57.2–84.5)

Mutation status[c]



ECOG PS



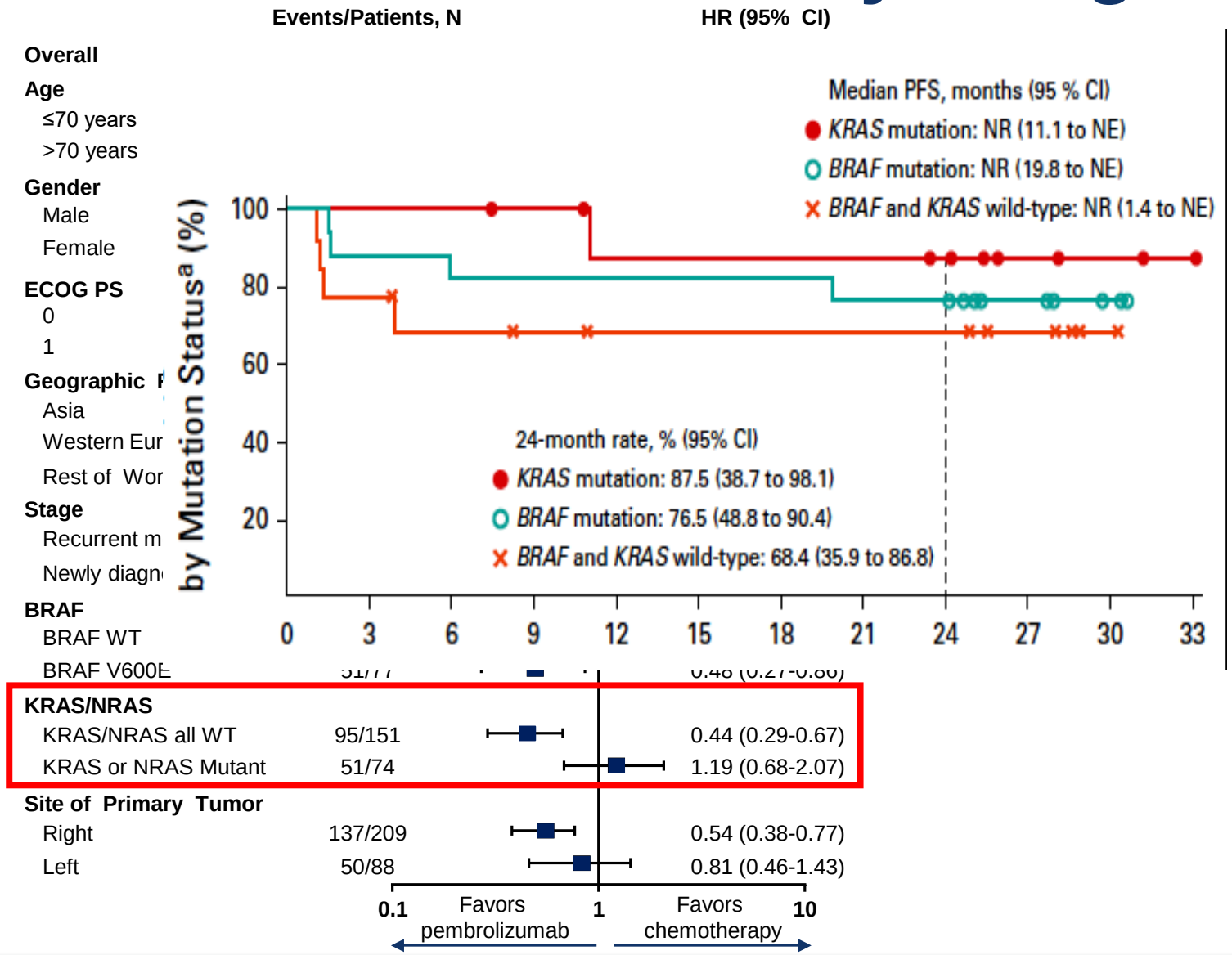
PFS in other key subgroups

	24-mo rate, % (95% CI)
Age, years	
< 65 (n = 22)	77 (49-91)
≥ 65 (n = 23)	70 (47-84)
Initial diagnosis stage[d]	
II-III (n = 28)	75 (53-88)
IV (n = 17)	71 (43-87)
Primary tumor location[e]	
Left-sided (n = 15)	57 (28-78)
Right-sided (n = 26)	84 (62-94)

- PFS benefit was observed with NIVO3 + IPI1 across all evaluated subgroups and consistent with that of the overall population
- Median PFS was not reached in any evaluated subgroup

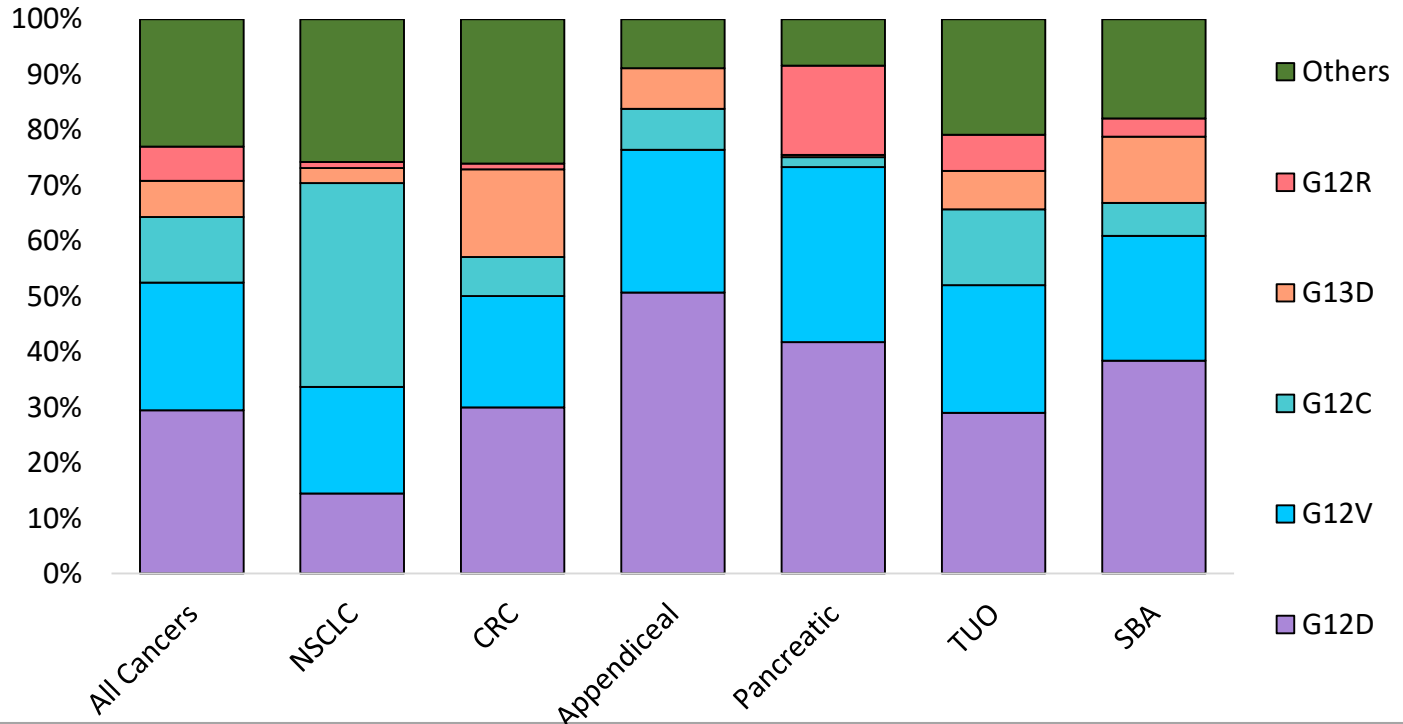
[a]Per investigator assessment. [b]Median follow-up 29.0 months. [c]Excluded 5 pts with unknown mutation status. [d]All patients had stage IV disease at study entry. [e]Excluded 4 patients with uncategorized primary tumor location.

Progression-Free Survival in Key Subgroups



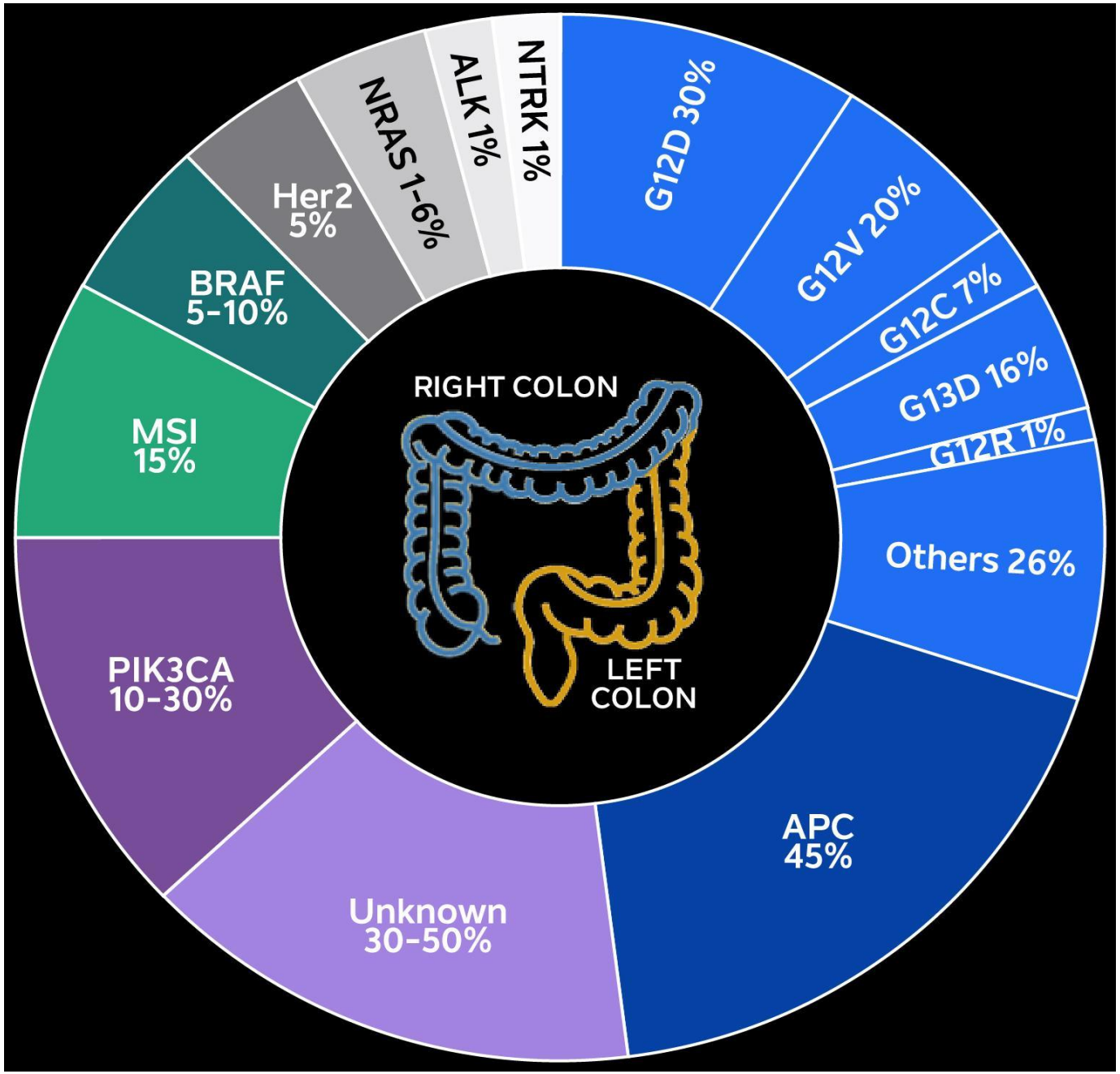
NA, North America; Data cut-off: 19Feb2020.

Most Common *KRAS V*ariants

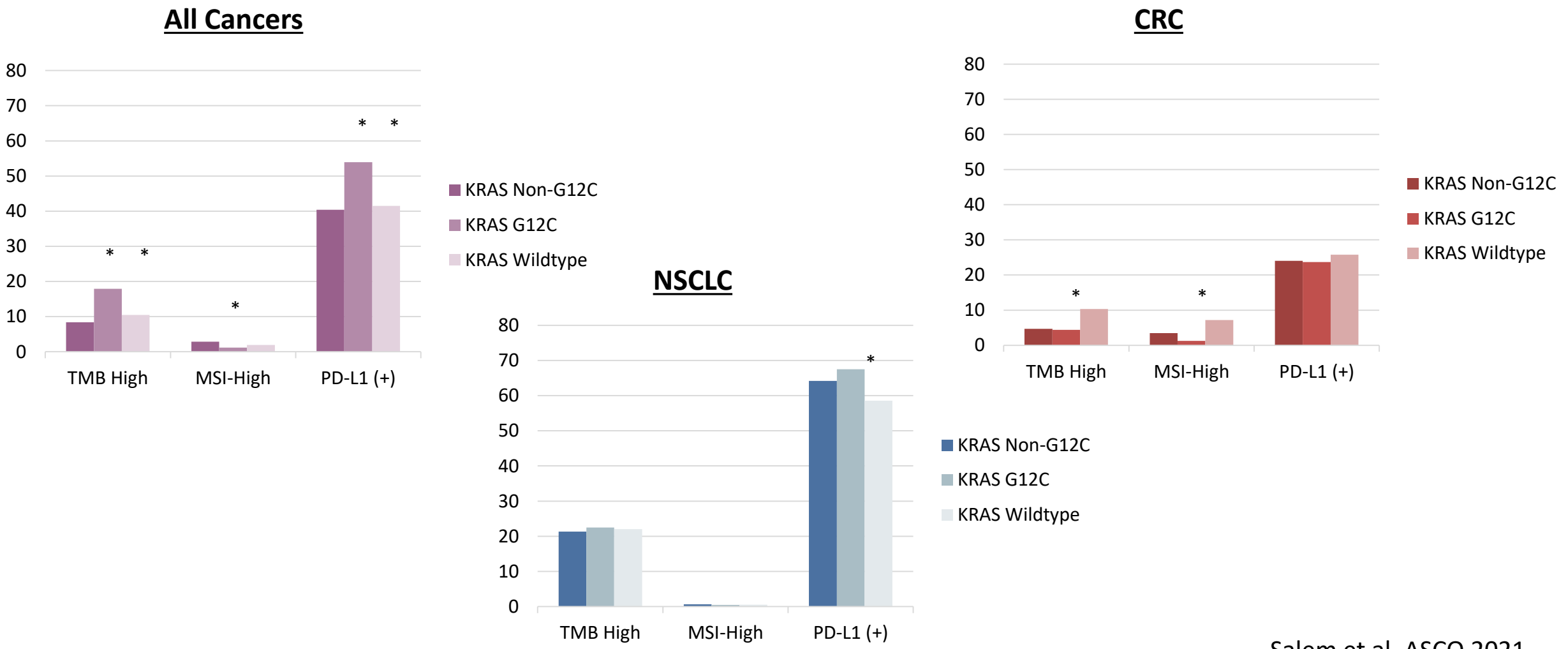


KRAS Variants	G12D	G12V	G12C	G13D	G12R	Others
All Cancers	4056 (29.5%)	3166 (23.0%)	1632 (11.9%)	895 (6.5%)	850 (6.2%)	3159 (22.9%)
NSCLC	343 (14.5%)	455 (19.2%)	871 (36.8%)	64 (2.7%)	26 (1.1%)	609 (25.7%)
CRC	889 (29.9%)	595 (20.0%)	208 (7.0%)	469 (15.8%)	31 (1.0%)	771 (26.3%)
Appendiceal	69 (50.7%)	35 (25.7%)	10 (7.4%)	10 (7.4%)	0 (0.0%)	12 (8.8%)
Pancreatic	1543 (41.8%)	1165 (31.6%)	66 (1.8%)	15 (0.4%)	595 (16.1%)	309 (8.3%)
TUO	719 (29.0%)	570 (23.0%)	339 (13.7%)	172 (6.9%)	161 (6.5%)	516 (20.9%)
SBA	58 (38.4%)	34 (22.5%)	9 (6.0%)	18 (11.9%)	5 (3.3%)	27 (17.9%)

Salem et al. ASCO 2021


NTRK 1%
ALK 1%
NRAS 1-6%
Her2 5%
BRAF 5-10%
MSI 15%
PIK3CA 10-30%
Unknown 30-50%
APC 45%
Others 26%
G12R 1%
G13D 16%
G12C 7%
G12V 20%
G12D 30%
RIGHT COLON
LEFT COLON

Evaluation of immune biomarkers by *KRAS*^{G12C}, *KRAS*$^{non\text{-}G12C}$, and *KRAS* wildtype status



Salem et al. ASCO 2021

Tumor Agnostic Approval of Pembrolizumab for TMB ≥10

Table 58: Efficacy Results for Patients with TMB-H Cancer in KEYNOTE-158

	TMB ≥10 mut/Mb n=102*
Objective Response Rate	
ORR (95% CI)	29% (21, 39)
Complete response rate	4%
Partial response rate	25%

Table 59: Response by Tumor Type (TMB ≥10 mut/Mb)

	N	Objective Response Rate n (%)	95% CI
Overall*	102	30 (29%)	(21%, 39%)
Small cell lung cancer	34	10 (29%)	(15%, 47%)
Cervical cancer	16	5 (31%)	(11%, 59%)
Endometrial cancer	15	7 (47%)	(21%, 73%)
Anal cancer	14	1 (7%)	(0.2%, 34%)
Vulvar cancer	12	2 (17%)	(2%, 48%)
Neuroendocrine cancer	5	2 (40%)	(5%, 85%)
Salivary cancer	3	PR, SD, PD	
Thyroid cancer	2	CR, CR	
Mesothelioma cancer	1	PD	

Fabrizio J of Gastro Onc 2018; Chen ASCO 2019

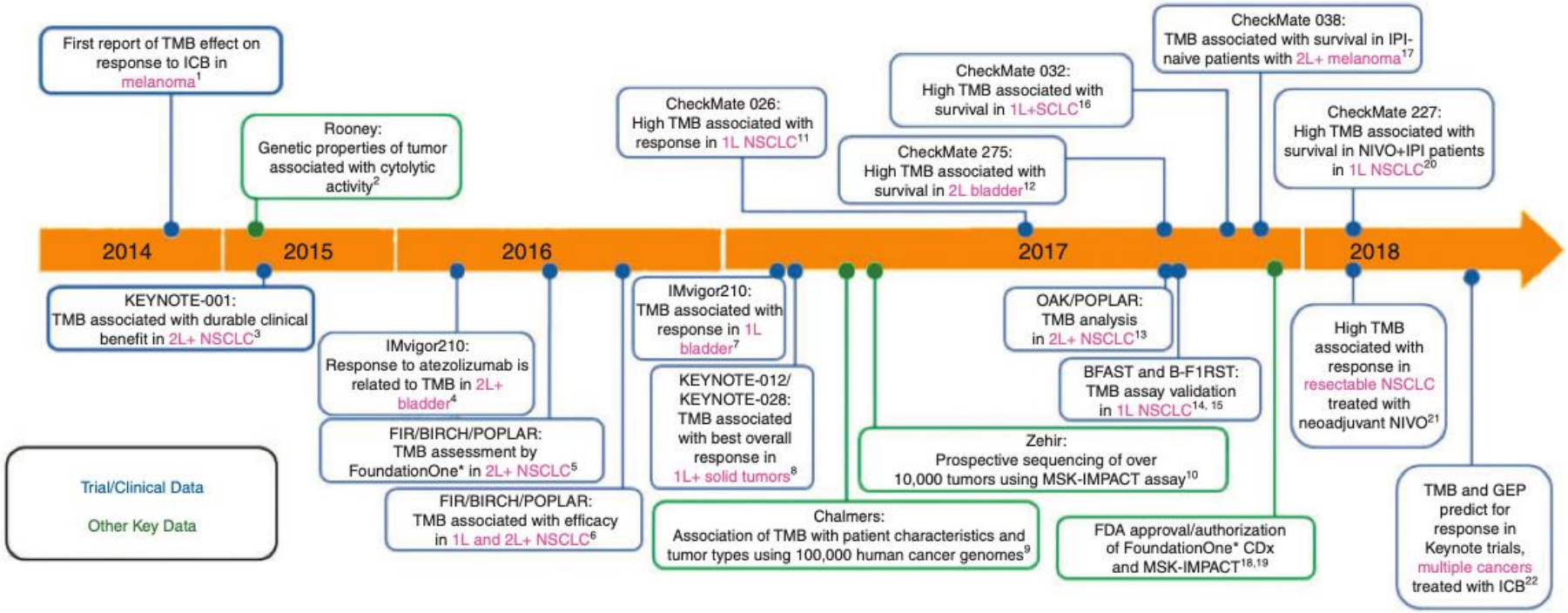
Pembrolizumab
FDA Approved 6/16/2020:

Tumor Mutational Burden-High (TMB-H) Cancer

- 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.[1] (1.16, 2.1)

FDA approved test:
FoundationOneCDx assay (Foundation Medicine, Inc.)

Development of tumor mutation burden as an immunotherapy biomarker: utility for the oncology clinic



Chan, et. al, Ann Oncol 30:44, 2019

Not all "TMB"s are created equal

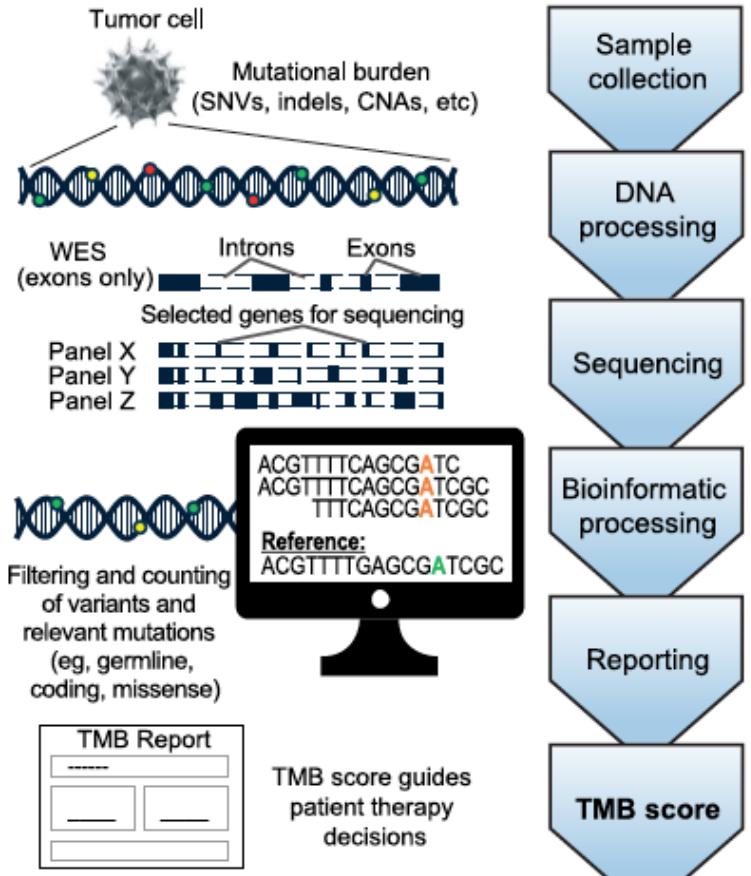
Table 1. Key parameters for some TMB assays

Parameter	WES	FM NGS (F1CDx)	MSKCC NGS (MSK-IMPACT)
No. of genes	~22 000 gene coding regions	324 cancer-related genes	468 cancer-related genes
Types of mutations captured	Coding missense mutations in tumor genome	Coding, missense, and indel mutations per Mb of tumor genome	Coding missense mutations per Mb of tumor genome
Germline mutations	Subtracted using patient-matched normal samples	Estimated via bioinformatics algorithms and subtracted	Subtracted using patient-matched blood samples
Capture region (tumor DNA)	~30 Mb	0.8 Mb	1.22 Mb
TMB definition	No. of somatic, missense mutations in the sequenced tumor genome	No. of somatic, coding mutations (synonymous and non-synonymous), short indels per Mb of tumor genome	No. of somatic, missense mutations per Mb of tumor genome

WES, whole exome sequencing; FM, Foundation Medicine; NGS, next generation sequencing; Mb, megabase.

Chan, et. al, Ann Oncol 30:44, 2019

Factors that impact TMB estimation and reporting



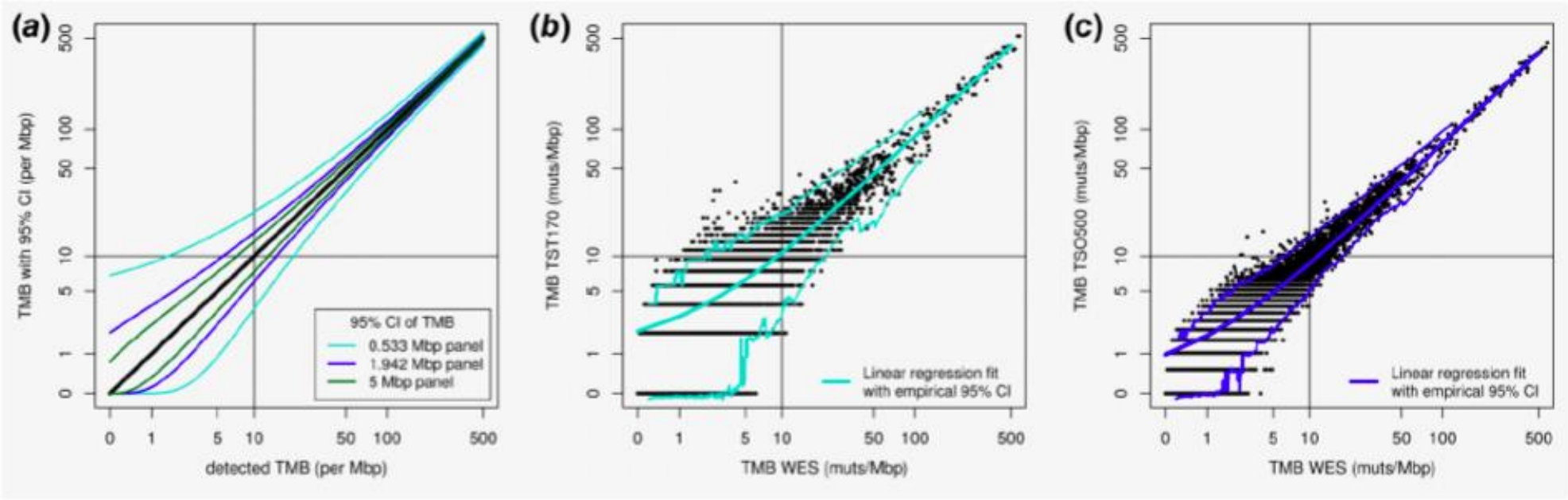
Biological[2,3,33,39,45,46]	• Sample type (eg, tissue, blood, plasma) • Tumor type • Tumor heterogeneity • Clonal evolution
Preanalytical[32,58,59]	• Sample type (eg, FFPE or fresh frozen tissue, blood, plasma) • Input material quality/quantity • Fixation methodology • FFPE-induced deamination artefacts
Sequencing[4,60–69]	• Capture region • Panel size • Enrichment technology • Depth of sequencing • Sequencing platform
Bioinformatics[4,33,48,70–78]	• Mutation types included • Filtering of germline variants • Variant allele frequency • Sample metric QC thresholds • Cutoffs for consideration and filtering • Reference transcript source
Cutpoint variables[2–4,18,21,28,33]	• Sample type • Tumor type • Assay used • Patient population • Therapy investigated

Stenzinger et al. Genes Chromosomes Cancer. 2019

IJC INTERNATIONAL JOURNAL of CANCER
UICC global cancer control

Tumor Markers and Signatures | Free Access

Size matters: Dissecting key parameters for panel-based tumor mutational burden analysis



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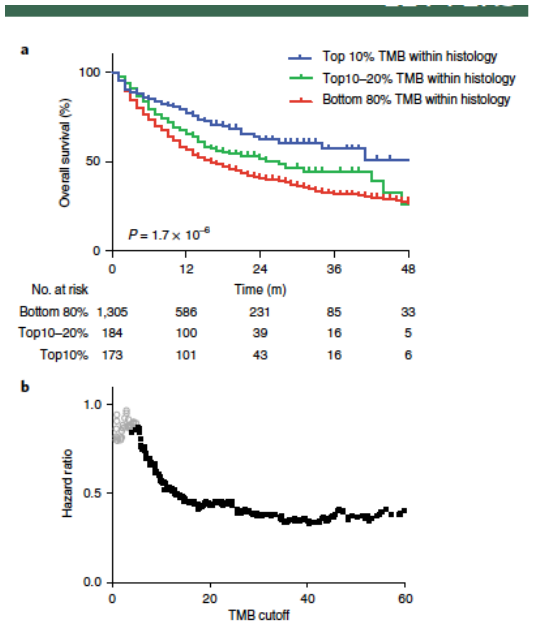
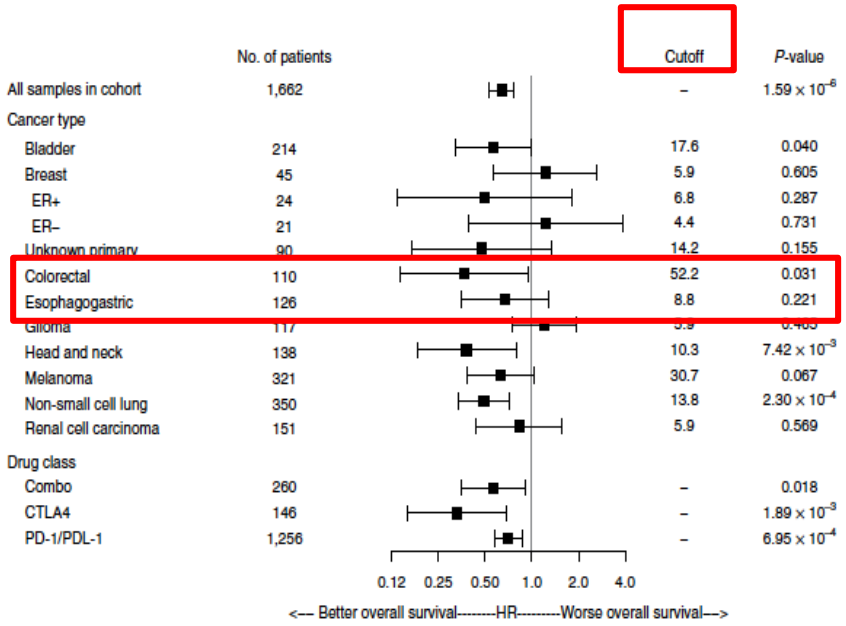
TMB: MSKCC outcome to IO

- N = 1662 ICI treated vs 5371 non–ICI
- MSK-IMPACT assay
- Explored cut off
- Data for top 20%ile



LETTERS
https://doi.org/10.1038/s41588-018-0312-8
nature genetics

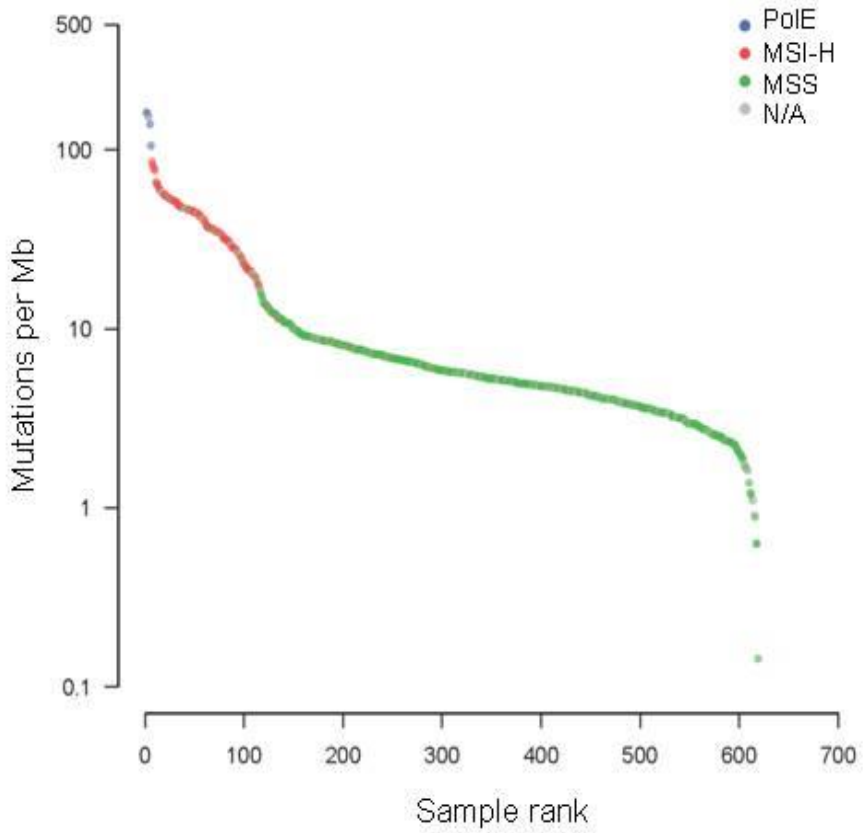
Tumor mutational load predicts survival after immunotherapy across multiple cancer types

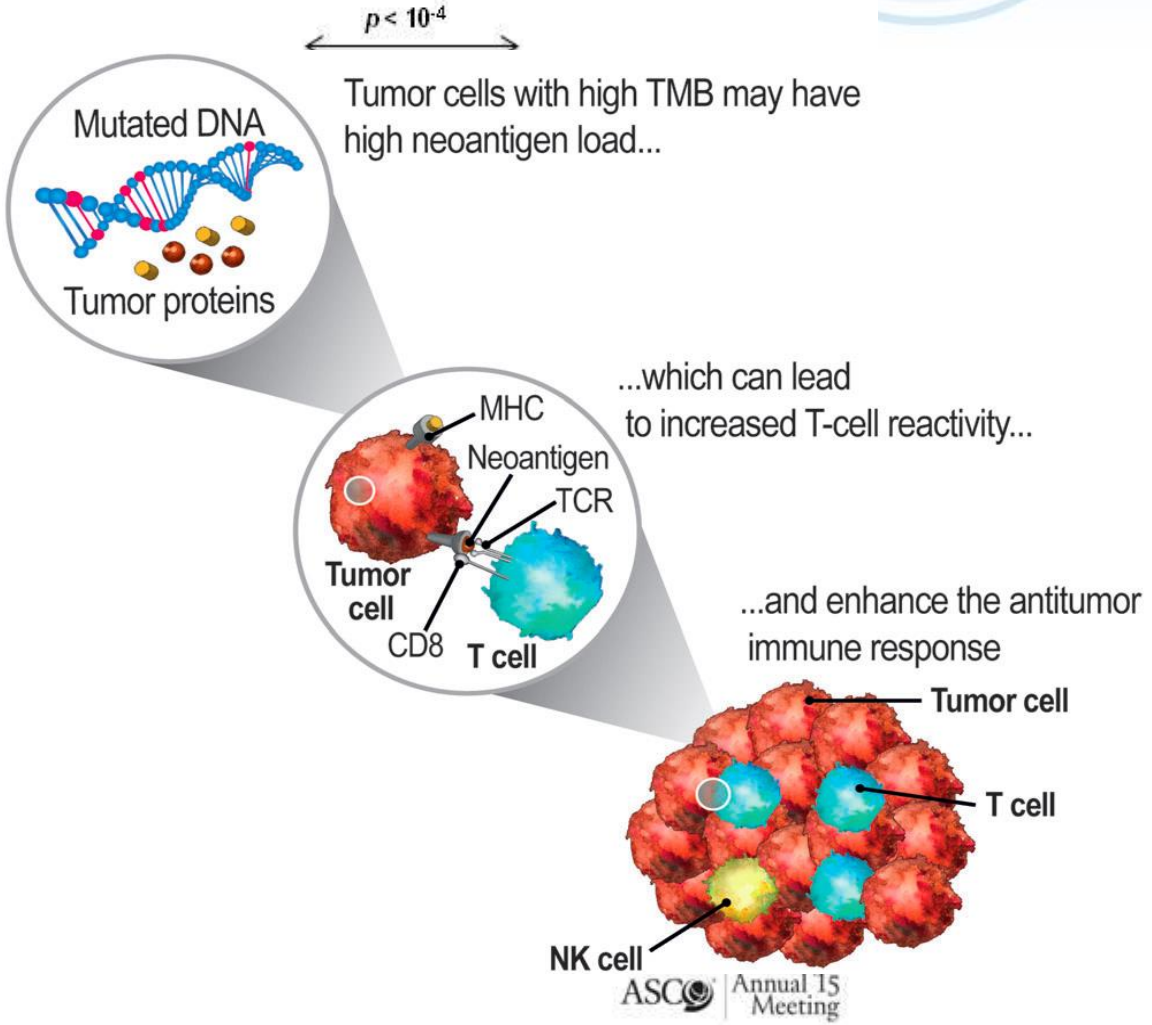


Samstein, et al, Nat Gen 51:202, 2019

Are all TMB created equal?

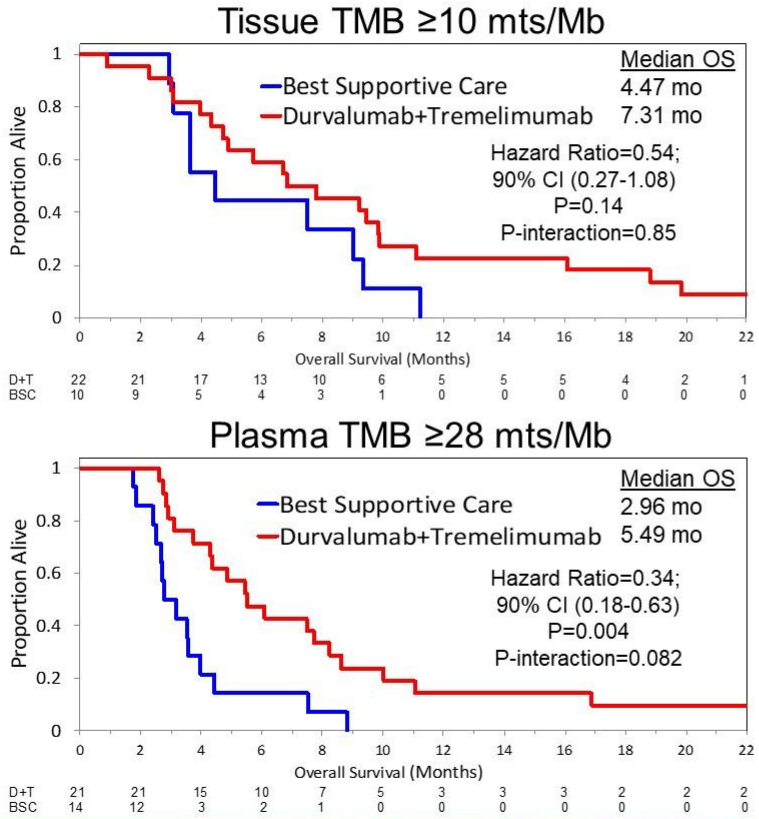
Hypermutated tumors harbor more neoantigens

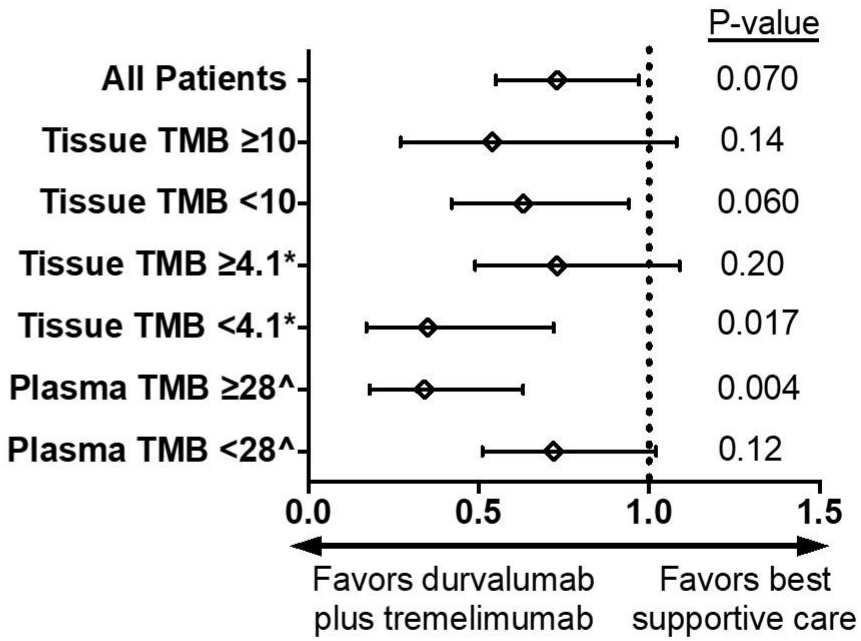




Presented By Marios Giannakis at 2015 ASCO Annual Meeting

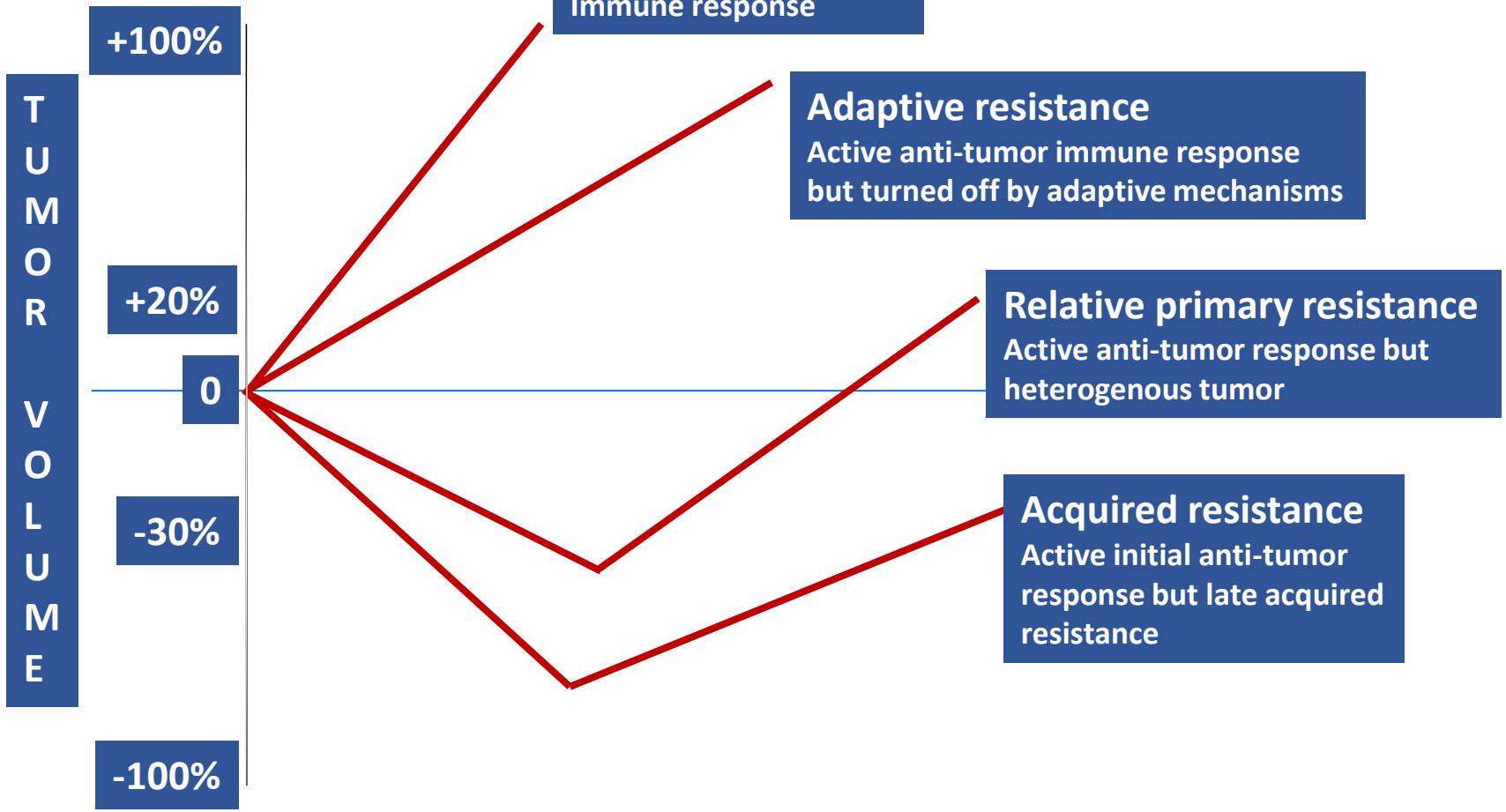
Results – High plasma TMB appeared predictive for efficacy of durvalumab + tremelimumab





*= Cut-point identified with minimum p–value approach
^= Cut-point previously identified in Chen et al, JAMA Oncology (2020)

Next Generation of Research –Resistance to Immunotherapy



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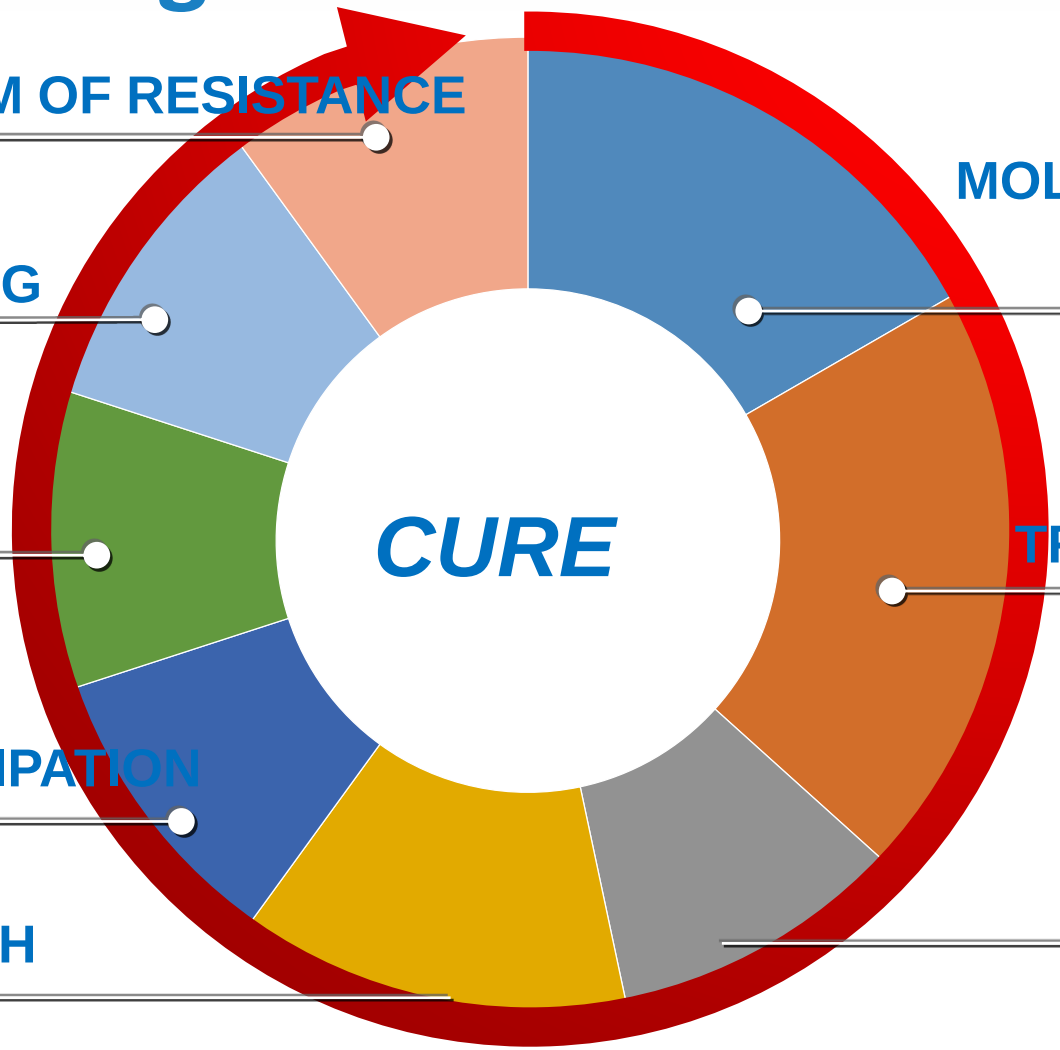
The way forward

Advances in Cancer Immunotherapy™

The Way Forward…

Collaborating Across the Continuum of Care



UNDERSTAND MECHANISM OF RESISTANCE

MOLECULAR DISCOVERY

new target
new biomarker
new concept

DATA SHARING

AFFORDABLE ACCESS

TRANSLATIONAL RESEARCH

CLINICAL TRIAL PARTICIPATION

DRUG DEVELOPMENT

CLINICAL RESEARCH

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THANK YOU

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