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Biomarker Updates

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Disclosures

- Consulting Fees: Astra-Zeneca, MSD, Eisai, BMS
- Fees for Non CE Services: Bayer, Astra-Zeneca, Eisai, Roche, MSD
- Contracted Research: MSD, Bayer, Eisai, Ipsen, SIRTEX

Outline (25 min)

- Introduction of different biomarkers for IO treatment
- Updates of biomarker data for IO
  - Colorectal cancers
  - Gastroesophageal adenocarcinoma
  - Hepatocellular carcinoma
- Conclusions

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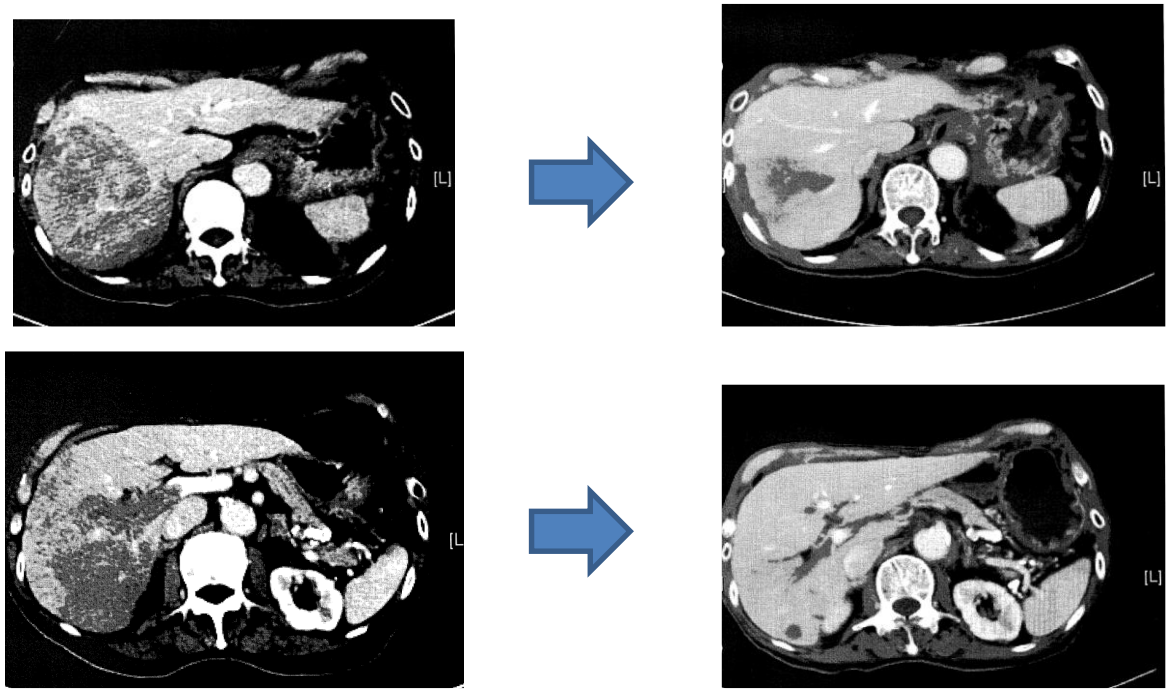
Background

Why do we need biomarker?

Anti-PD1 Antibody

- Potentially deep and durable response



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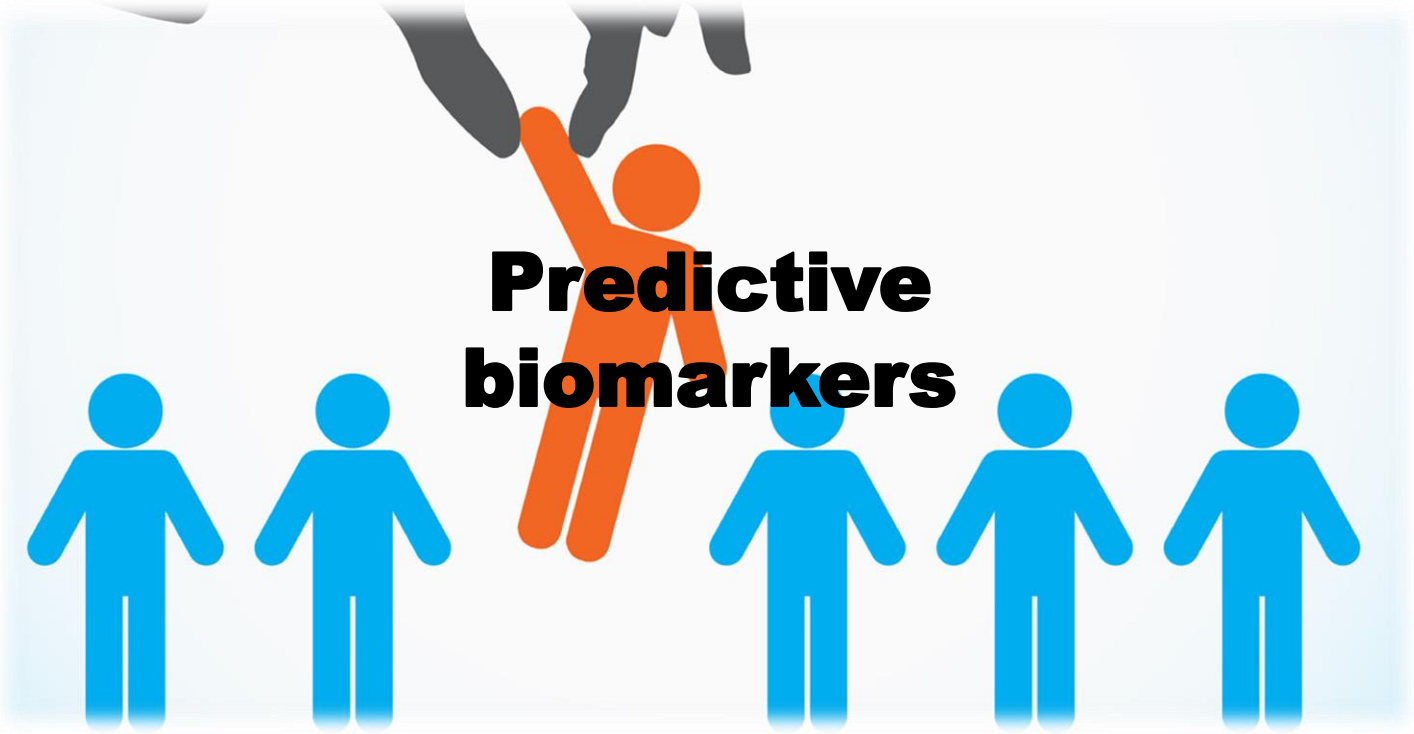
CR: 1%


Predictive
biomarkers

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Biomarkers

PD-L1

PD-L1

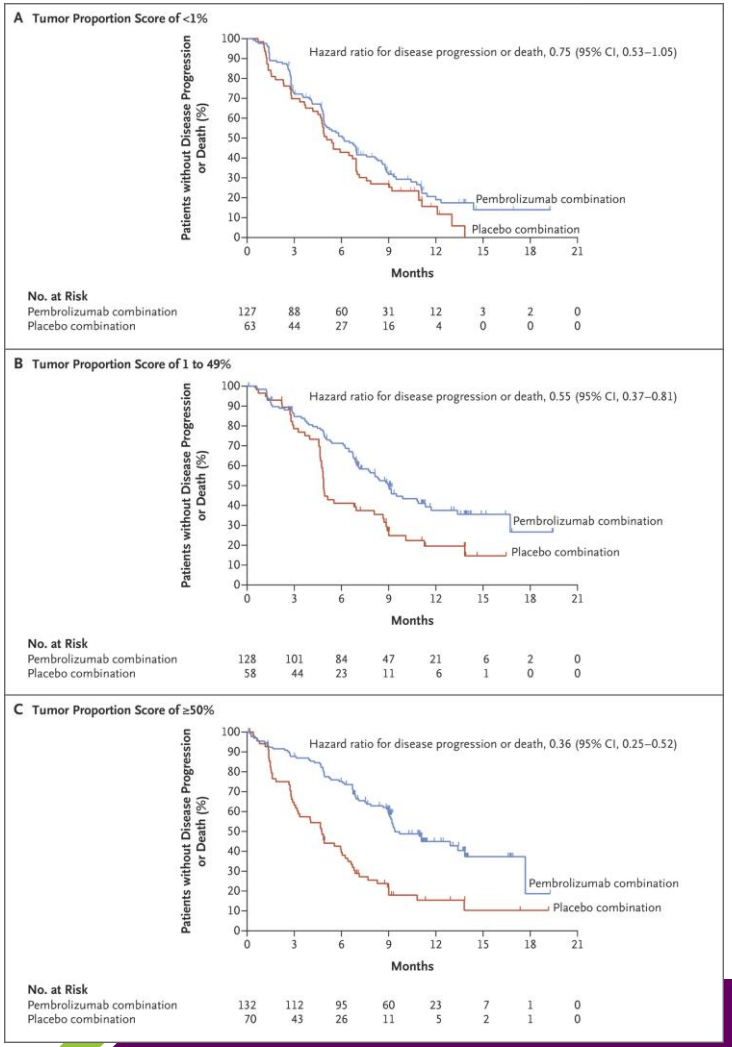
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer

L. Gandhi, D. Rodríguez-Abreu, S. Gadgeel, E. Esteban, E. Felip, F. De Angelis, M. Domine, P. Clingan, M.J. Hochmair, S.F. Powell, S.Y.-S. Cheng, H.G. Bischoff, N. Peled, F. Grossi, R.R. Jennens, M. Reck, R. Hui, E.B. Garon, M. Boyer, B. Rubio-Viqueira, S. Novello, T. Kurata, J.E. Gray, J. Vida, Z. Wei, J. Yang, H. Raftopoulos, M.C. Pietanza, and M.C. Garassino, for the KEYNOTE-189 Investigators*

KEYNOTE-189 phase 3 trial



Gandhi L et al. N Engl J Med. 2018; 378(22):2078-2092

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Pembrolizumab (anti-PD-1)

PD-L1 clone 22C3

Dako Autostainer Link-48 EnVision FLEX

Nivolumab (anti-PD-1)

PD-L1 clone 28-8

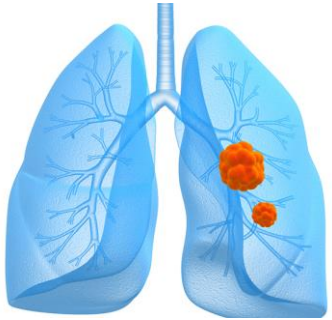
Atezolizumab (anti-PD-L1)

PD-L1 clone SP142

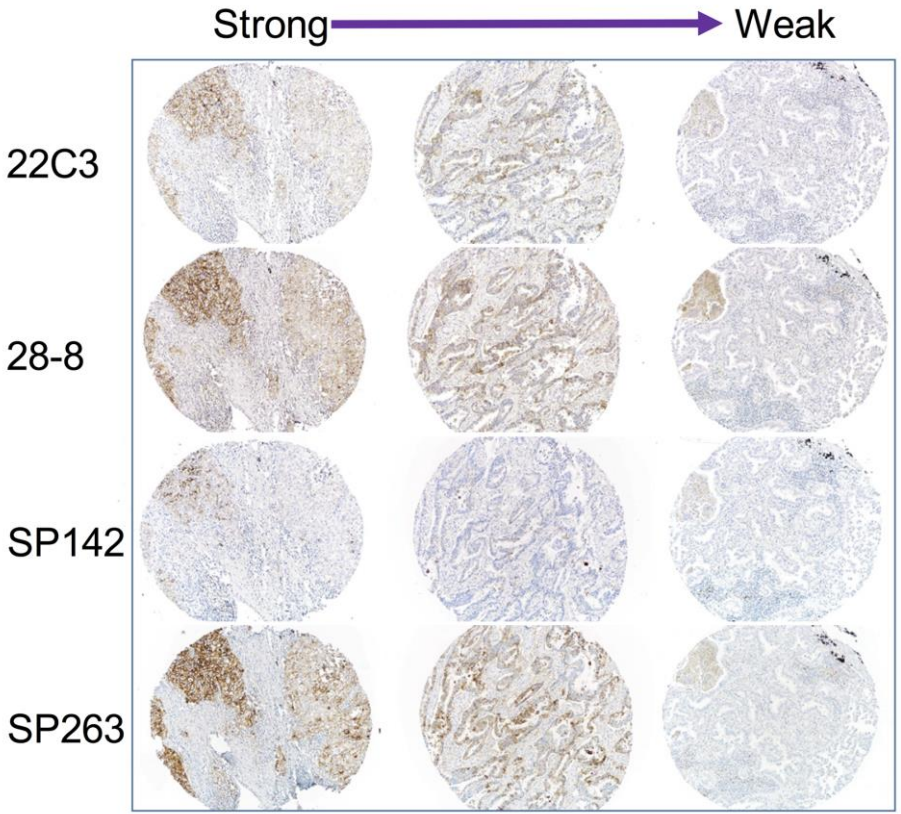
Ventana BenchMark Ultra OptiView

Durvalumab (anti-PD-L1)

PD-L1 clone SP263

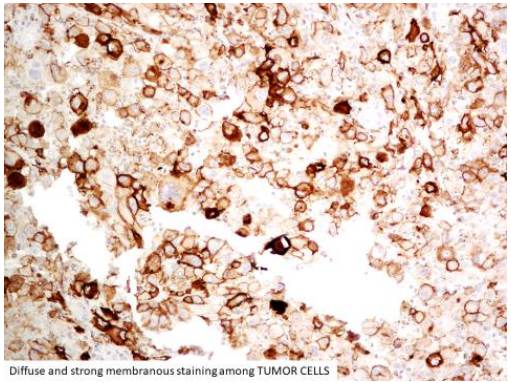


Non-small cell lung carcinoma (n=713)

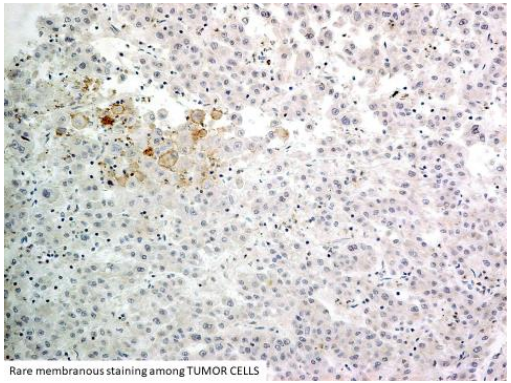


Chan AW et al. Mod Pathol. 2018

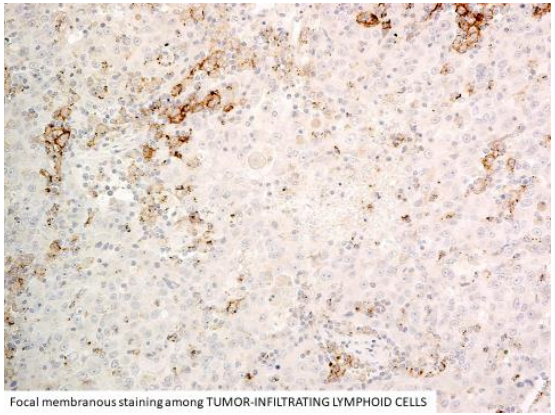
Different staining patterns of PDL1



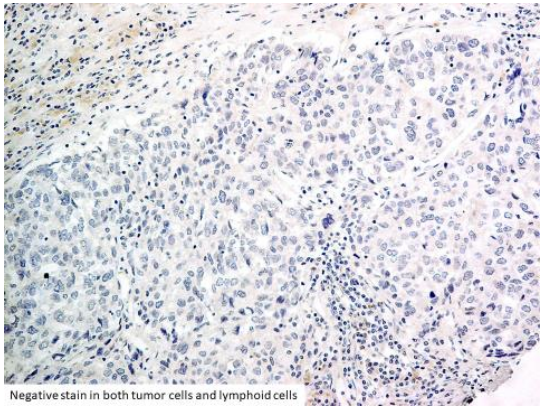
Diffuse and strong membranous staining among TUMOR CELLS



Rare membranous staining among TUMOR CELLS



Focal membranous staining among TUMOR-INFILTRATING LYMPHOID CELLS



Negative stain in both tumor cells and lymphoid cells

Computation of PDL1 in tissues

Tumor Proportion Score (TPS)

The percentage of PD-L1 expressing tumor cells (partial or complete membrane staining) relative to total number of tumor cells. This scoring method is used for NSCLC.

$$\text{TPS} = \frac{\#\ PD\text{–}L1\ positive\ tumor\ cells}{Total\ \#viable\ \ tumor\ cells} \times 100$$

Combined Positive Score (CPS)

Measures the number of PD-L1 staining cells, including tumor cells, lymphocytes, and macrophages, divided by the total number of viable tumor cells multiplied by 100

$$\text{CPS} = \frac{\#\ PD\text{–}L1\ staining\ cells}{Total\ \#viable\ \ tumor\ cells} \times 100$$

CPS score is used more frequently in GI cancers (e.g. GEJ caners)

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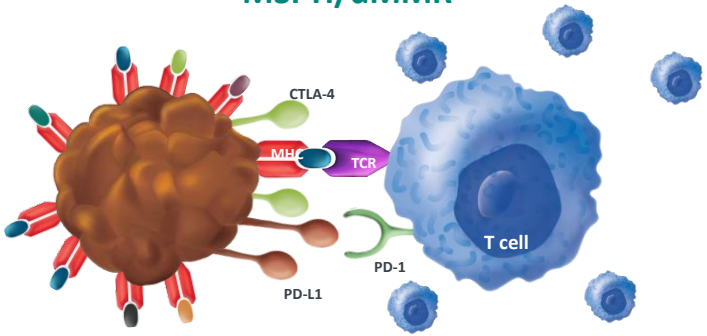
Biomarkers

MSI-H/MMR/TMB

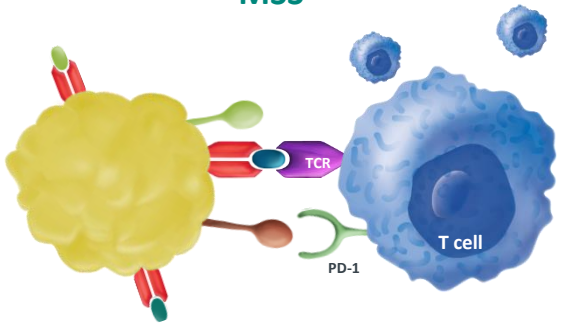
MSI-H Phenotype Confers Responsiveness to PD-1 Inhibition Independent of Tumor Type[1]

MSI-H/dMMR Relationship to PD-L1/PD-1 [3]

MSI-H/dMMR[2]



MSS[3]



Adapted by permission from Macmillan Publishers Ltd: Pardoll DM. *Nat Rev Cancer.* 2012;12(4):252–264. Copyright 2012.

- MSI-H/dMMR tumors are characterized by hypermutation, resulting in:
  - 10–50 times more tumor-specific neoantigens than MSS tumors[3]
  - High level of TILs and an active T helper 1 cell/cytotoxic T lymphocyte (TH1/CTL) environment[3]
  - High expression of checkpoint molecules, such as PD-1, PD-L1, CTLA-4, LAG-3, and IDO[3]

MSI-H/dMMR immunogenic phenotype—due to the tumor's genotype—renders tumors susceptible when treated with ICIs [1]

1. Le DT et al. *Science.* 2017; 357(6349):409–413. 2. Pardoll DM. *Nat Rev Cancer.* 2012;12(4):252–264. 3. Llosa NJ et al. *Cancer Discov.* 2015;5(1):43–51.

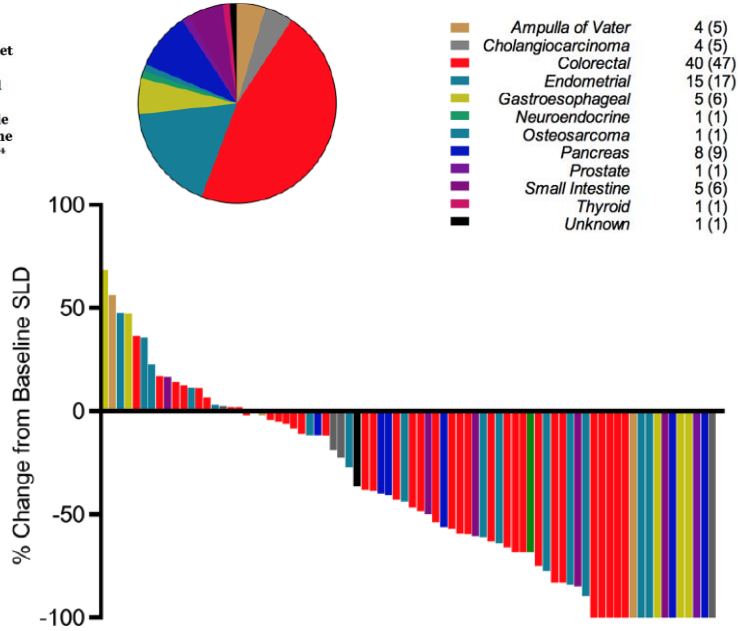
Science REPORTS

Cite as: D. T. Le *et al.*, *Science* 10.1126/science.aan6733 (2017).

Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade

Dung T. Le,[1,2,3] Jennifer N. Durham,[1,2,3*] Kellie N. Smith,[1,3*] Hao Wang,[3*] Bjarne R. Bartlett,[2,4*] Laveet K. Aulakh,[2,4] Steve Lu,[2,4] Holly Kemberling,[3] Cara Wilt,[3] Brandon S. Luber,[3] Fay Wong,[2,4] Nilofer S. Azad,[1,3] Agnieszka A. Rucki,[1,3] Dan Laheru,[3] Ross Donehower,[3] Atif Zaheer,[5] George A. Fisher,[6] Todd S. Crocenzi,[7] James J. Lee,[8] Tim F. Greten,[9] Austin G. Duffy,[9] Kristen K. Ciombor,[10] Aleksandra D. Eyring,[11] Bao H. Lam,[11] Andrew Joe,[11] S. Peter Kang,[11] Matthias Holdhoff,[3] Ludmila Danilova,[1,3] Leslie Cope,[1,3] Christian Meyer,[3] Shibin Zhou,[1,3,4] Richard M. Goldberg,[12] Deborah K. Armstrong,[3] Katherine M. Bever,[3] Amanda N. Fader,[13] Janis Taube,[1,3] Franck Housseau,[1,3] David Spetzler,[14] Nianqing Xiao,[14] Drew M. Pardoll,[1,3] Nickolas Papadopoulos,[3,4] Kenneth W. Kinzler,[3,4] James R. Eshleman,[15] Bert Vogelstein,[1,3,4] Robert A. Anders,[1,3,15] Luis A. Diaz Jr.[1,2,3†‡]

Stage IV dMMR tumor (n=86)



53% Objective response

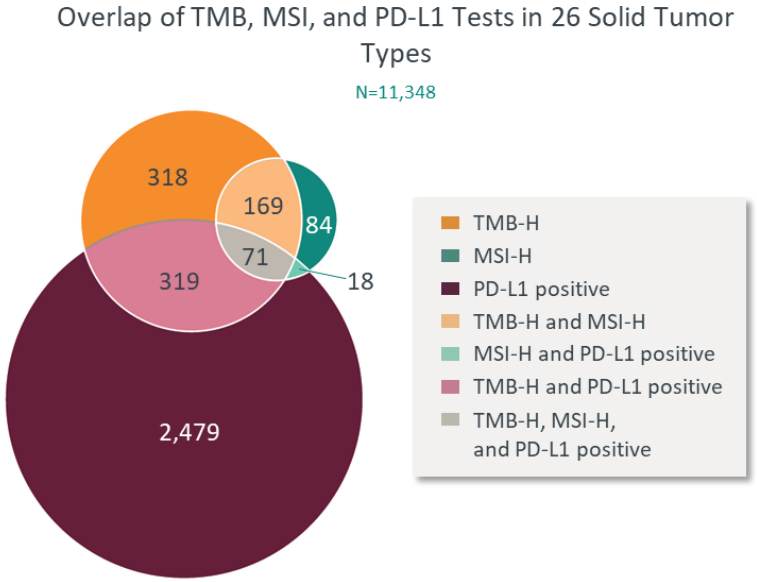
77% Disease control

Methods to detect MSI-H/dMMR

	Tests	
Method of measurement	Nucleic-acid based (NGS; PCR)	IHC
Description	Panel of microsatellite markers to detect size shifts in different loci	Test to determine the presence of MMR proteins
Patient sample type	Tumor tissue	Tumor tissue
Reagents to targets	Probes to the following: ▪ BAT25, BAT26, NR21, NR24, Mono27 or ▪ BAT25, BAT26, DI5S346, DI2S123, DI17S250	Antibodies to MLH1/MSH2/MSH6/PMS2
Results	≥2 of 5 loci differ in size from corresponding normal loci	Any 1 (or more) of 4 proteins absent
Biological feature	MSI-H	dMMR

Tumor mutation burden

- TMB correlates with overall neoantigen load[1]
  - TMB is technically easier and less expensive than measuring neoantigen load
- TMB is defined as the total number of mutations (changes) found in the DNA of cancer cells[2]
  - Tumors that have a high number of mutations appear to be more likely to respond to certain types of immunotherapy
  - TMB is being used as a type of biomarker
- While the tumor may be suppressing the immune response locally, reactivation of antitumor immune activity using ICI may improve cancer cell clearance and clinical responses[3]



MSI-H Tumors Tend to be TMB-H, But Not All TMB-H Tumors Are MSI-H

1. Fancello L et al. *J Immunother Cancer*. 2019;7:1-13. 2. National Cancer Institute. Dictionary of Terms—tumor mutation burden. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/tumor-mutational-burden. Accessed August 19, 2020. 3. Arora S et al. *Adv Ther*. 2019;36(10):2638–2678. 4. Büttner R et al. ESMO Open. 2019;4(1):e000442.

1. Vanderwalde A et al. *Cancer Med*. 2018;7(3):746–756.

Assays of TMB

Table 2 Examples of NGS gene panels in development or currently available to assess TMB

Status	Test name	Number of genes	Coverage (Mb)*	Gene variants	Sample type
FDA-approved or authorised diagnostic assays†	MSK-IMPACT[15 56 68]	468	1.5	SNVs, indels, rearrangements/ fusions, CNAs, parallel analysis of genomic signatures (eg, TMB and dMMR/MSI)	FFPE
	Foundation Medicine FoundationOne CDx[14 49]	324	0.8	SNVs, indels, CNAs, select rearrangements, parallel analysis of genomic signatures (eg, TMB and dMMR/MSI)	FFPE
Commercial assays for research use only	Caris Molecular Intelligence[132]	592	1.4	Somatic missense mutations	FFPE
	Illumina TruSight 500 gene panel[133]	500	2.0	SNVs and indels	FFPE
	Thermo Fisher Scientific Oncomine Tumor Mutation Load Assay[77]	409	1.7	SNVs	FFPE
	NEO New Oncology NEOplus v2 RUO[134]	>340	1.1	SNVs, indels, fusions, CNAs, parallel analysis of TMB, MSI, and driver mutations	FFPE
	Foundation Medicine FoundationOne[50]	315	1.1	SNVs, indels, CNAs, select gene rearrangements, genomic signatures for MSI and TMB	FFPE
	Foundation Medicine bTMB assay[68 122]	394	1.1	SNVs	Blood
	TruSight Tumor 170[135]	170	0.5	Fusions, splice variants, SNVs, indels, amplifications	FFPE
	QIAGEN GeneRead DNAseq Comprehensive Cancer Panel[97]	160	0.7	SNVs, CNAs, indels, and fusions	FFPE
	NEO New Oncology NEOplus[105 136]	94		SNVs, indels, CNAs, rearrangements, and fusions	FFPE

Buttner R et al. ESMO open. 2019; 4:e000442

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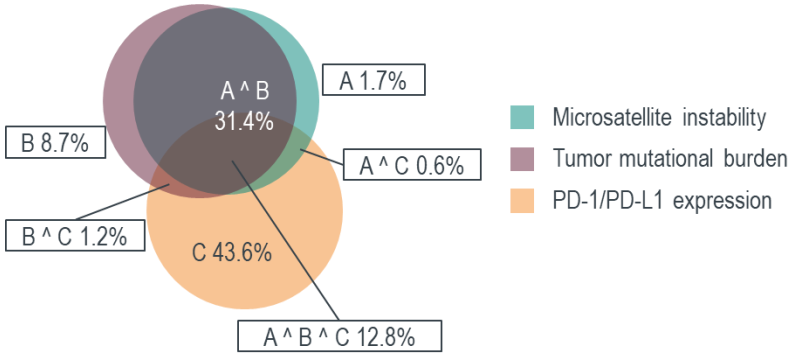
Biomarker in different cancer types

Colorectal cancer

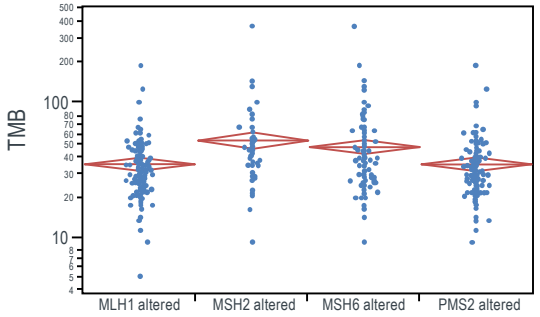
Overlap of MSI and TMB in Colorectal Cancer

- In a study of 1,057 MSI-H tumors, MSI-H CRCs carried the highest TMB compared with MSI-H endometrial cancers and other MSI-H solid tumors[2]
  - MSH2 and/or MSH6 alterations were associated with a significantly higher TMB compared with MLH1 and/or PMS2 alterations across CRC and other cancer types[2]

Presence of TMB-H, MSI-H, and PD-L1 Expression in CRC[1,a]



TMB in MLH1, PMS2, MSH2, and MSH6-altered Cohorts in CRC[2]



		CRC		*P*<0.0001	
Level	**Number**	**Mean**	**Std Error**	**Lower 95%**	**Upper 95%**
MLH1 altered	182	34.736	2.082	30.646	38.827
MSH2 altered	53	52.528	3.859	44.949	60.108
MSH6 altered	128	46.406	2.483	41.529	51.284
PMS2 altered	187	34.583	2.054	30.548	38.618

[a]Percentages are based on a total of 4,186 patients with MSI-H and/or high TMB and/or PD-L1-positive status.

1. Luchini C et al. *Ann Oncol.* 2019;30:1232–1243. 2. Salem ME et al. Presented at ASCO 2018; Abstract 3572.

Utility of MSI-H and dMMR in Clinical Practice

Prognostic Value

Predictive Value
Improved Sensitivity to Immunotherapy

- MSI status is a prognostic marker in early stage CRC[1]
  - An analysis of data from 17 different trials in the ACCENT (Adjuvant Colon Cancer End Points) database investigated how MSI status affected outcome in patients with stage II or III CRC undergoing surgery alone or surgery followed by 5-FU based adjuvant treatment[3]
  - Results showed that outcomes with surgery alone were better for the patients with MSI-H tumors than for those with MSS tumors[3]

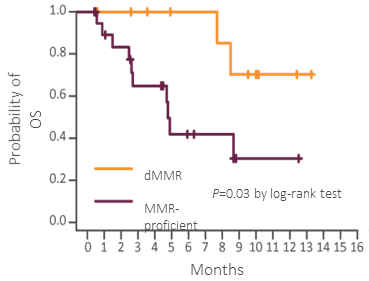
1. Benatti P et al. *Clinical Cancer Res*. 2005;11(23):8332–8340. 2. Gelsomino F et al. *Cancer Treat Rev*. 2016;51:19–26. 3. Sargent DJ et al. *J Clin Oncol.* 2014;32(15)(suppl).

Utility of MSI-H and dMMR in Clinical Practice

Prognostic Value

- MSI-H/dMMR is biologically interrelated to an increase in neoantigens. MSI-H/dMMR tumors are characterized by upregulation of inhibitory checkpoint inhibitors and correlates positively to immunotherapy response[1,2]
- Brief efficacy results from proof of concept trial
  - Le et al published the results of KEYNOTE-016, a Phase 2 study in 32 patients with stage IV colorectal cancer (dMMR, n=11; MMR-proficient, n=21) receiving pembrolizumab therapy. The objective response rates were 40% for the dMMR cohort and 0% for the MMR-proficient cohort. Median PFS and OS were not reached in the dMMR cohort but were 2.2 and 5.0 months in the MMR-proficient cohort[3]
- Other clinical trials have evaluated PD-1 inhibitors in patients with MSI-H/dMMR advanced colorectal cancer[4-6]

Predictive Value
Improved Sensitivity to Immunotherapy



OS in patients with stage IV CRC who received pembrolizumab therapy[1]

Trial Identifier	Assay Details	Treatment Arm	Phase
KEYNOTE-164[4]	MSI and/or MMR testing by PCR or IHC; local testing	Pembrolizumab	2
KEYNOTE-177[5]	MSI and/or MMR testing by PCR or IHC; local testing	Pembrolizumab	3
Checkmate-142[6]	Testing for MSI-H by an accredited lab	Nivolumab or nivolumab/ipilimumab	1/2

Benatti P et al. *Clinical Cancer Res*. 2005;11(23):8332–8340. 2. Gelsomino F et al. *Cancer Treat Rev*. 2016;51:19–26. 3. Le DT et al. *N Engl J Med*. 2015;372(26):2509–2520. 4. ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/NCT02460198. 5. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02563002. 6. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02060188

Overview of MMR/MSI testing in guidelines

NCCN guidelines

Guideline	Testing	Therapy
Colon Cancer[1]	Universal MMR[a] or MSI[a] testing is recommended in all newly diagnosed patients with colon cancer.	Pembrolizumab, nivolumab, or nivolumab plus ipilimumab are recommended as treatment options for patients with metastatic MSI-H/dMMR colorectal cancer
Rectal Cancer[2]	Universal MMR[a] or MSI[a] testing is recommended in all newly diagnosed patients with rectal cancer.	Pembrolizumab, nivolumab, or nivolumab plus ipilimumab are recommended as treatment options for patients with metastatic MSI-H/dMMR colorectal cancer.

ESMO Recommendation: MSI Testing

- MSI testing in the metastatic disease setting can assist clinicians in genetic counseling[1]
- MSI testing has strong predictive value for the use of ICIs in the treatment of patients with mCRC[1]
- MSI testing is recommended by ESMO for all CRC-related cancers[2]

1. Van Cutsem E et al. *Ann Oncol*. 2016;27(8):1386–1422. 2. Microsatellite Instability – Defective DNA Mismatch Repair: ESMO Biomarker Factsheet. https://oncologypro.esmo.org/Education-Library/Factsheets-on-Biomarkers/Microsatellite-Instability-Defective-DNA-Mismatch-Repair. Accessed June 19, 2019

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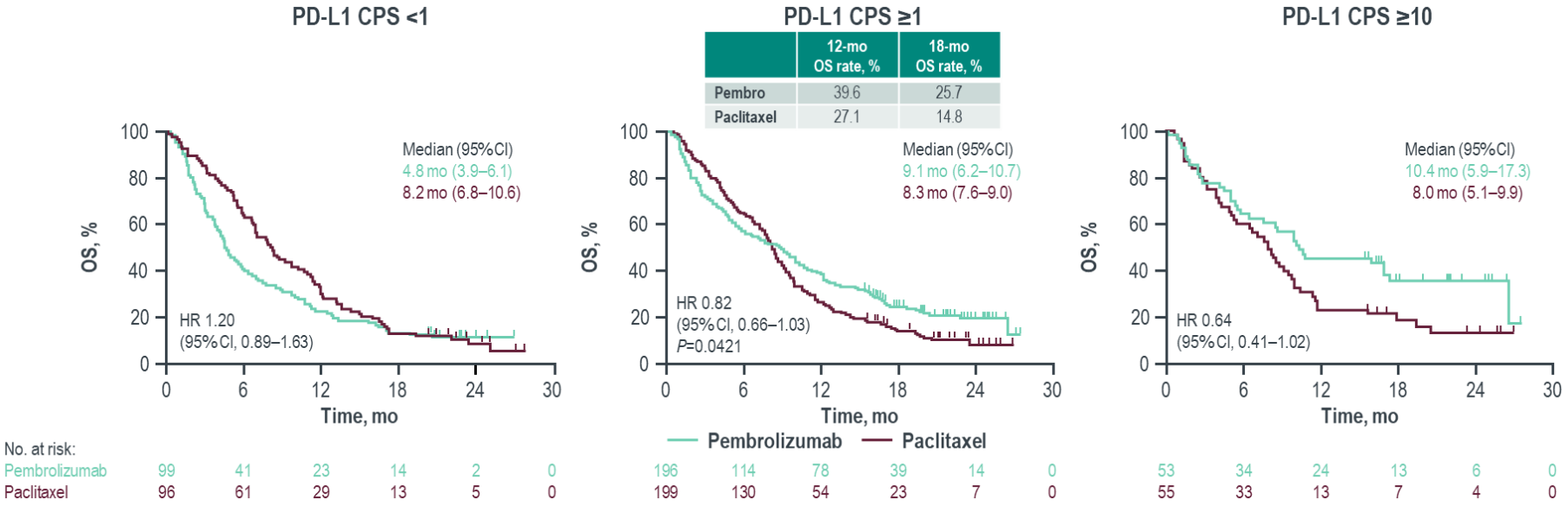
Biomarker in different cancer types

Gastroesophageal adenocarcinomas

KN-061: High CPS ≥10 is required for benefits of monotherapy

(Data cutoff date: October 26, 2017)[1]



	12-mo OS rate, %	18-mo OS rate, %
Pembro	39.6	25.7
Paclitaxel	27.1	14.8

1. Shitara K et al. *Lancet*. 2018;392(10142):123-133.

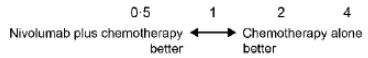
Lower cut-off of CPS score seem to required benefits of chemo + Anti-PD1

CM649

Figure S1: **Subgroup analysis by PD-L1 CPS subpopulations**

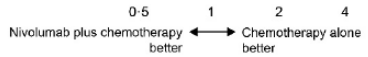
A Overall survival

Population*	Median overall survival, months		Unstratified hazard ratio for death (95% CI)	Interaction test p value
	Nivolumab plus chemotherapy	Chemotherapy alone		
Overall (N=1581)	13·8	11·6	0·79 (0·70–0·89)	
PD-L1 CPS <1 (n=265)	13·1	12·5	0·92 (0·70–1·23)	
PD-L1 CPS ≥1 (n=1296)	14·0	11·3	0·76 (0·67–0·87)	0·2041
PD-L1 CPS <5 (n=606)	12·4	12·3	0·94 (0·78–1·13)	
PD-L1 CPS ≥5 (n=955)	14·4	11·1	0·70 (0·60–0·81)	0·0107†



B Progression-free survival

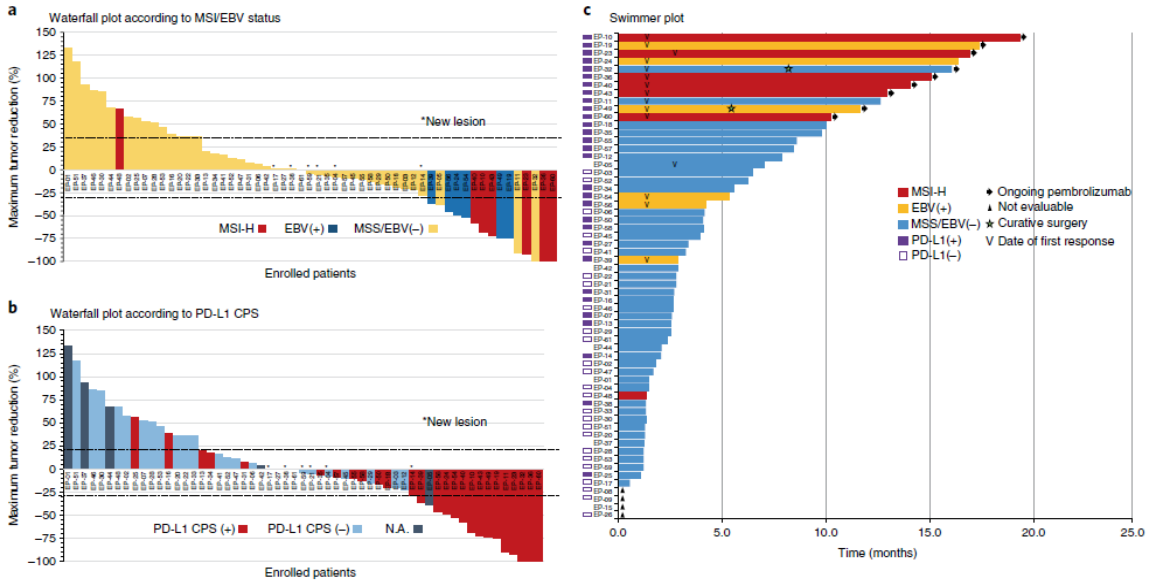
Population*	Median progression-free survival, months		Unstratified hazard ratio for progression/death (95% CI)	Interaction test p value
	Nivolumab plus chemotherapy	Chemotherapy alone		
Overall (N=1581)	7·7	6·9	0·77 (0·68–0·87)	
PD-L1 CPS <1 (n=265)	8·7	8·1	0·93 (0·69–1·26)	
PD-L1 CPS ≥1 (n=1296)	7·5	6·9	0·75 (0·65–0·85)	0·1391†
PD-L1 CPS <5 (n=606)	7·5	8·2	0·93 (0·76–1·12)	
PD-L1 CPS ≥5 (n=955)	7·7	6·1	0·69 (0·59–0·80)	0·0073†



Janjigian YY et al. Lancet 2021; 398: 37-40

Comprehensive molecular characterization of clinical responses to PD-1 inhibition in metastatic gastric cancer

Seung Tae Kim[1,8], Razvan Cristescu[2,8], Adam J. Bass[3,8], Kyoung-Mee Kim[4,8], Justin I. Odegaard[5,8], Kyung Kim[1], Xiao Qiao Liu[2], Xinwei Sher[2], Hun Jung[2], Mijin Lee[1], Sujin Lee[1], Se Hoon Park[1], Joon Oh Park[1], Young Suk Park[1], Ho Yeong Lim[1], Hyuk Lee[6], Mingew Choi[7], AmirAli Talasaz[5], Peter Soonmo Kang[2], Jonathan Cheng[2], Andrey Loboda[2], Jeeyun Lee[1*] and Won Ki Kang[1*]



Three predictors for anti-PD1

- High CPS
- EBV +
- MSI-H

Kim ST et al. Nature Med. 2018: 24: 1449-1458.

Overview of Biomarker Testing in Gastric Cancer: NCCN, ESMO, JSMO, and CSCO Guidelines

Biomarker	NCCN[1]	ESMO[2]	JSMO[3]	CSCO[4]	Recommendations
PD-L1	X				May be considered for locally advanced, recurrent, or metastatic gastric carcinoma in patients who are candidates for treatment with PD-1 inhibitors (category 2A)[1,a]
HER2	X	X	X	X	For patients with inoperable locally advanced, recurrent, or metastatic AC of the stomach for whom trastuzumab therapy is being considered (category 2A)[1,b] Used to select patients with metastatic disease for treatment with a trastuzumab-containing regimen [I, A][2] HER2 testing is strongly recommended in all patients who will receive chemotherapy for unresectable/metastatic gastric cancer[3] All cases of gastric AC should undergo HER2 assessment (Recommendation level I - universally accepted measures with clear indications for diagnosis and treatment; Evidence level 1A - uniform consensus reached [support level: ≥80%])[4]
MSI/MMR	X			X	Universal testing for MSI by PCR or MMR by IHC should be performed for all newly diagnosed gastric cancers (category 2A)[1,c] MSI/MMR status may help to screen gastric cancer patients favorable for preoperative chemotherapy (Recommendation level III - lack of strong evidence-based data, however, there is satisfactory consensus; Evidence level III - no consensus reached and has major disagreement [support level: < 60%])[4]
TMB					No specific recommendations.

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Gastric Cancer V4.2021 © National Comprehensive Cancer Network, Inc. 2021. All rights reserved.
Accessed September 13, 2021. To view the most recent and complete version of the guideline, go to NCCN.org. 2. Smyth EC et al. *Ann Oncol*. 2016;27(suppl 5):v38–v49. 3. Japanese Gastric Cancer Association.
Japanese gastric cancer treatment guidelines 2018 (5th edition). *Gastric Cancer.* 2020 Feb 14 [E-pub ahead of print]. 4. Wang F-H et al. *Cancer Commun (Lond).* 2019;39(1):10. 5. Mosele F et al. *Ann Oncol.* 2020; https://www.annalsofoncology.org/article/S0923-7534(20)39971-3/fulltext [in press].

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Biomarker in different cancer types

Hepatocellular carcinomas

HEPATOLOGY

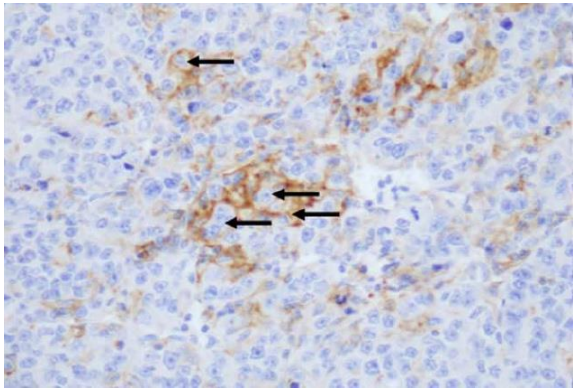
HEPATOLOGY, VOL. 64, NO. 6, 2016 HEPATOBILIARY MALIGNANCIES

Programmed Death Ligand 1 Expression in Hepatocellular Carcinoma: Relationship With Clinical and Pathological Features

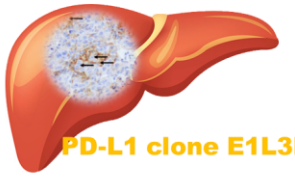
Julien Calderaro,[1–3] Benoit Rousseau,[2–4] Giuliana Amaddeo,[2,3,5] Marion Mercey,[2] Cécile Charpy,[1] Charlotte Costentin,[5] Alain Luciani,[2,3,6] Elie-Serge Zafrani,[1] Alexis Laurent,[7] Daniel Azoulay,[3,7] Fouad Lafdil,[2,3] and Jean-Michel Pawlotsky[2,3,8]

199 HCC patients, 217 tumors

PD-L1 clone E1L3N



Positive PD-L1 in **Tumour Cells**



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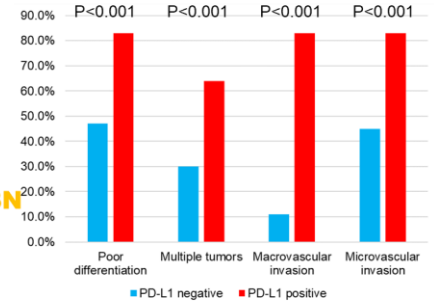
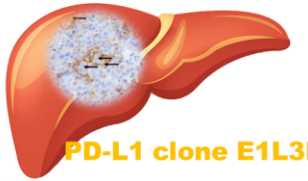
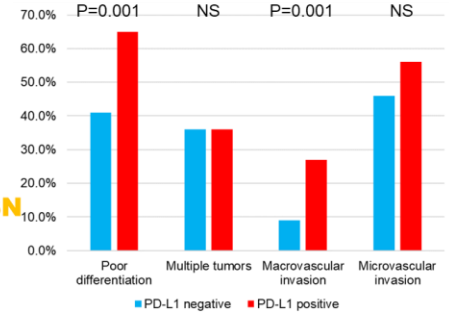


Positive PD-L1 in **Inflammatory Cells**



51%



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Calderaro J et al. Hepatology. 2016;64(6):2038-2046

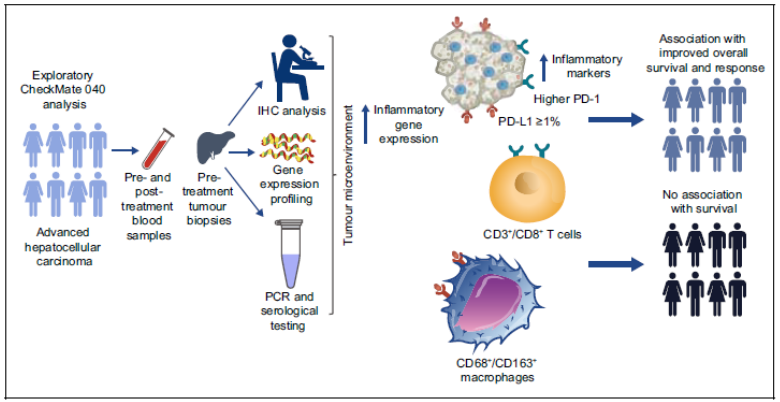
Research Article
Hepatic and Biliary Cancer

JOURNAL OF HEPATOLOGY

Association of inflammatory biomarkers with clinical outcomes in nivolumab-treated patients with advanced hepatocellular carcinoma

Bruno Sangro[1,*,†], Ignacio Melero[2,†], Samir Wadhawan[3,‡], Richard S. Finn[4], Ghassan K. Abou-Alfa[5,6], Ann-Lii Cheng[7], Thomas Yau[8], Junji Furuse[9], Joong-Won Park[10], Zachary Boyd[3,‡], Hao (Tracy) Tang[3], Yun Shen[3], Marina Tschaika[3], Jaclyn Neely[3,§], Anthony El-Khoueiry[11,§]

Graphical abstract



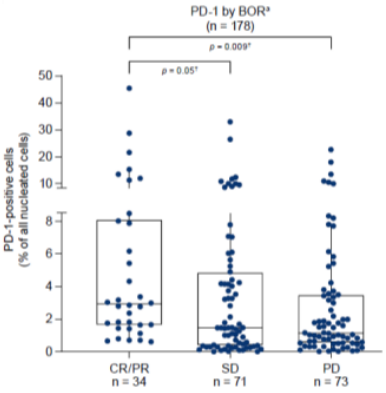
Markers evaluated

- Tissue
  - PDL1 IHC
  - Inflammatory gene expression (CD274, CD8A, LAG3, STAT1)
- Serum
  - AFP
  - HBV DNA/HCV RNA
  - NLR
  - Platelets
  - T-cell markers

PDL1 in association with more CR/PR but CR also seen in PDL1 <1%

Response, n (%)	Overall population (SOR-naive and SOR-experienced) (n = 195)	SOR-experienced (n = 137)
PD-L1 <1%		
Total, n (%)	159 (82)	110 (80)
Objective response rate, % (95% CI)	16 (11–22)	13 (8–20)
Complete response, n (%)	6 (4)	4 (4)
Partial response, n (%)	19 (12)	10 (9)
Stable disease, n (%)	66 (42)	49 (45)
Progressive disease, n (%)	59 (37)	42 (38)
PD-L1 ≥1%		
Total, n (%)	36 (18)	27 (20)
Objective response rate, % (95% CI)	28 (16–44)	26 (13–45)
Complete response, n (%)	2 (6)	1 (4)
Partial response, n (%)	8 (22)	6 (22)
Stable disease, n (%)	9 (25)	8 (30)
Progressive disease, n (%)	15 (42)	10 (37)

PD-L1, programmed death-ligand 1; SOR, sorafenib.
Responses not determined in overall population: 9 patients with PD-L1 <1% and 2 patients with PD-L1 ≥1%; sorafenib-experienced population: 5 patients with PD-L1 <1% and 2 patients with PD-L1 ≥1%.



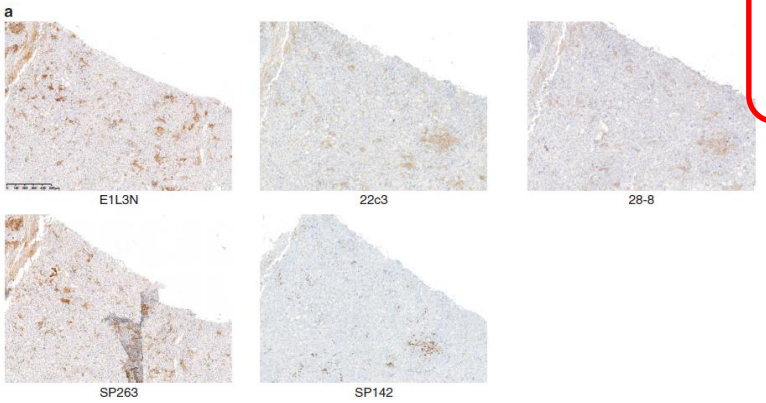
Journal of Hepatology 2020 vol. 73 | 1460–1469

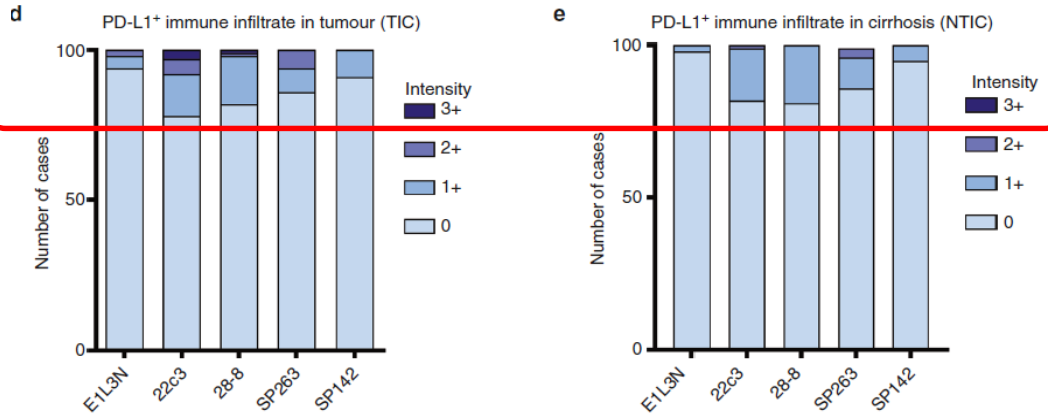
BJC British Journal of Cancer
www.nature.com/bjc

BRIEF COMMUNICATION
Translational Therapeutics

Clinical implications of heterogeneity in PD-L1 immunohistochemical detection in hepatocellular carcinoma: the Blueprint-HCC study

David J. Pinato[1], Francesco A. Mauri[1], Paolo Spina[2,3], Owen Cain[4], Abdul Siddique[1], Robert Goldin[1], Stephane Victor[1], Corinna Pizio[3], Ayse U. Akarca[5], Renzo L. Boldorini[3], Luca Mazzucchelli[2], James R. M. Black[1], Shishir Shetty[4], Teresa Marafioti[5] and Rohini Sharma[1]





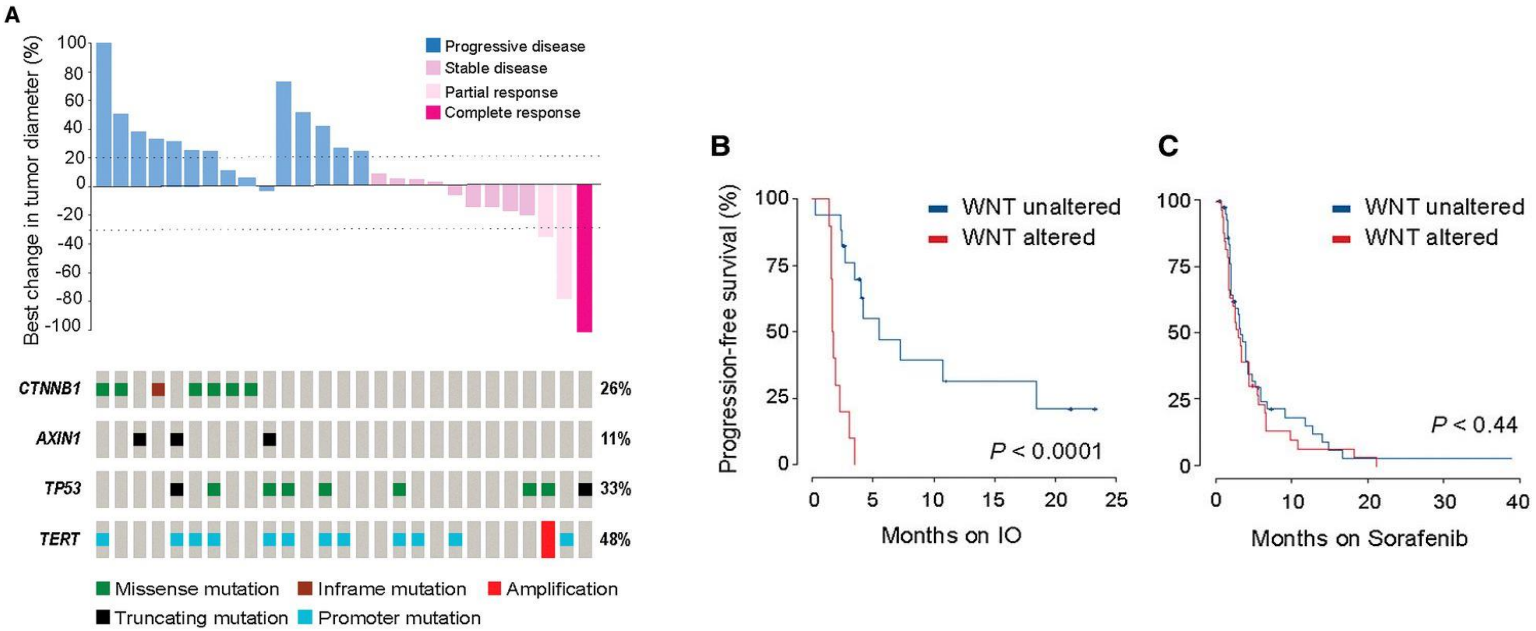
British Journal of Cancer (2019) 120:1033–1036; https://doi.org/10.1038/s41416-019-0466-x

Precision Medicine and Imaging

Clinical Cancer Research

Prospective Genotyping of Hepatocellular Carcinoma: Clinical Implications of Next-Generation Sequencing for Matching Patients to Targeted and Immune Therapies

James J. Harding[1], Subhiksha Nandakumar[2], Joshua Armenia[2], Danny N. Khalil[1], Melanie Albano[1], Michele Ly[1], Jinru Shia[3], Jaclyn F. Hechtman[3], Ritika Kundra[2], Imane El Dika[1], Richard K. Do[4], Yichao Sun[2,5], T. Peter Kingham[6], Michael I. D'Angelica[6], Michael F. Berger[3,5], David M. Hyman[1], William Jarnagin[6], David S. Klimstra[3], Yelena Y. Janjigian[1], David B. Solit[1,2,5], Nikolaus Schultz[2,5,7], and Ghassan K. Abou-Alfa[1]



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DOI: 10.1158/1078-0432.CCR-18-2293 Published April 2019

dMMR-MSI-H: literatures

Tumor type	dMMR/MSI-H (%)	High TMB (%)	References
Esophageal cancer	0–3.3	3.5–17.5	[38–41, 45]
Gastroesophageal junction cancer	4–8	3.1	[40, 43]
Gastric cancer	7.5–21.9	8.3–13.3	[38–43]
Small intestinal cancer	12	10.2–30.0	[40, 42]
Gastrointestinal stromal cancer	0	0–6.9	[40, 42]
Right-sided colon cancer	13.5–27	14.6	[38–43]
Left-sided colon cancer	2.0–2.2	3.5	[40, 43]
Rectal cancer	2.2–9.2	3.0	[38–41, 43]
Pancreatic cancer	0–1.3	1.4–27.9	[39–41, 43, 60, 61]
Biliary tract cancers	0–3	3.7–26.1	[10, 40–42, 66]
Hepatocellular carcinoma	0–2.9	2.2–7.4	[38–42, 70]
Neuroendocrine tumor/cancer	0	1.3–14.8	[40, 42]

dMMR mismatch repair deficient, *MSI-H* microsatellite instability-high, *TMB* tumor mutation burden

Conclusions

- Predictive biomarker for ICI is being developed rapidly for GI cancers.
- For CRC, the most clinically applicable biomarker for IO remains MSI-H/d-MMR.
- For GC, there is more understanding about PD-L1 CPS. High CPS ≥ 10 is required for monotherapy anti-PD1 while chemo + anti-PD1 benefits lower CPS.
- For HCC, there is still lack of predictive biomarker for ICI.
- More novel biomarkers are expected in future.