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Ilustre Colegio Oficial de Médicos de Madrid. Aula Jiménez Díaz. Madrid

CHECKPOINT INHIBITORS EN SUBPOBLACIONES INFRECUENTES DE TUMORES FRECUENTES

Luis de la Cruz Merino
Jefe de Servicio de Oncología Médica
Hospital Universitario Virgen Macarena, Sevilla

Disclosures

- Employment: none
- Consultant or Advisory Role: MSD-Merck, Roche Farma, Bristol-Myers-Squibb, Pierre-Fabré, Amgen, Novartis
- Stock Ownership: none
- Research Funding: MSD-Merck, Roche Farma, Celgene
- Speaking: MSD-Merck, Roche Farma, Bristol-Myers-Squibb, Amgen
- Grant support: Bristol-Myers-Squibb, Roche Farma
- Other: none

OUTLINE

1) CANCER IMMUNOEDITING

2) BREAST CANCER: TNBC

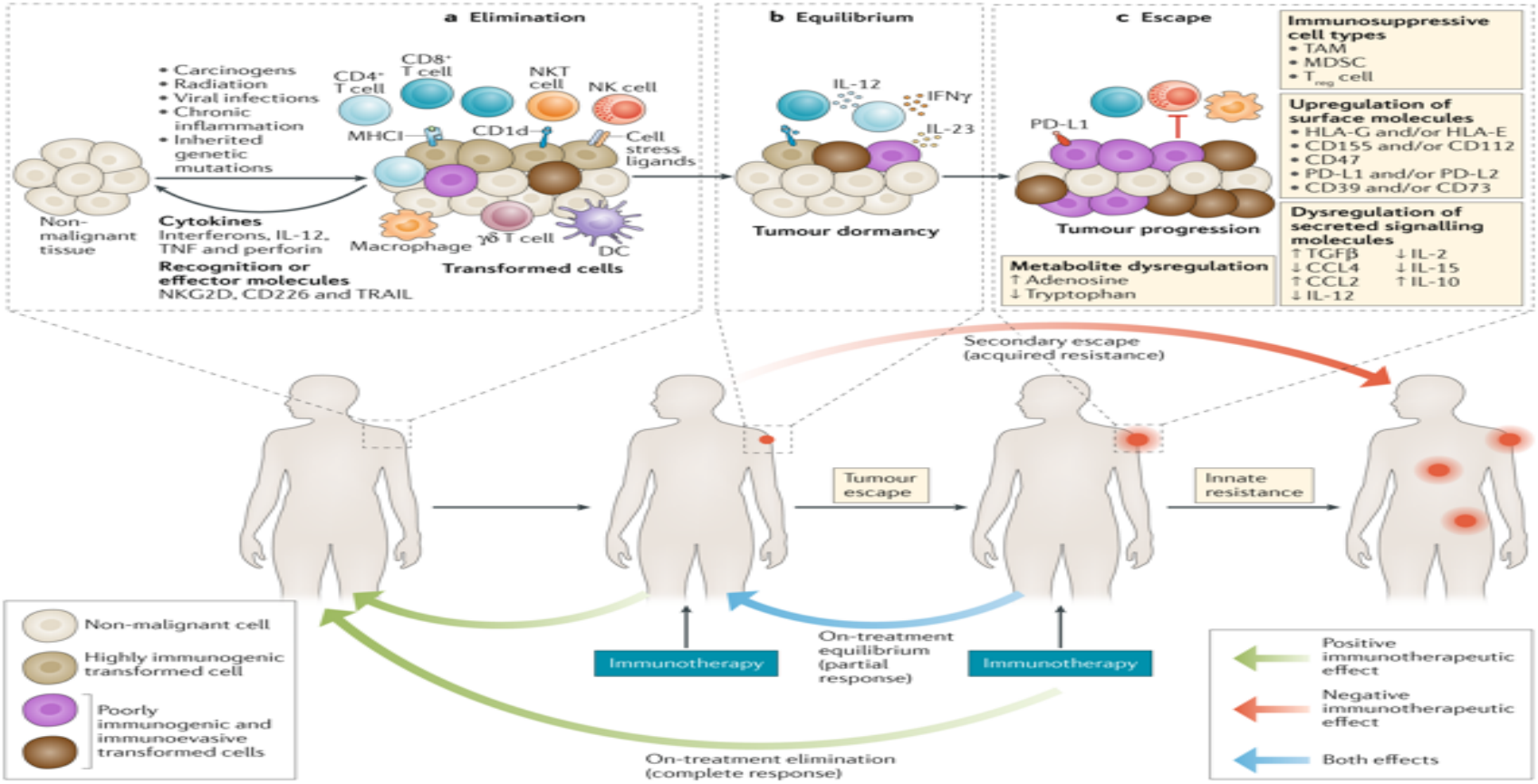
2) COLORECTAL CANCER

3) GASTROINTESTINAL NON-COLORECTAL TUMORS

4) MISCELLANEOUS CANCERS (PROSTATE, GYNECOLOGIC TUMORS)

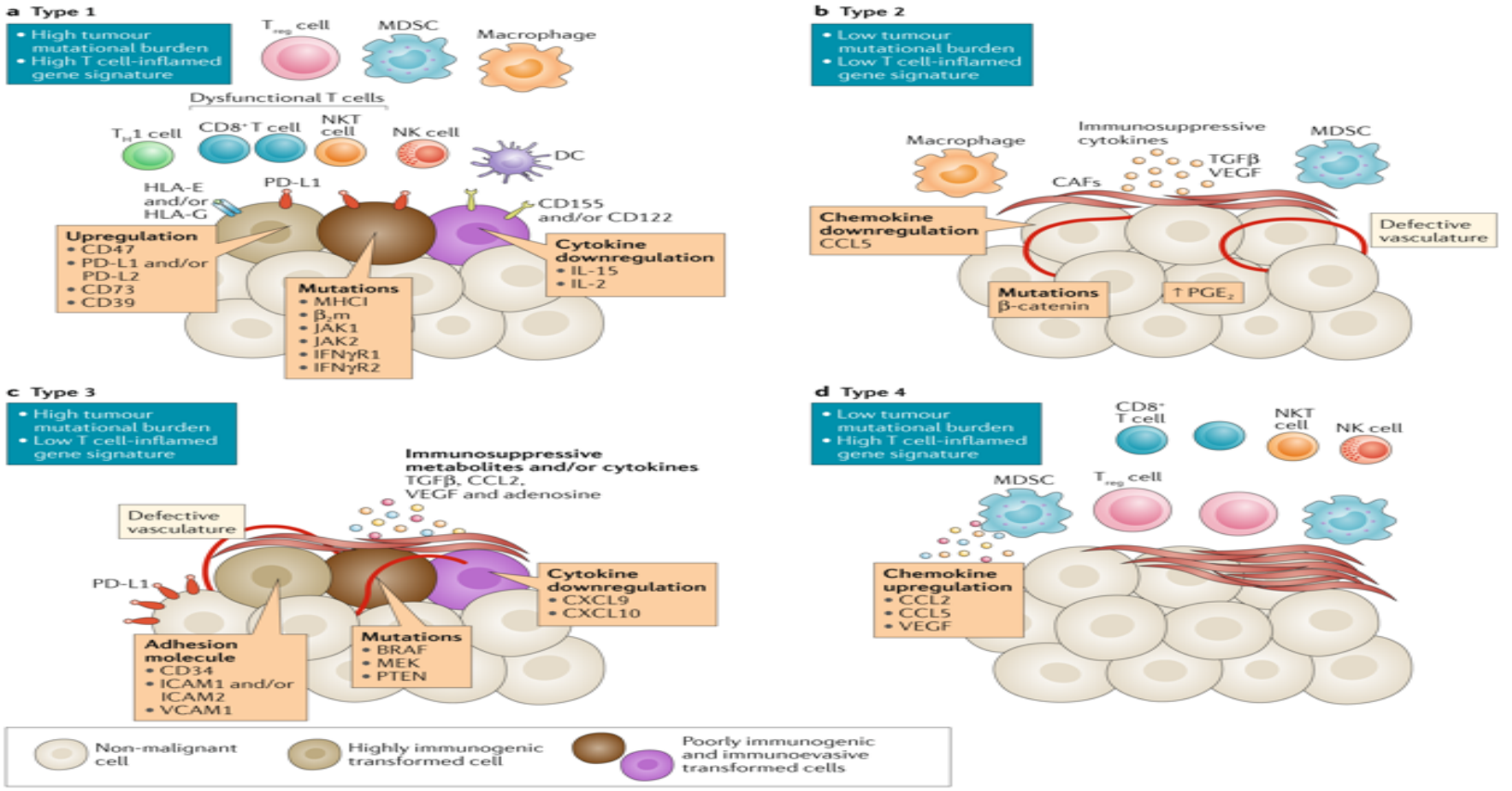
5) CONCLUSIONS AND FUTURE PERSPECTIVES

CANCER IMMUNOEDITION



O´Donnell Nature 2019

Stroma subtypes depending on TMB & gene signatures

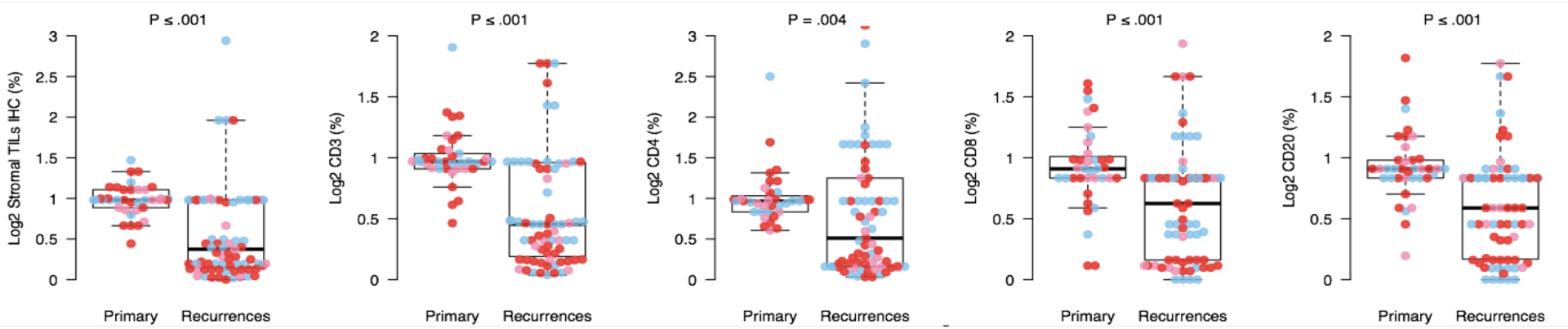


O´Donnell Nature 2019

CANCER IMMUNOEDITION IN BREAST CANCER

San Antonio Breast Cancer Symposium®, December 4-8, 2018

Comparison primary & recurrences using IHC



ER+/HER2-
HER2+
TN

Lower levels of immune infiltration in recurrence as compared to the primary samples.

FIRST TRIALS WITH IMMUNE-CHECKPOINT INHIBITORS IN BC

Clinical and Translational Oncology
https://doi.org/10.1007/s12094-018-1907-3

REVIEW ARTICLE

New horizons in breast cancer: the promise of immunotherapy

L. de la Cruz-Merino[1] · N. Palazón-Carrión[1] · F. Henao-Carrasco[1] · E. Nogales-Fernández[1] · M. Álamo-de la Gala[1] · A. Vallejo-Benítez[2] · M. Chiesa[3] · V. Sánchez-Margalet[4] on behalf of GEICAM (Spanish Breast Cancer Research Group) and GÉTICA (Spanish Group for Cancer Immuno-Biotherapy)

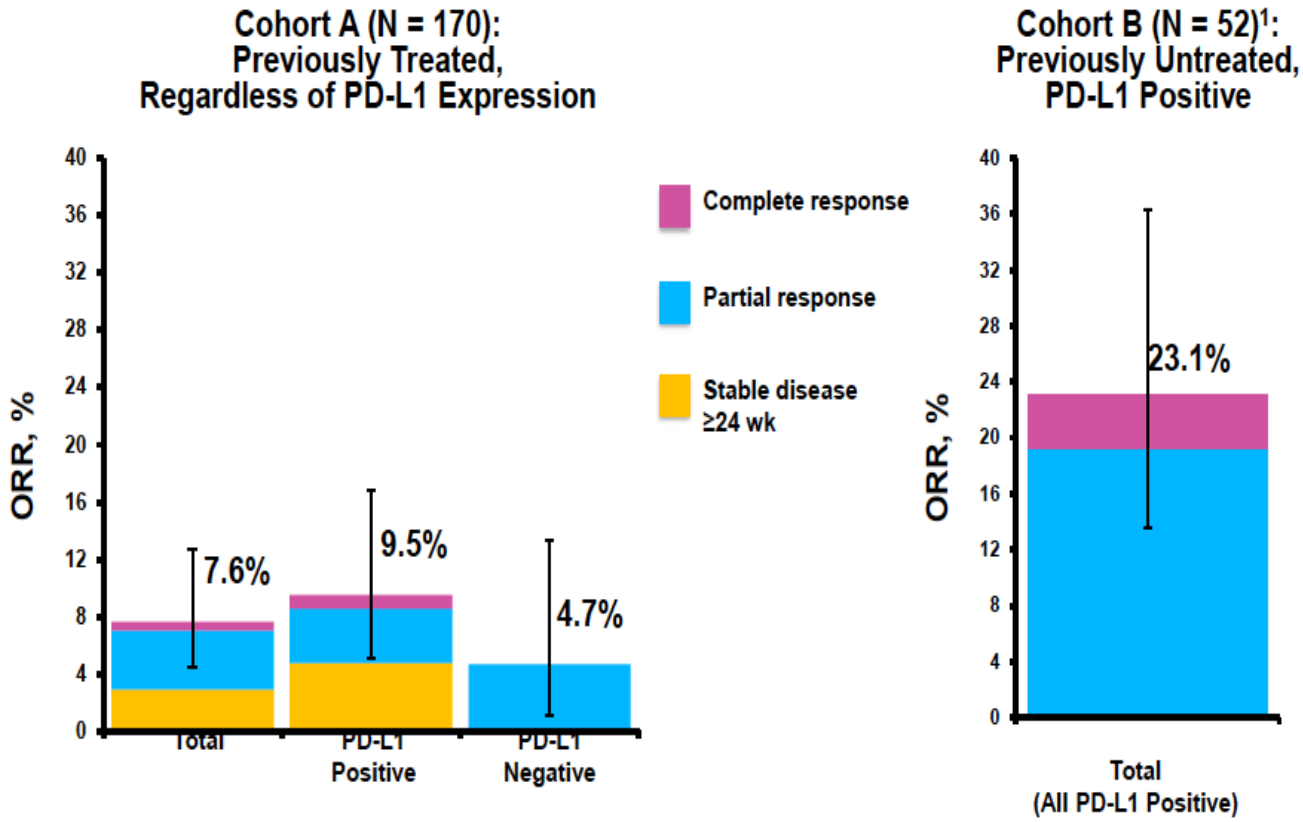
Received: 28 April 2018 / Accepted: 4 June 2018

Table 1 First clinical results with monoclonal antibodies against immune checkpoint inhibitors in breast cancer as single therapy

Trial (reference)	Phase	*n*	BC subtype	Median age	Immunotherapy	PDL1 status (% pos)	ORR (%)	Grade 3–4 toxicity (%)
Keynote 012 (NCT01848834) [18]	IB	32	TNBC	50.5	Pembrolizumab	58.6	18.5	15.6
Keynote-028 (NCT02054806) [21]	IB	25	ER+ HER2-	53	Pembrolizumab	19	14	16
Keynote-086 (NCT02447003) [22]	II	170	TNBC	54	Pembrolizumab	62	4.7	12
Keynote-086 (NCT02447003) [23]	II	52	TNBC	53	Pembrolizumab	100	23.1	8
PCD4989 g trial (NCT01375842) [25]	IA	112	TNBC	48	Atezolizumab	74	10	11
JAVELIN (NCT01943461) [28]	IA	168	Mixed	N/R	Avelumab	63.2	4.8	13.7

de la Cruz-Merino et al, Clin&Transl Oncol 2018

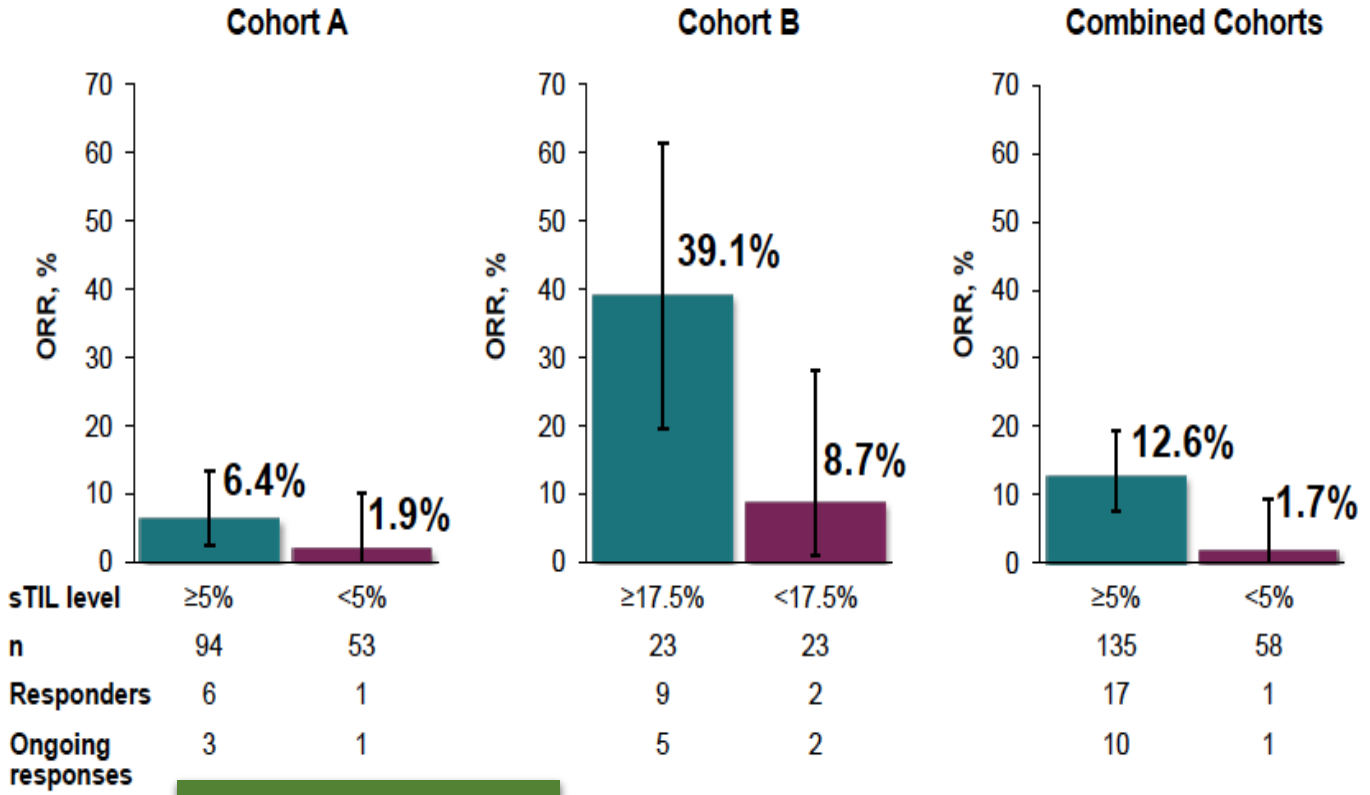
KEYNOTE-86, Pembro: ORR depending on PDL1 expression



Keynote-086 Trial

Adams S et al. J Clin Oncol 2017

KEYNOTE-86, Pembro: ORR depending on TILs



Keynote-086 Trial

Loi S et al. Ann Oncol 2017

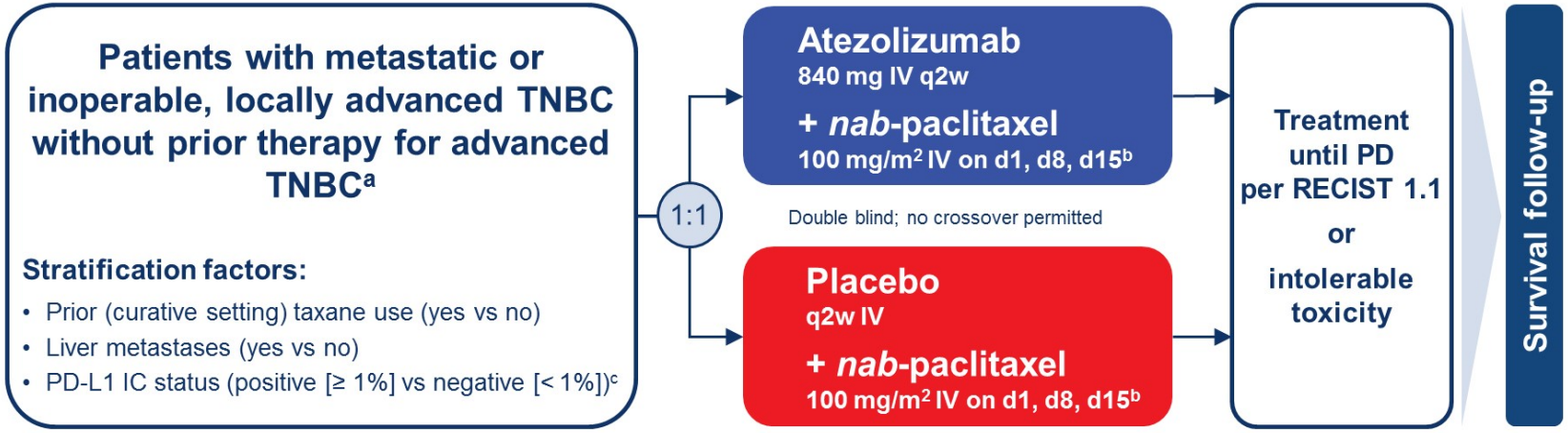
IMPASSION 130, UPDATED DATA

IMpassion130: updated OS from a global, randomized, double-blind, placebo-controlled, Phase III study of atezolizumab + *nab*-paclitaxel in previously untreated locally advanced or metastatic TNBC

Peter Schmid,[1] Sylvia Adams,[2] Hope S. Rugo,[3] Andreas Schneeweiss,[4] Carlos H. Barrios,[5] Hiroji Iwata,[6] Véronique Diéras,[7] Volkmar Henschel,[8] Luciana Molinero,[9] Stephen Y. Chui,[9] Amreen Husain,[8] Eric P. Winer,[10] Sherene Loi,[11] Leisha A. Emens[12]

[1]Barts Cancer Institute, Queen Mary University of London, London, UK; [2]New York University Langone Medical Center, New York, NY; [3]University of California San Francisco Comprehensive Cancer Center, San Francisco, CA; [4]University Hospital and German Cancer Research Center Heidelberg, Heidelberg, Germany; [5]Centro de Pesquisa Clínica, HSL, PUCRS, Porto Alegre, Brazil; [6]Aichi Cancer Center Hospital, Nagoya, Japan; [7]Department of Medical Oncology, Centre Eugène Marquis, Rennes, France; [8]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [9]Genentech, Inc, South San Francisco, CA; [10]Dana-Farber Cancer Institute, Boston, MA; [11]Peter MacCallum Cancer Centre, Melbourne, Australia; [12]University of Pittsburgh Medical Center Hillman Cancer Center, Pittsburgh, PA

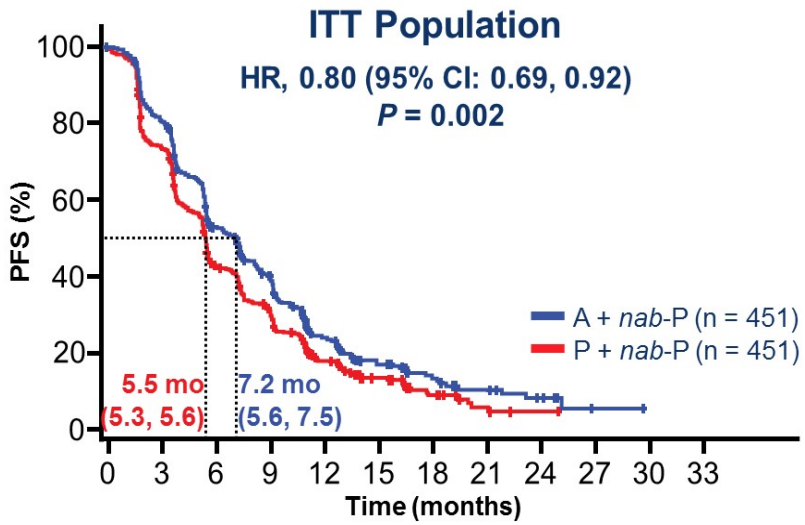
IMpassion130 Study Design

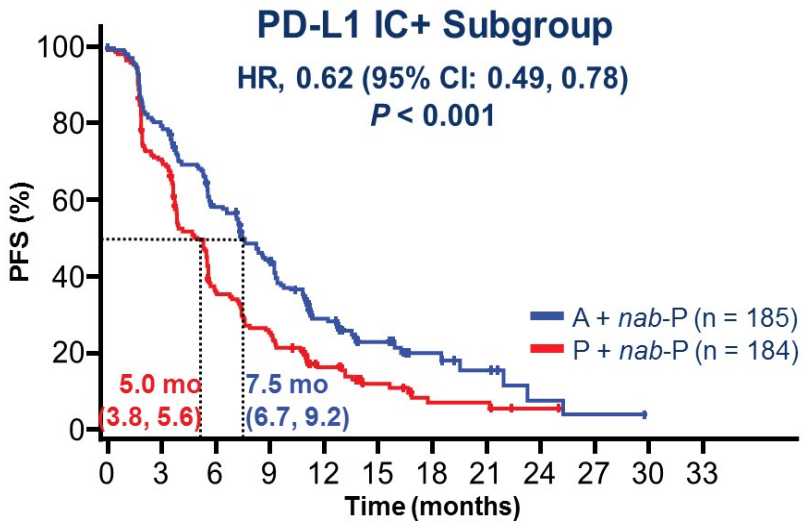


- Co-primary endpoints in ITT and PD-L1 IC+: PFS and OS[d]
- Pre-specified hierarchical testing of OS in ITT and, if significant, in PD-L1 IC+ patients
- In both treatment arms, 41% of patients were PD-L1 IC+

[a] Prior chemotherapy in the curative setting allowed if treatment-free interval ≥ 12 months. [b] 28-day cycle. [c] Centrally evaluated per VENTANA SP142 IHC assay.
[d] Efficacy endpoints assessed by investigators per RECIST 1.1. NCT02425891.

Primary PFS Analysis in the ITT and PD-L1 IC+ Subgroup



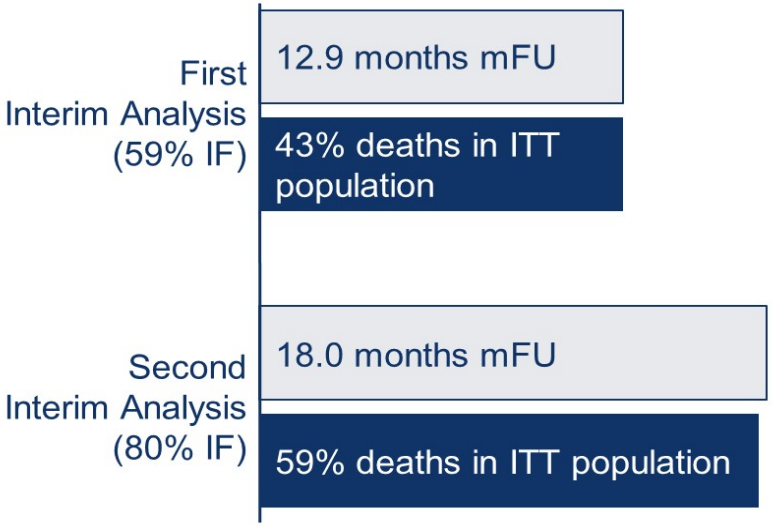


- PFS benefit driven by PD-L1 IC+ patients, as a treatment effect was not observed in PD-L1 IC− patients[1]
- Based on these data,[2] atezolizumab + *nab*-paclitaxel received accelerated approval by the FDA[3] and is recommended for patients with PD-L1 IC+ mTNBC in the NCCN[4] and AGO[5] guidelines

Data cutoff: April 17, 2018. Median follow-up (ITT): 12.9 months.

1. Emens SABCS 2018. 2. Schmid *New Engl J Med.* 2018. 3. Tecentriq (atezolizumab) [package insert]. South San Francisco, CA: Genentech USA, Inc; 2019.
4. NCCN Clinical Practice Guidelines. Breast Cancer. V1.2019. 5. AGO Guidelines Breast Version 2019.1.

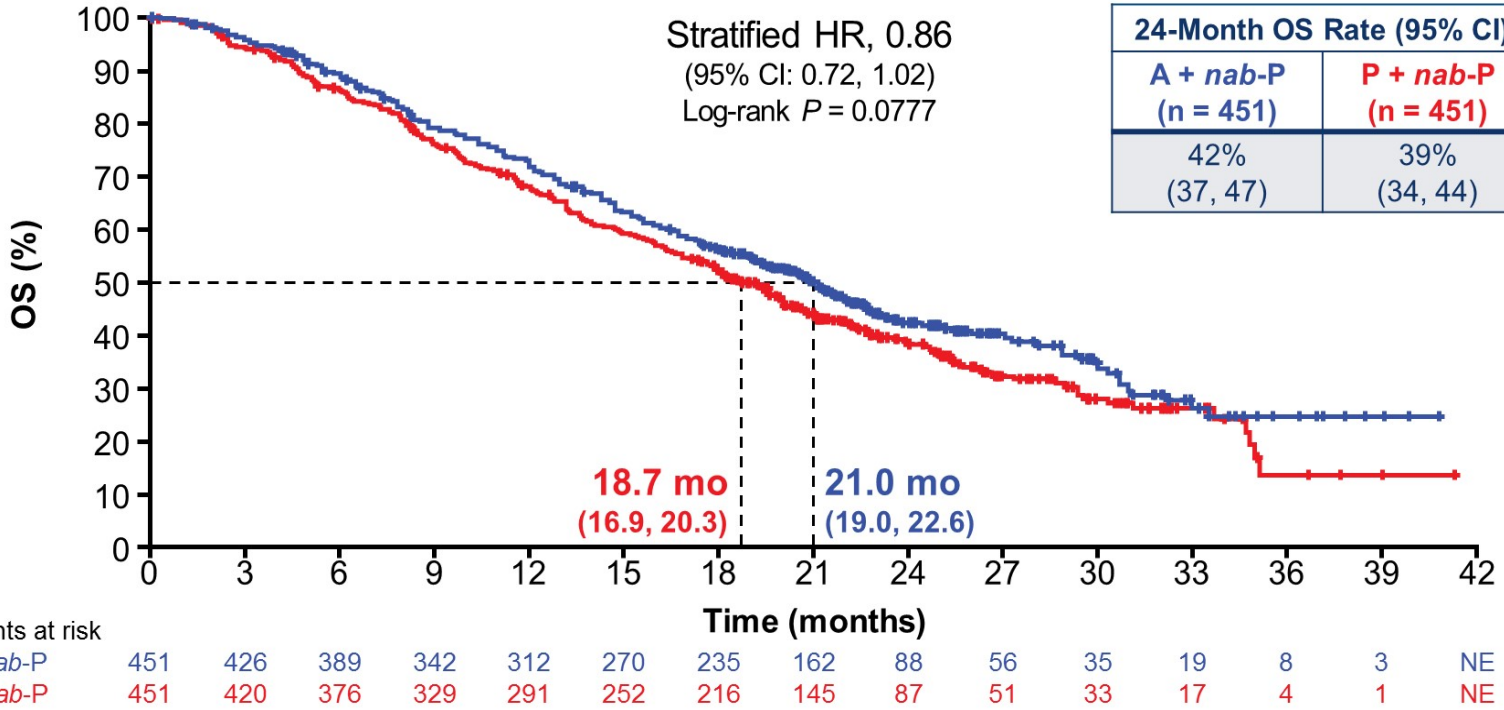
Patient Disposition at Second Interim OS Analysis



Second Interim OS Analysis		
Patient Disposition	**Atezolizumab + *nab*-paclitaxel (n = 451)**	**Placebo + *nab*-paclitaxel (n = 451)**
Patients on study, n (%)		
Alive on treatment	39 (9%)	13 (3%)
Alive in survival follow-up	133 (30%)	135 (30%)
Patients who discontinued study, n (%)		
Dead	255 (57%)	279 (62%)
Lost to follow-up	24 (5%)	24 (5%)

IF, information fraction; mFU, median follow-up.
Clinical cutoff date: January 2, 2019.
[a] Compared with Schmid et al. *New Engl J Med.* 2018.

OS in ITT Population

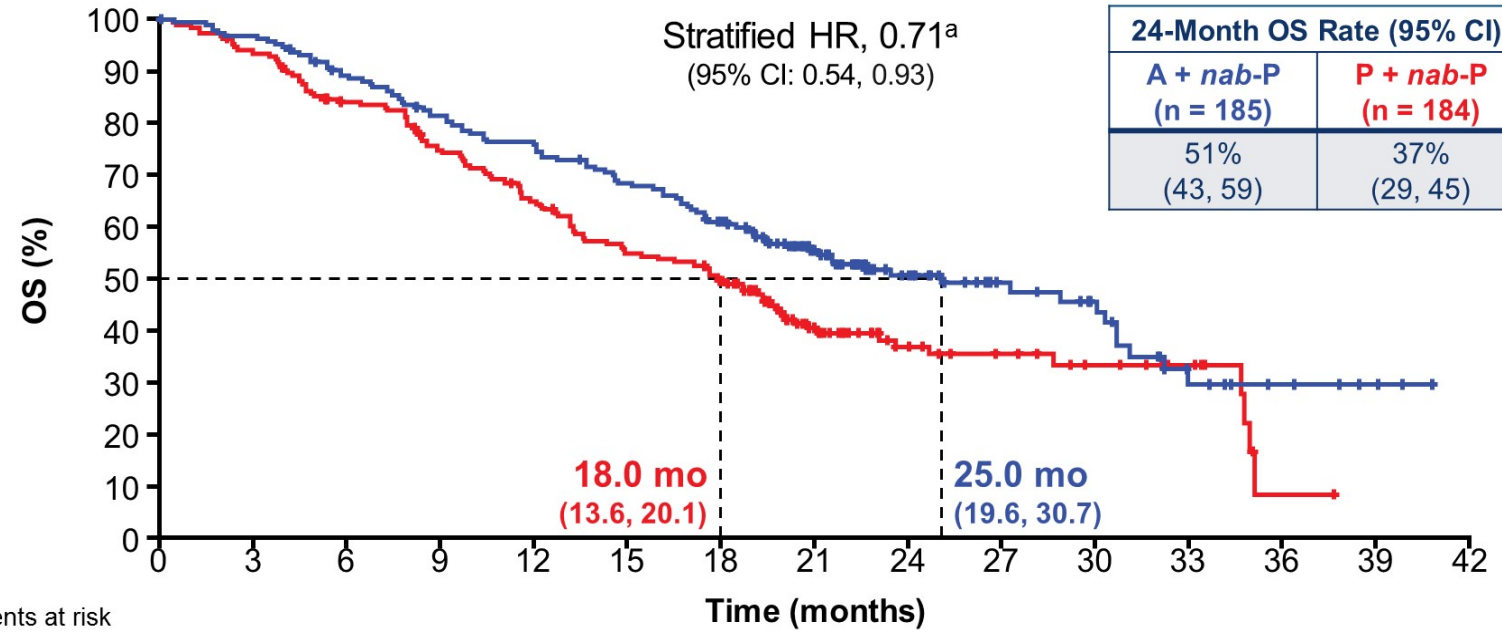


24-Month OS Rate (95% CI)	
A + *nab*-P (n = 451)	P + *nab*-P (n = 451)
42% (37, 47)	39% (34, 44)

Patients at risk															
A + *nab*-P	451	426	389	342	312	270	235	162	88	56	35	19	8	3	NE
P + *nab*-P	451	420	376	329	291	252	216	145	87	51	33	17	4	1	NE

NE, not estimable. Clinical cutoff date: January 2, 2019. Median PFS (95% CI) is indicated on the plot. Median FU (ITT): 18.0 mo.

OS in PD-L1+ Population



24-Month OS Rate (95% CI)	
A + *nab*-P (n = 185)	P + *nab*-P (n = 184)
51% (43, 59)	37% (29, 45)

Patients at risk

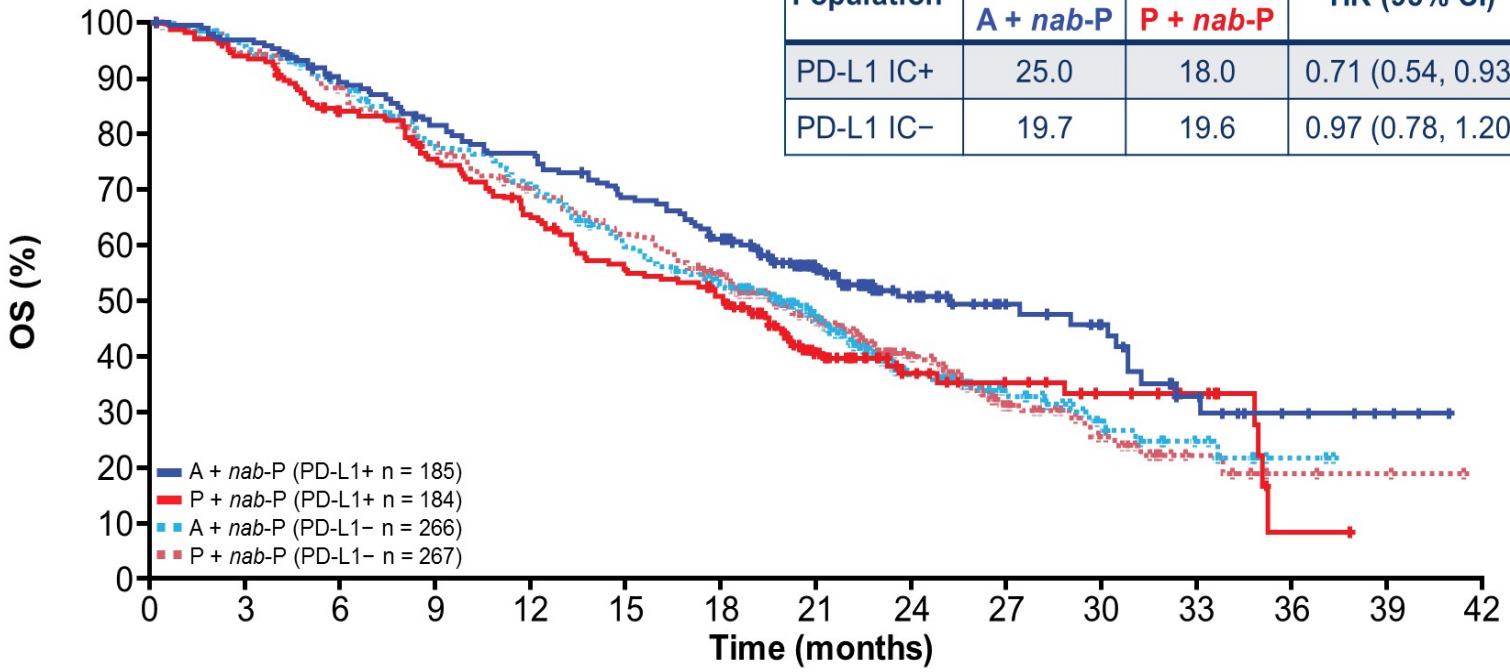
A + *nab*-P	185	177	160	145	135	121	106	69	43	28	21	10	6	3	NE
P + *nab*-P	184	170	147	129	111	93	81	47	26	20	15	10	1	NE	NE

[a] Not formally tested due to pre-specified hierarchical analysis plan.

Clinical cutoff date: January 2, 2019. Median PFS (95% CI) is indicated on the plot. Median FU (ITT): 18.0 months.

Comparison of OS in PD-L1+ and PD-L1− Populations

Population	Median OS, mo		HR (95% CI)
	A + *nab*-P	P + *nab*-P	
PD-L1 IC+	25.0	18.0	0.71 (0.54, 0.93)
PD-L1 IC−	19.7	19.6	0.97 (0.78, 1.20)



Clinical cutoff date: January 2, 2019.

FDA approves atezolizumab for PD-L1 positive unresectable locally advanced or metastatic triple-negative breast cancer

On March 8, 2019, the Food and Drug Administration granted accelerated approval to atezolizumab (TECENTRIQ, Genentech Inc.) in combination with paclitaxel protein-bound for adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] of any intensity covering ≥ 1% of the tumor area), as determined by an FDA-approved test.

FDA also approved the VENTANA PD-L1 (SP142) Assay as a companion diagnostic device for selecting TNBC patients for atezolizumab.

San Antonio Breast Cancer Symposium®
December 4-8, 2018

IMpassion130: Efficacy in immune biomarker subgroups from the global, randomized, double-blind, placebo-controlled, Phase III study of atezolizumab + *nab*-paclitaxel in patients with treatment-naive, locally advanced or metastatic triple-negative breast cancer

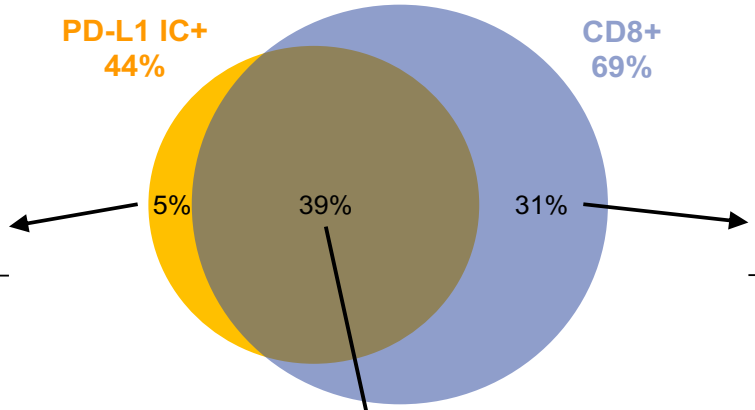
Leisha A. Emens,[1] Sherene Loi,[2] Hope S. Rugo,[3] Andreas Schneeweiss,[4] Véronique Diéras,[5] Hiroji Iwata,[6] Carlos H. Barrios,[7] Marina Nechaeva,[8] Luciana Molinero,[9] Anh Nguyen Duc,[10] Roel Funke,[9] Stephen Y Chui,[9] Amreen Husain,[10] Eric P. Winer,[11] Sylvia Adams,[12] Peter Schmid[13]

[1]UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA; [2]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [3]University of California San Francisco Comprehensive Cancer Center, San Francisco, CA; [4]University Hospital Heidelberg, Heidelberg, Germany; [5]Department of Medical Oncology, Centre Eugène Marquis, Rennes, France; [6]Aichi Cancer Center Hospital, Aichi, Japan; [7]Department of Medicine, PUCRS School of Medicine, Porto Alegre, Brazil; [8]Arkhangelsk Regional Clinical Oncology Dispensary, Arkhangelsk, Russia; [9]Genentech, Inc., South San Francisco, CA; [10]F. Hoffmann-La Roche AG, Basel, Switzerland; [11]Dana-Farber Cancer Institute, Boston, MA; [12]New York University Langone Medical Center, New York, NY; [13]Barts Cancer Institute, Queen Mary University of London, London, UK

Emens LA, et al. IMpassion130 biomarkers.
SABCS 2018 (program #GS1-04)

San Antonio Breast Cancer Symposium®
December 4-8, 2018

CD8+ IHC has clinical benefit if co-occurring with PD-L1 IC+



CD8–/PD-L1 IC+ (n = 37)

	HR (95% CI)	*P* Value
PFS	0.33 (0.13, 0.87)	0.03
OS	0.25 (0.06, 1.02)	0.05

CD8+/PD-L1 IC+ (n = 280)

	HR (95% CI)	*P* Value
PFS	0.61 (0.46, 0.80)	≤ 0.005
OS	0.55 (0.38, 0.80)	≤ 0.005

CD8+/PD-L1 IC– (n = 220)

	HR (95% CI)	*P* Value
PFS	0.89 (0.66, 1.20)	0.45
OS	0.77 (0.50, 1.17)	0.21

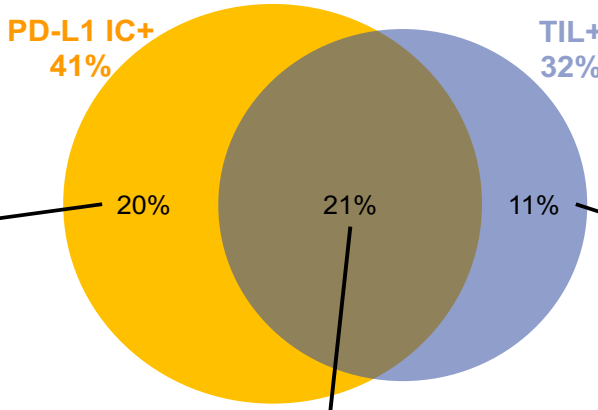
- PD-L1 IC+ are enriched in CD8+ ($P < 0.0001$) and CD8+ are enriched in PD-L1 IC+ ($P < 0.0001$)[a]
- ***Patients with CD8+ tumors derived clinical benefit (PFS/OS) only if their tumors were also PD-L1 IC+***

BEP (CD8): n = 720. A CD8+ cutoff of 0.5% was selected based on Phase Ib study in TNBC (Adams *JAMA Oncol* 2018). All *P* values are nominal.
[a] Data derived from contingency table with Fisher exact tests.

Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)

San Antonio Breast Cancer Symposium®
December 4-8, 2018

Stromal TILs has clinical benefit if co-occurring with PD-L1 IC+



TIL–/PD-L1 IC+ (n = 176)

	HR (95% CI)	*P* Value
PFS	0.74 (0.54, 1.03)	0.07
OS	0.65 (0.41, 1.02)	0.06

TIL+/PD-L1 IC– (n = 94)

	HR (95% CI)	*P* Value
PFS	0.99 (0.62, 1.57)	0.97
OS	1.53 (0.76, 3.08)	0.24

TIL+/PD-L1 IC+ (n = 190)

	HR (95% CI)	*P* Value
PFS	0.53 (0.38, 0.74)	≤ 0.005
OS	0.57 (0.35, 0.92)	0.02

- TIL+ were enriched for PD-L1 IC+ ($P < 0.0001$) but PD-L1 IC+ were not enriched for TIL+ (P = ns)[a]
- ***Patients with TIL+ tumors derived clinical benefit (PFS/OS) only if their tumors were also PD-L1 IC+***

BEP (TILs): n = 893. Cutoff of 10% was used to distinguish low vs intermediate/high levels of TILs (Denkert *Lancet Oncol* 2018). All *P* values are nominal.
[a] Data derived from contingency table with Fisher exact tests.

Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)

JAMA Oncology | Original Investigation

Open-label Clinical Trial of Niraparib Combined With Pembrolizumab for Treatment of Advanced or Metastatic Triple-Negative Breast Cancer

TOPACIO TRIAL

Shaveta Vinayak, MD, MS; Sara M. Tolaney, MD, MPH; Lee Schwartzberg, MD; Monica Mita, MD; Georgia McCann, MD; Antoinette R. Tan, MD; Andrea E. Wahner-Hendrickson, MD; Andres Forero, MD; Carey Anders, MD; Gerburg M. Wulf, MD, PhD; Patrick Dillon, MD; Filipa Lynce, MD; Corrine Zarwan, MD; John K. Erban, MD; Yinghui Zhou, PhD; Nathan Buerstatte, BS, MPH; Julie R. Graham, PhD; Sujata Arora, MS; Bruce J. Dezube, MD; Melinda L. Telli, MD

Figure 1. Flow Diagram of Study Enrollment, Treatment, and Outcomes

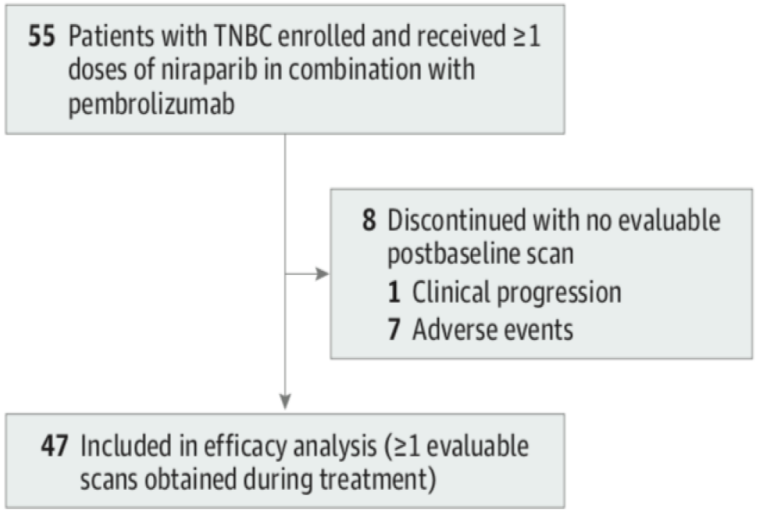


Table 1. Best Overall Tumor Responses in the Full-Analysis and Efficacy-Evaluable Populations

Best Overall Response	Study Population	
	Full Analysis (N = 55)	Efficacy Evaluable (n = 47)
Complete response, No. (%)	5 (9)	5 (11)
Partial response, No. (%)	5 (9)	5 (11)
Stable disease, No. (%)	13 (24)	13 (28)
Progressive disease, No. (%)	24 (44)	24 (51)
Not performed or not evaluable, No. (%)	8 (15)	NA
ORR, No. (%) [90% CI][a]	10 (18) [10-29]	10 (21) [12-33]
DCR, No. (%) [90% CI][b]	23 (42) [31-54]	23 (49) [36-62]

Vinayak JAMA Oncol 2019

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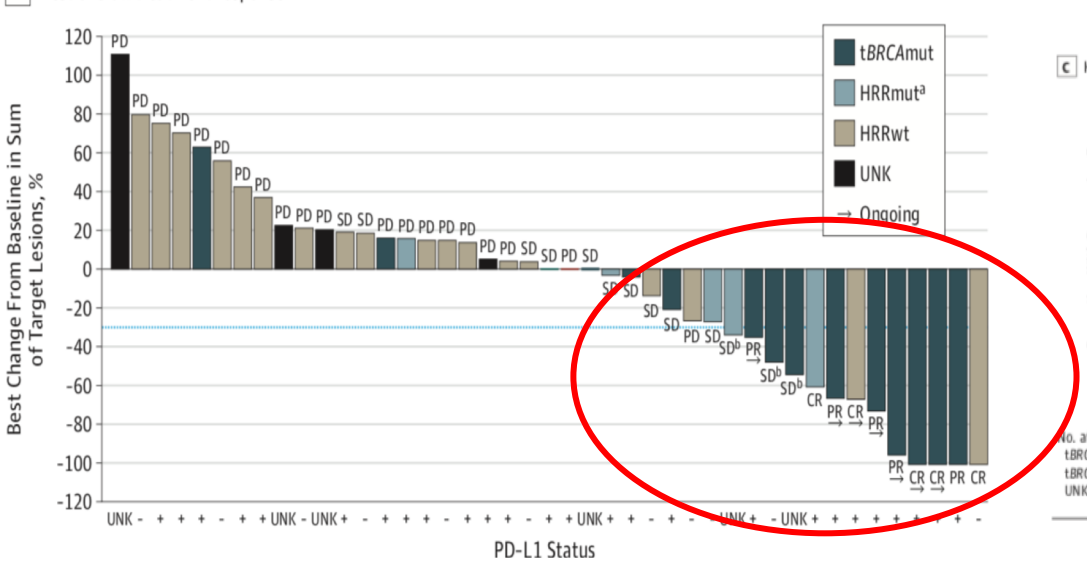
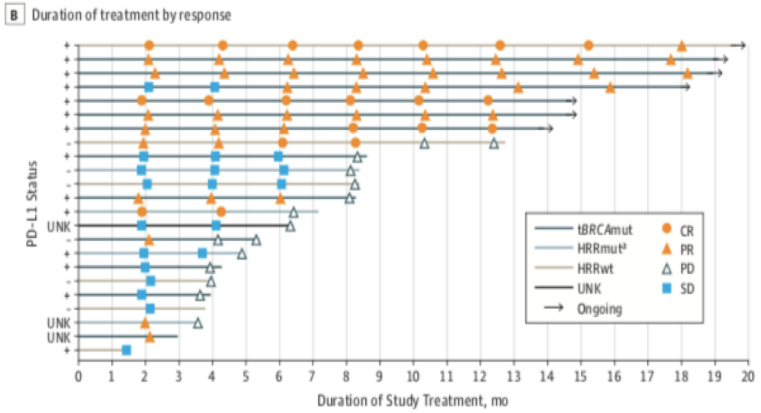
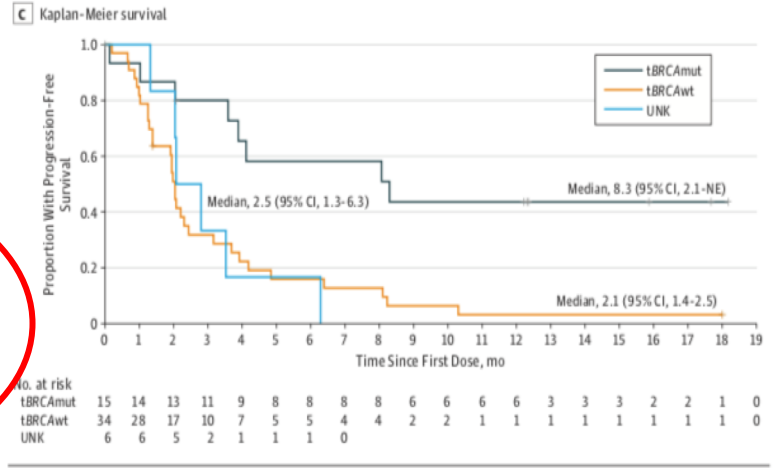
Figure 2. Antitumor Activity of Niraparib in Combination With Pembrolizumab by Biomarker Status







Vinayak JAMA Oncol 2019

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Table 2. Response Rates in Biomarker-Defined, Efficacy-Evaluable Population

Biomarker Status	No.	ORR, No. (%) [90% CI]	DCR, No. (%) [90% CI]
BRCA			
t*BRCA*mut	15	7 (47) [24-70]	12 (80) [56-94]
t*BRCA*wt	27	3 (11) [3-26]	9 (33) [19-51]
t*BRCA* unknown	5	0 (0) [0-45]	2 (40) [8-81]
HRR[a]			
HRRmut	20	8 (40) [22-61]	16 (80) [60-93]
HRRwt	22	2 (9) [2-26]	6 (27) [13-47]
HRR unknown	5	0 (0) [0-45]	1 (20) [1-66]
PD-L1			
Positive	28	9 (32) [18-49]	14 (50) [33-67]
Negative	13	1 (8) [0.4-32]	6 (46) [22-71]
Unknown	6	0 (0) [0-39]	3 (50) [15-85]

Vinayak JAMA Oncol 2019

BARCELONA 2019 ESMO congress

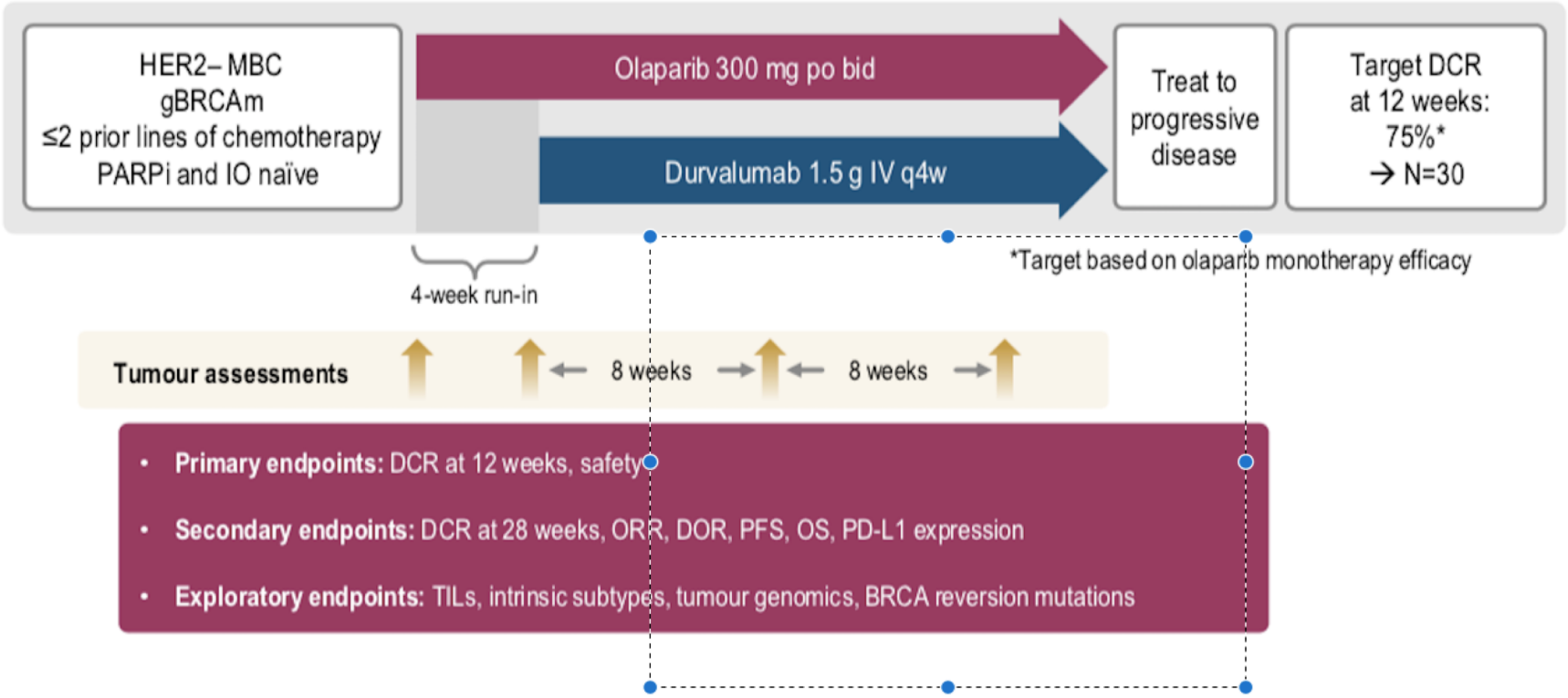
Phase II study of olaparib and durvalumab (MEDIOLA): Updated results in patients with germline BRCA-mutated metastatic breast cancer

Susan M Domchek,[1] Sophie Postel-Vinay,[2] Seock-Ah Im,[3] Yeon Hee Park,[4] Jean-Pierre Delord,[5] Antoine Italiano,[6] Jerome Alexandre,[7] Benoit You,[8] Sara Bastian,[9] Matthew G Krebs,[10] Ding Wang,[11] Saiama Waqar,[12] Mark Lanasa,[13] Helen K Angell,[14] Zhongwu Lai,[15] Christopher Gresty,[14] Laura Opincar,[13] Pia Herbolsheimer[13] and Bella Kaufman[16]

[1]Basser Center for BRCA University of Pennsylvania, Philadelphia, PA, USA; [2]Institut Gustave Roussy, Villejuif, France; [3]Seoul National University Hospital, Seoul, South Korea; [4]Samsung Medical Center, Seoul, South Korea; [5]Institut Universitaire du Cancer de Toulouse, Toulouse, France; [6]Institut Bergonié, Bordeaux, France; [7]Hôpital Cochin, Paris, France; [8]Centre Hospitalier Lyon Sud, Pierre-Bénite, France; [9]Kantonsspital Graubuenden, Chur, Switzerland; [10]The Christie NHS Foundation Trust and The University of Manchester, Manchester, UK; [11]Henry Ford Medical Center, Detroit, MI, USA; [12]Washington University School of Medicine, Saint Louis, MO, USA; [13]AstraZeneca, Gaithersburg, MD, USA; [14]AstraZeneca, Cambridge, UK; [15]AstraZeneca, Boston, MA, USA; [16]Chaim Sheba Medical Center, Tel Hashomer, Israel

esmo.org

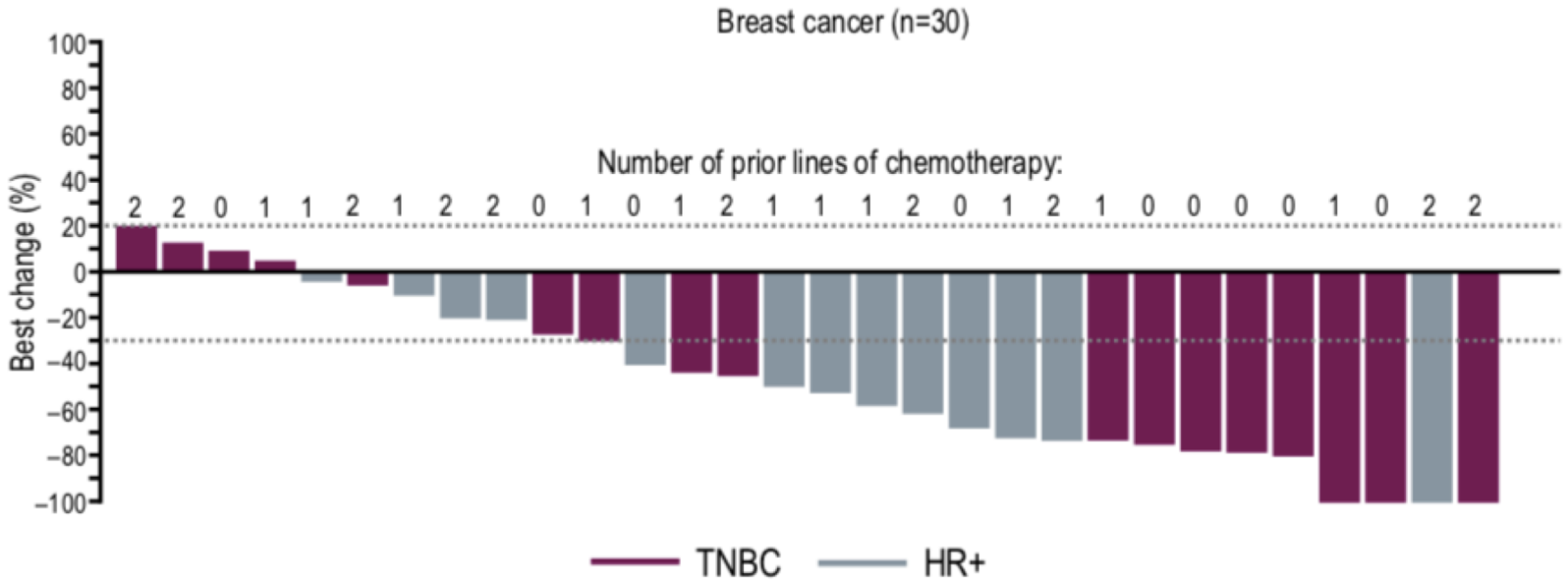
Schema



BARCELONA 2019 ESMO congress

bid, twice daily; DCR, disease control rate; IO, immuno-oncology; IV, intravenous; PARPi, PARP inhibitor; po, oral; q4w, every 4 weeks; TILs, tumour-infiltrating lymphocytes

Efficacy: objective response rate



Endpoint	FAS, % n=30	TNBC, % n=17	HR+, % n=13	0–1 prior line, % n=20	Two prior lines, % n=10
ORR (95% CI)	63.3 (43.9, 80.1)	58.8 (32.9, 81.6)	69.2 (38.6, 90.9)	70.0 (45.7, 88.1)	50.0 (18.7, 81.3)

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Dashed lines at –30% and 20% indicate thresholds for partial response and progressive disease, respectively

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

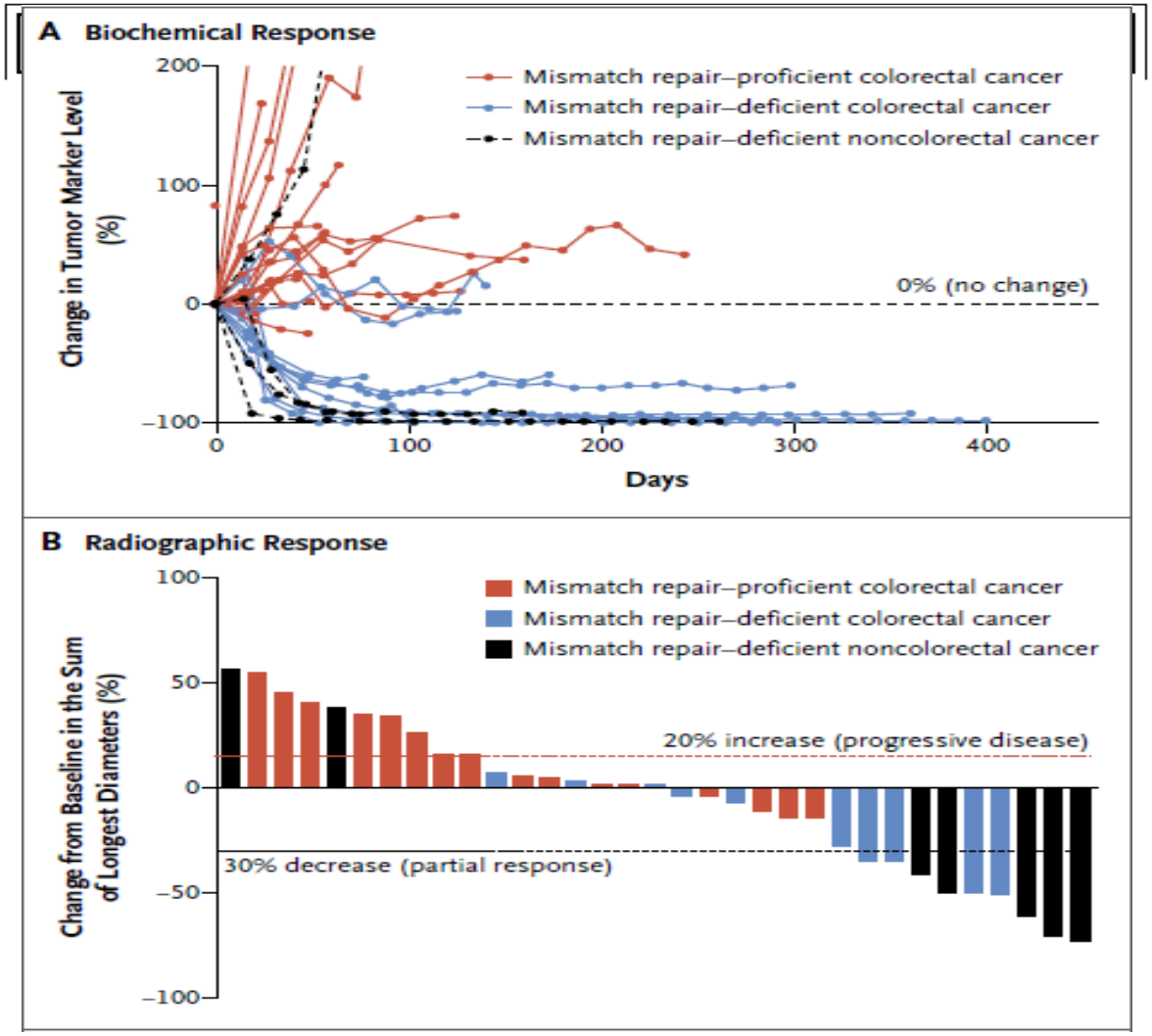
PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.

Le DT N Engl J Med. Jun 2015

V SIMPOSIO GETHI

The NEW ENGLAND JOURNAL of MEDICINE



Le DT N Engl J Med. Jun 2015

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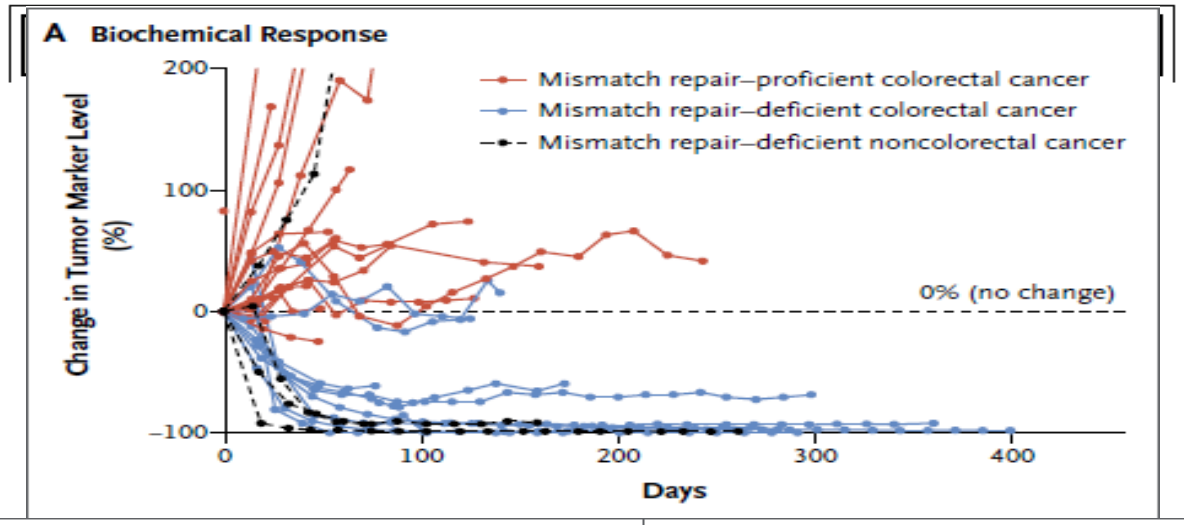

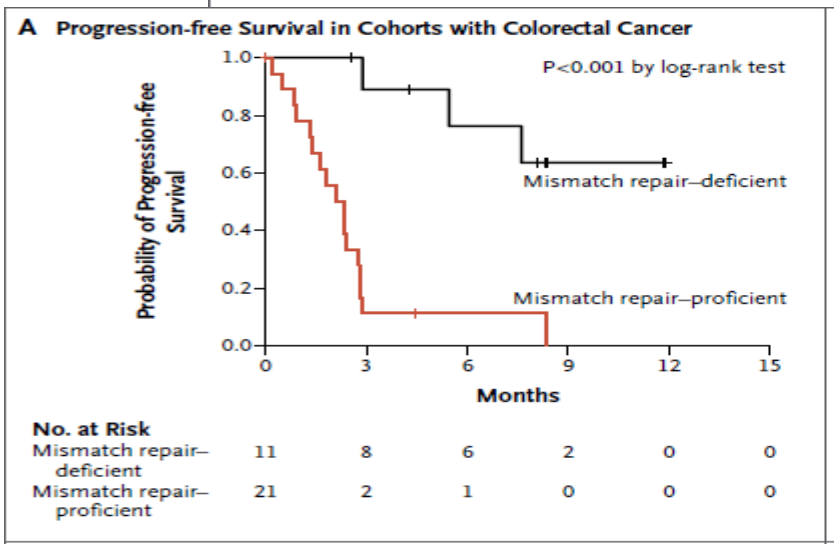

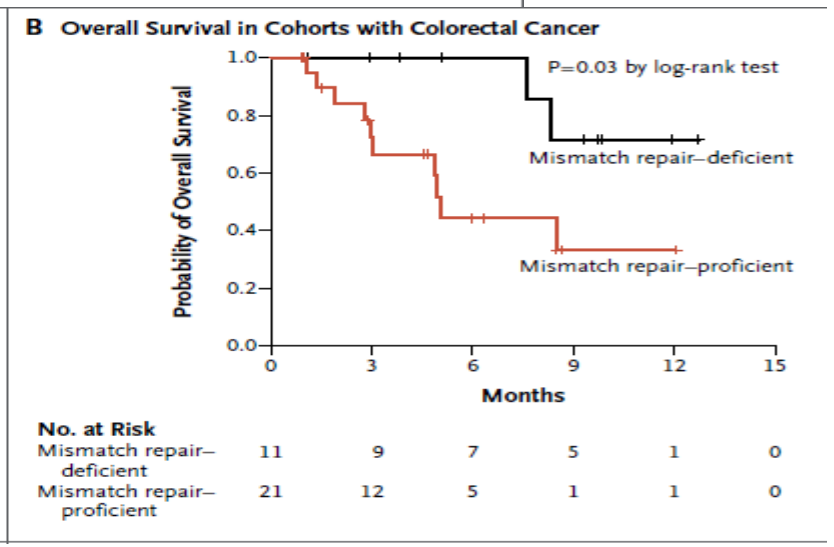

Le DT N Engl J Med. Jun 2015

Lancet Oncol. 2017 September ; 18(9): 1182–1191. doi:10.1016/S1470-2045(17)30422-9.

Nivolumab in patients with metastatic DNA mismatch repair deficient/microsatellite instability–high colorectal cancer (CheckMate 142): results of an open-label, multicentre, phase 2 study

Michael J. Overman, MD[1], Ray McDermott, MD[2], Joseph L. Leach, MD[3], Sara Lonardi, MD[4],

Prior systemic treatments, n (%)	
0	1 (1)
1	11 (15)
2	22 (30)
≥3	40 (54)
Prior therapies received, n (%)	
Fluoropyrimidines (5-fluorouracil or capecitabine)	73 (99)
Oxaliplatin	71 (96)
VEGF inhibitors[†]	57 (77)
Irinotecan	55 (74)
EGFR inhibitors[‡]	31 (42)
Regorafenib	12 (16)
Other	11 (15)
Prior radiotherapy, n (%)	27 (36)
Mutation status, n (%)	
BRAF/KRAS wild type	29 (39)
BRAF mutation	12 (16)
KRAS mutation	26 (35)
Unknown	7 (9)

	dMMR/MSI-H per local assessment (N=74)		dMMR/MSI-H per central assessment (N=53)	
Patients, n (%)	**Investigator**	**BICR**	**Investigator**	**BICR**
			19 (35·8)	19 (35·8)
Objective response rate	23 (31·1)	24 (32·4)		
[95% CI]	[20·8–42·9]	[22·0–44·3]		
			[23·1–50·2]	[23·1–50·2]
Best overall response				
Complete response	0	2 (2.7)	0	1 (1·9)
Partial response	23 (31·1)	22 (29·7)	19 (35·8)	18 (34·0)
Stable disease	28 (37·8)	25 (33·8)	20 (37·0)	19 (35·8)
Progressive disease	19 (25·7)	21 (28·4)	11 (20·8)	12 (22·6)
Not determined	4 (5·4)	4 (5·4)	3 (5·7)	3 (5·7)
Disease control for ≥12				
	51 (68·9)	47 (63·5)	39 (73·6)	37 (69·8)
weeks				
	[57·1–79·2]	[51·5–74·4]		
[95% CI]				
			[59·7–84·7]	[55·7–81·7]

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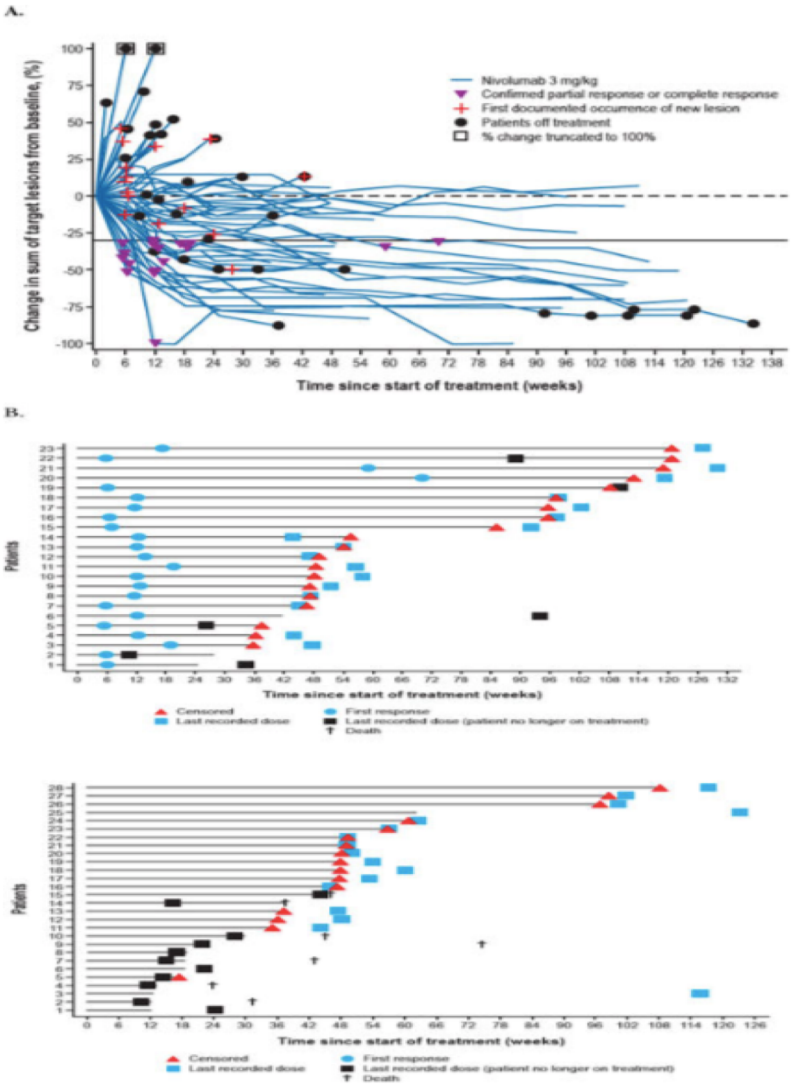

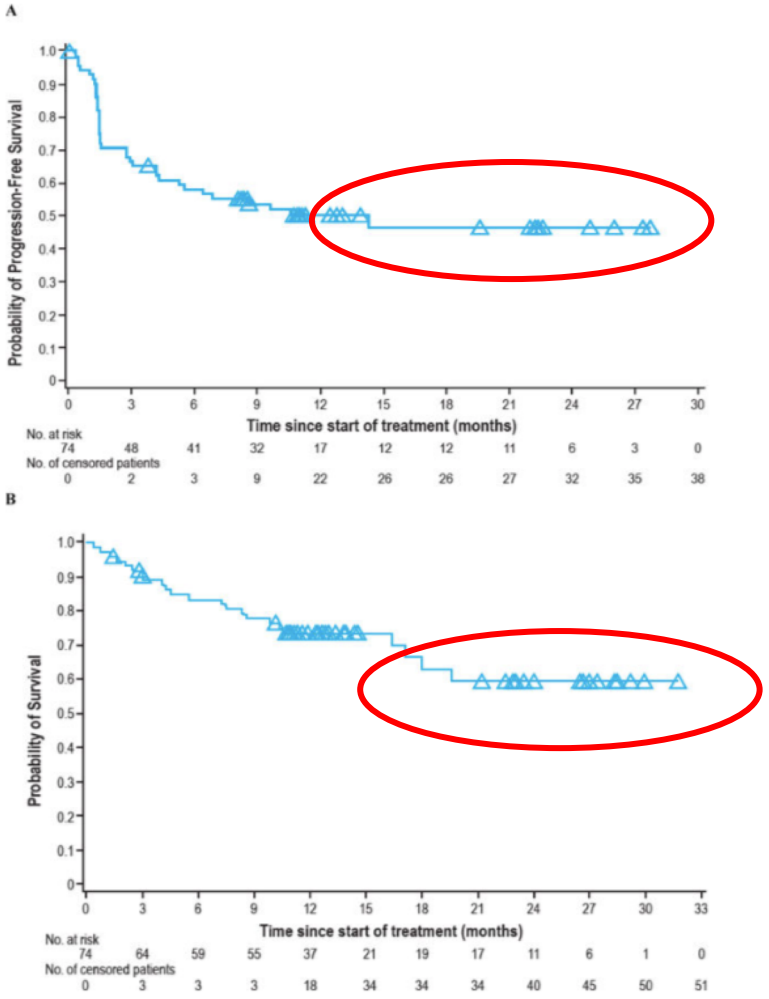

Overman Lancet Oncol 2017

IO-Combos in mCRC

Table 3
Selection of ongoing clinical trial investigating the combination of immunotherapy with chemotherapy and target agents.

Study name	Agent	Target	Study population	Primary endpoint	Phase	Recruitment status
CheckMate9X8 (NCT03414983)	FOLFOXBevacizumab/Nivolumab Vs FOLFOX/Bevacizumab	PD-1	First line CRC (MMR not spciefied)	PFS	II/III	Active, recruiting
MEDITREME (NCT03202758)	FOLFOX/Durvalumab/Tremelimumab	PD-1 CTLA- 4	First line CRC (MMR not spciefied)	Safety	Ib/II	Active,recruiting
ElevetiION:CRC 101 (NCT03176264)	FOLFOX/Bevacizumab/PDR001	PD1	First line MSS CRC	DLT ORR	I	Terminated
AVETUX (NCT03174405)	FOLFOX/Cetuximab/Avelumab	PD-L1	First line CRC (MMR not spciefied)	PFS	II	Active, recruitment completed
BACCI (NCT02873195)	Capecitabine Bevacizumab/Atezolizumab vs Capecitabine/Bevacizumab	PD-L1	Pretreated metastatic CRC (MMR not spciefied)	PFS	II	Active, recruitment completed
NCT02860546	TAS-102/Nivolumab	PD-1	Pretreated metastatic MSS CRC	irORR	II	Completed
NCT03396926	Capecitabine/Bevacizumab/Pembrolizumab	PD-1	Pretreated metastatic MSS CRC	ORR	II	Active, recruiting
NCT02848443	TAS 102/Oxaliplatin/Nivolumab ± Bevacizumab	PD-1	Pretreated metastatic MSS CRC	Safety	I	Active, recruiting
CAVE Colon (Eudract 2017-004392-32)	Cetuximab/Avelumab	PD-L1	Pretreated metastatic CRC (MMR not spciefied)	OS	II	Active, recruiting

Ciardiello Cancer Treat Rev2019

Science. 2017 July 28; 357(6349): 409–413. doi:10.1126/science.aan6733.

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.

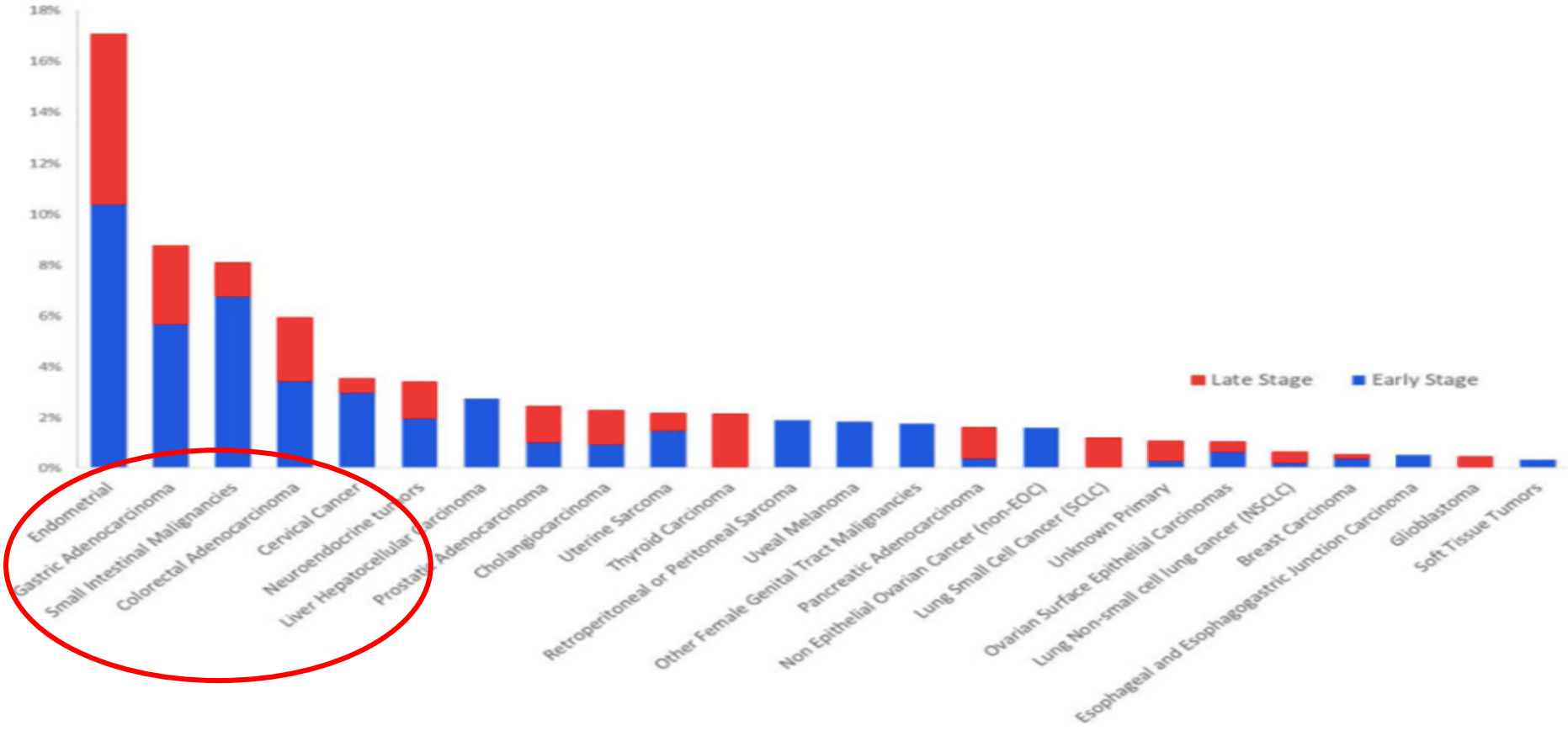

Fig. 3. Mismatch repair deficiency across 12,019 tumors

Le Science 2017

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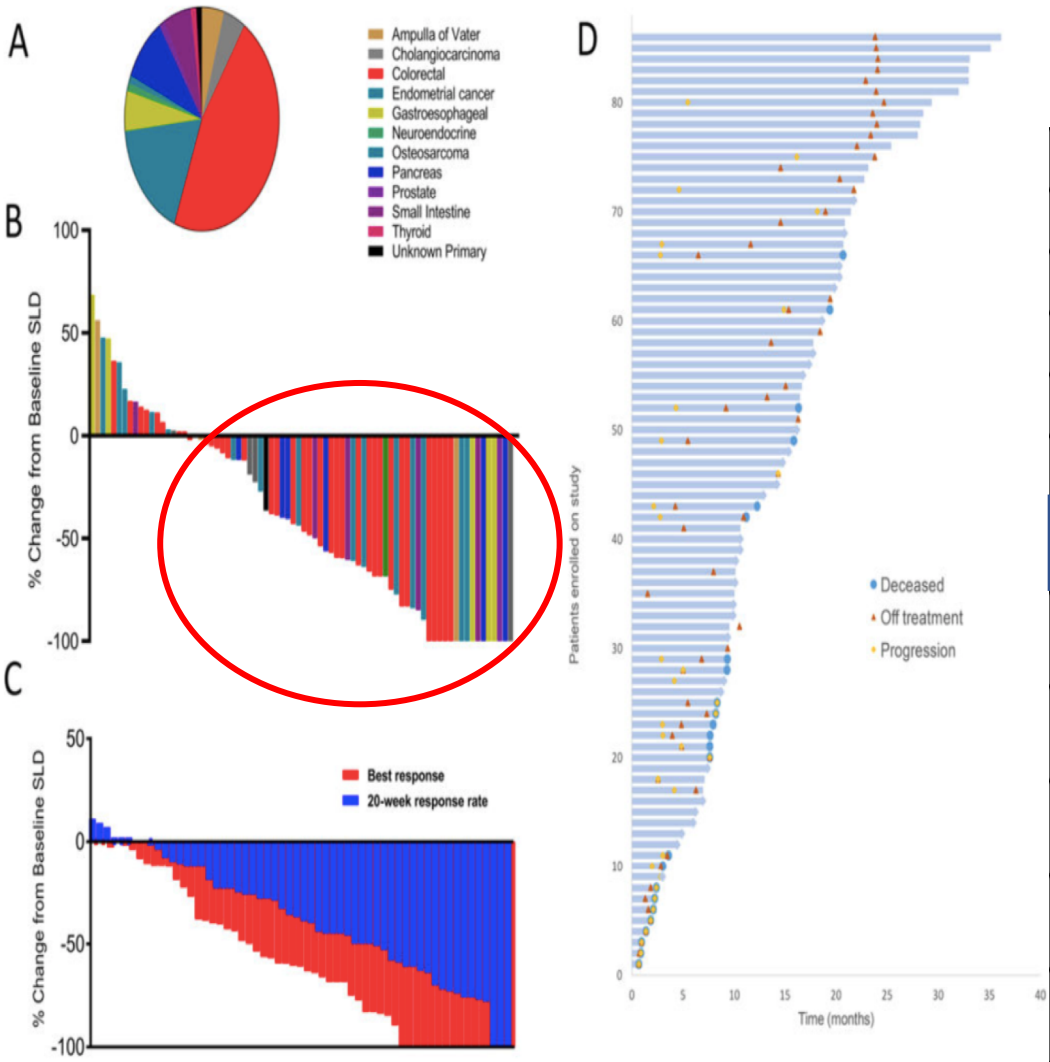

Type of response	Patients ($n = 86$)
Complete response	18 (21%)
Partial response	28 (33%)
Stable disease	20 (23%)
Progressive disease	12 (14%)
Not evaluable	8 (9%)
Objective response rate 95% CI	53% 42% to 64%
Disease control rate 95% CI	77% 66% to 85%
Median progression-free survival time 95% CI	NR 14.8 months to NR
2-year progression-free survival rate 95% CI	53% 42% to 68%
Median overall survival time 95% CI	NR NR to NR
2-year overall survival rate 95% CI	64% 53% to 78%

Le Science 2017

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The NEW ENGLAND JOURNAL of MEDICINE

Perspective

OCTOBER 12, 2017

First FDA Approval Agnostic of Cancer Site — When a Biomarker Defines the Indication

Steven Lemery, M.D., M.H.S., Patricia Keegan, M.D., and Richard Pazdur, M.D.

Pembrolizumab Response Rate by Tumor Type.*

Tumor Type	No. of Tumors	Patients with a Response	Range of Response Duration
		no. (%)	*mo*
Colorectal cancer	90	32 (36)	1.6+ to 22.7+
Endometrial cancer	14	5 (36)	4.2+ to 17.3+
Biliary cancer	11	3 (27)	11.6+ to 19.6+
Gastric or gastroesophageal junction	9	5 (56)	5.8+ to 22.1+
Pancreatic cancer	6	5 (83)	2.6+ to 9.2+
Small-intestine cancer	8	3 (38)	1.9+ to 9.1+
Breast cancer	2	2 (100)	7.6 to 15.9
Prostate cancer	2	1 (50)	9.8+
Other cancers	7	3 (43)	7.5+ to 18.2+

Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/ Mismatch Repair–Deficient Cancer: Results From the Phase II KEYNOTE-158 Study

Aurelien Marabelle, MD, PhD[1]; Dung T. Le, MD[2]; Paolo A. Ascierto, MD[3]; Anna Maria Di Giacomo, MD[4]; Ana De Jesus-Acosta, MD[2]; Jean-Pierre Delord, MD, PhD[5]; Ravit Geva, MD, MSc[6]; Maya Gottfried, MD[7]; Nicolas Penel, MD, PhD[8]; Aaron R. Hansen, MBBS[9]; Sarina A. Piha-Paul, MD[10]; Toshihiko Doi, MD, PhD[11]; Bo Gao, MBBS, PhD[12]; Hyun Cheol Chung, MD, PhD[13]; Jose Lopez-Martin, MD, PhD[14]; Yung-Jue Bang, MD, PhD[15]; Ronnie Shapira Frommer, MD[16]; Manisha Shah, MD[17]; Razi Ghori, PhD[18]; Andrew K. Joe, MD[18]; Scott K. Pruitt, MD, PhD[18]; and Luis A. Diaz Jr, MD[19]

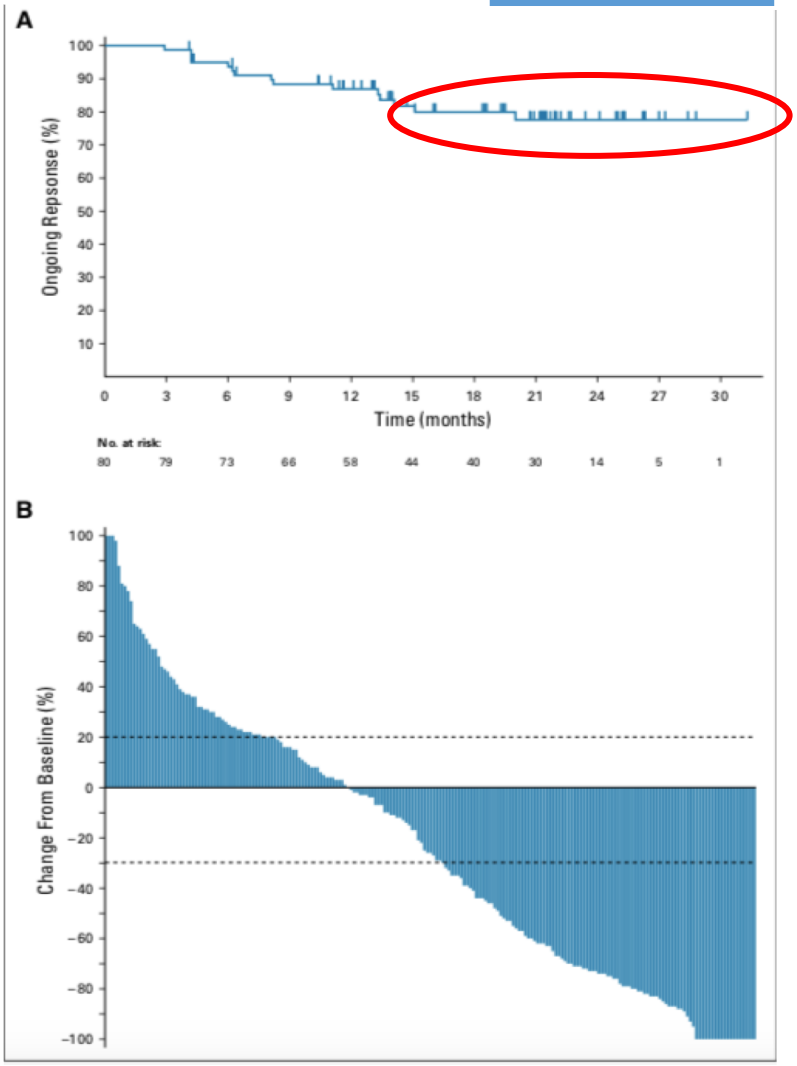
Prior lines of therapy for recurrent/ metastatic disease	
0*	7 (3.0)
1	87 (37.3)
2	61 (26.2)
3	41 (17.6)
≥ 4	37 (15.9)
Cancer type of primary diagnosis	
Endometrial	49 (21.0)
Gastric	24 (10.3)
Cholangiocarcinoma	22 (9.4)
Pancreatic	22 (9.4)
Small intestine	19 (8.2)
Ovarian	15 (6.4)
Brain	13 (5.6)
Sarcoma	9 (3.9)
Neuroendocrine tumor	7 (3.0)
Cervical	6 (2.6)
Prostate	6 (2.6)
Adrenocortical	5 (2.1)
Breast	5 (2.1)
Thyroid	5 (2.1)
Urothelial	5 (2.1)
Mesothelioma	4 (1.7)
Small-cell lung cancer	4 (1.7)
Renal	3 (1.3)
Salivary	2 (0.9)
Anal	1 (0.4)
Head and neck squamous cell carcinoma	1 (0.4)
Nasopharyngeal	1 (0.4)
Retroperitoneal	1 (0.4)
Testicular	1 (0.4)
Tonsil	1 (0.4)
Vaginal	1 (0.4)
Vulvar	1 (0.4)

Marabelle J Clin Oncol 2019

Keynote-158

TABLE 2. Best Overall Response per RECIST Version 1.1 by Independent Central Radiologic Review

Response	Evaluable Patients (N = 233)
Objective response	
No. (%; 95% CI)	80 (34.3; 28.3 to 40.8)
Median time to response, months (range)*	2.1 (1.3-10.6)
Median duration of response, months† (range)	NR (2.9-31.3+)
Best overall response, No. (%)	
Complete response	23 (9.9)
Partial response	57 (24.5)
Stable disease	42 (18.0)
Progressive disease	92 (39.5)
Nonevaluable	2 (0.9)
No assessment‡	17 (7.3)
Kaplan-Meier estimate of patients with extended duration of response, months†, No. (%)	
≥ 12	58 (86.9)
≥ 18	40 (79.9)
≥ 24	14 (77.6)

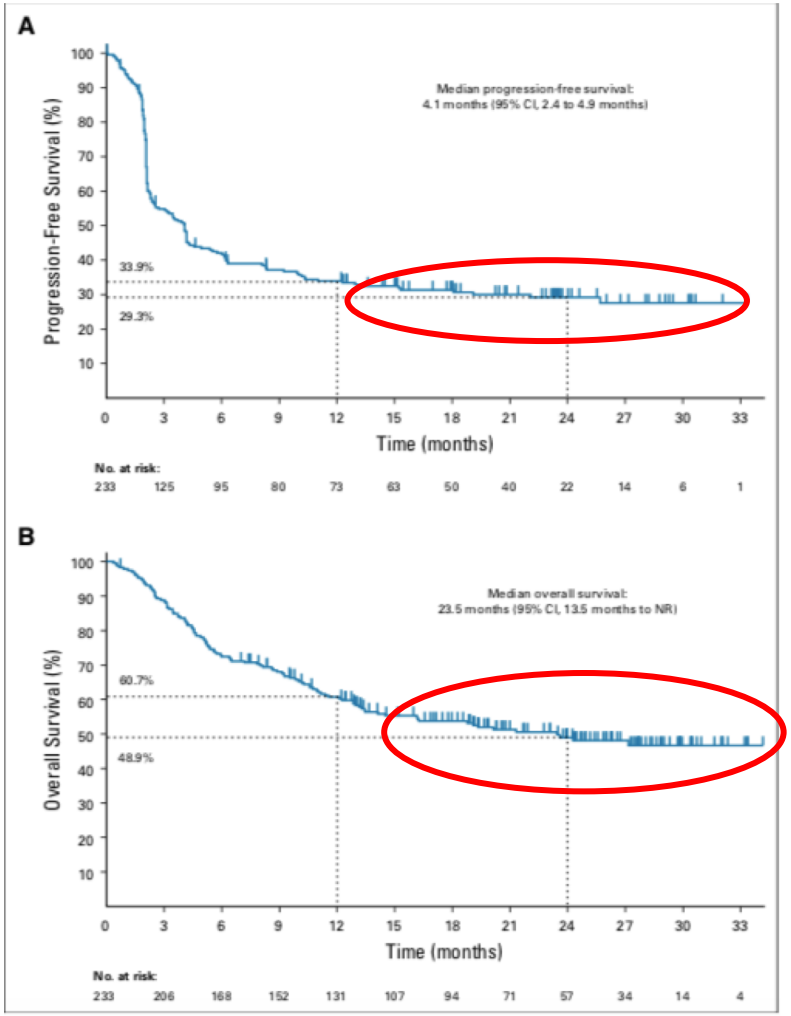


Marabelle J Clin Oncol 2019

Keynote-158

TABLE 3. Antitumor Activity for Tumor Types With Greatest Enrollment

Tumor Type	No.	CR, No.	PR, No.	ORR, % (95% CI)	Median PFS, Months (95% CI)	Median OS, Months (95% CI)	Median DOR, Months (range)
Endometrial	49	8	20	57.1 (42.2 to 71.2)	25.7 (4.9 to NR)	NR (27.2 to NR)	NR (2.9 to 27.0+)
Gastric	24	4	7	45.8 (25.6 to 67.2)	11.0 (2.1 to NR)	NR (7.2 to NR)	NR (6.3 to 28.4+)
Cholangiocarcinoma	22	2	7	40.9 (20.7 to 63.6)	4.2 (2.1 to NR)	24.3 (6.5 to NR)	NR (4.1+ to 24.9+)
Pancreatic	22	1	3	18.2 (5.2 to 40.3)	2.1 (1.9 to 3.4)	4.0 (2.1 to 9.8)	13.4 (8.1 to 16.0+)
Small intestine	19	3	5	42.1 (20.3 to 66.5)	9.2 (2.3 to NR)	NR (10.6 to NR)	NR (4.3+ to 31.3+)
Ovarian	15	3	2	33.3 (11.8 to 61.6)	2.3 (1.9 to 6.2)	NR (3.8 to NR)	NR (4.2 to 20.7+)
Brain	13	0	0	0.0 (0.0 to 24.7)	1.1 (0.7 to 2.1)	5.6 (1.5 to 16.2)	-



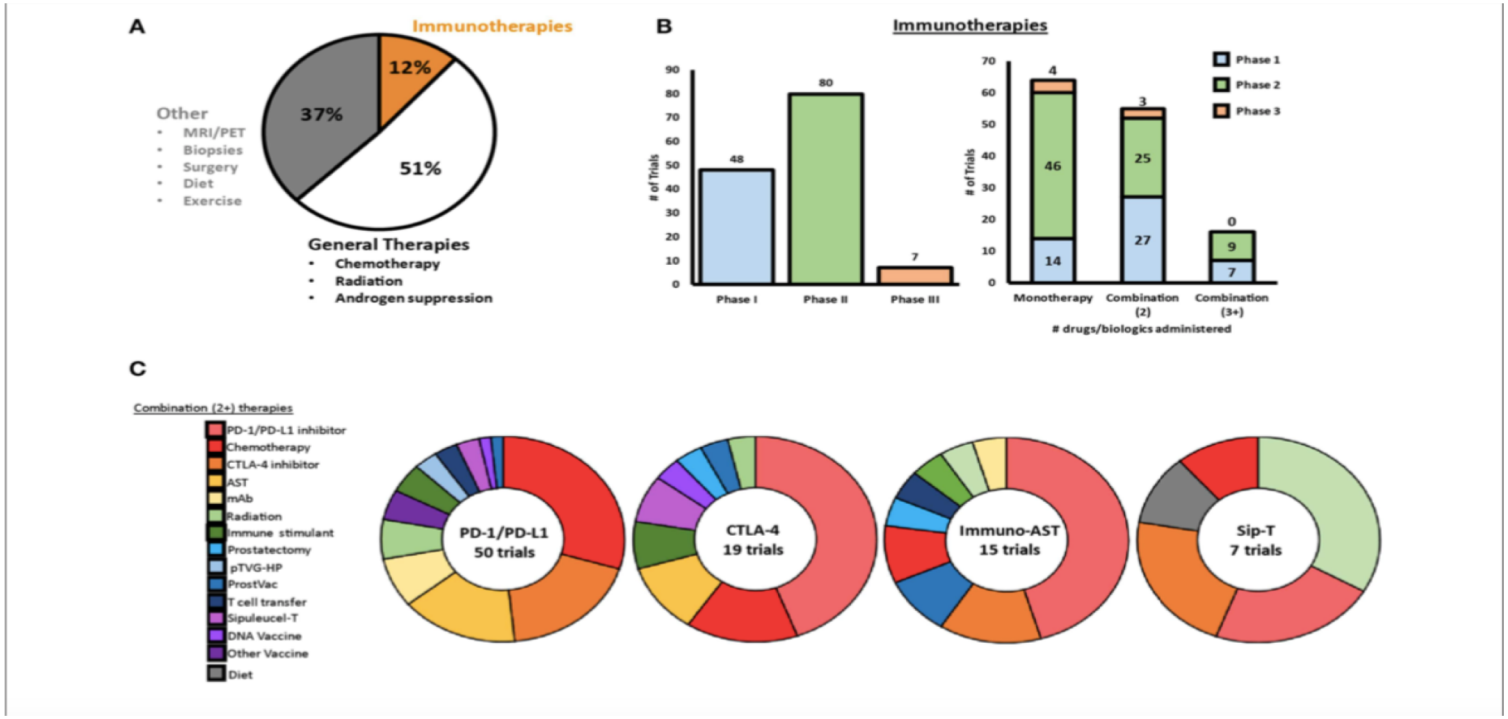
Marabelle J Clin Oncol 2019

frontiers in Oncology

REVIEW
published: 11 September 2019
doi: 10.3389/fonc.2019.00884

Past, Current, and Future of Immunotherapies for Prostate Cancer

*Adeline N. Boettcher[1], Ahmed Usman[2], Alicia Morgans[2], David J. VanderWeele[2], Jeffrey Sosman[2] and Jennifer D. Wu[1,3]**



Boettcher Front Oncol 2019

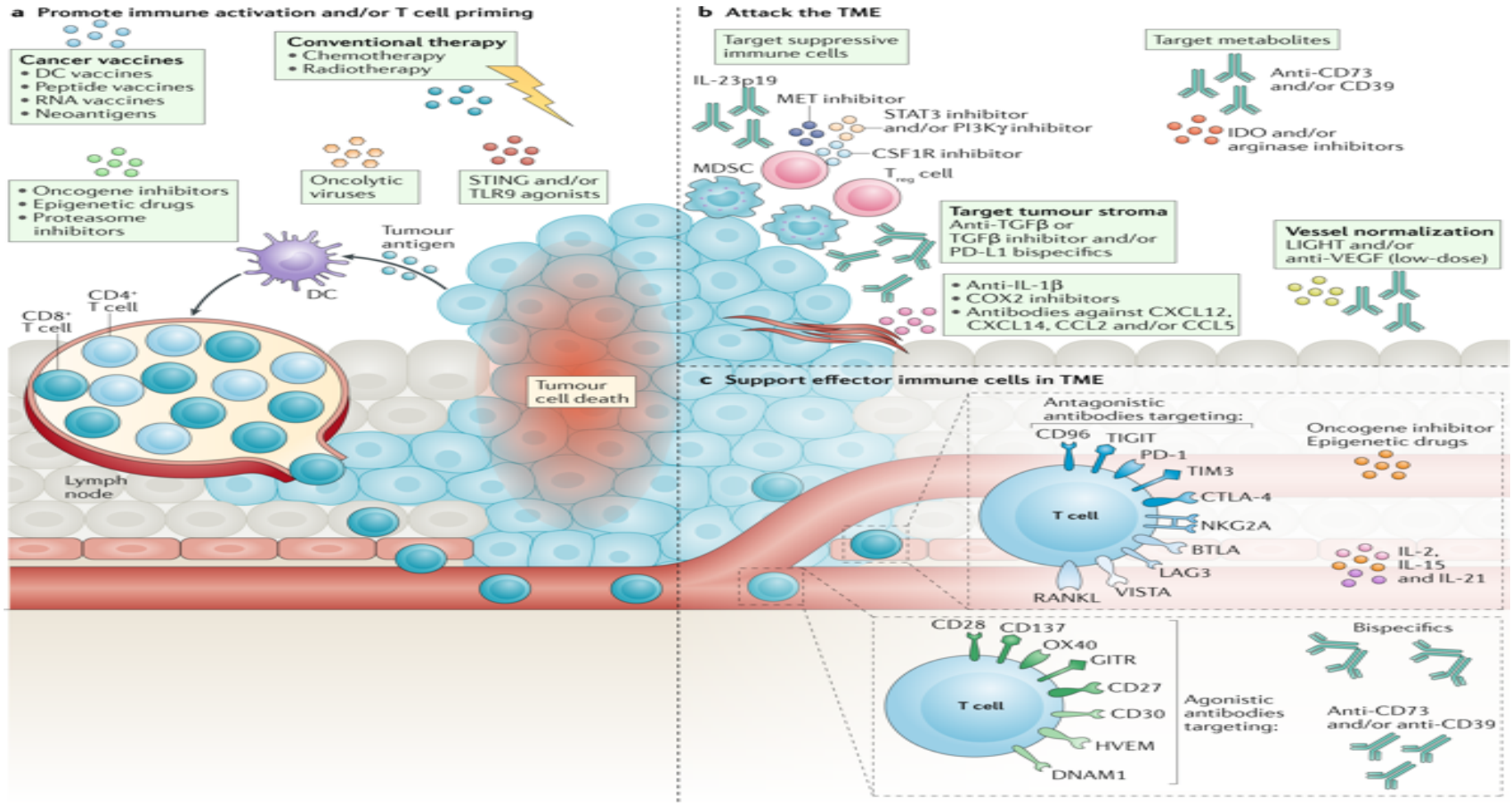
4. Clinical Research Examining Checkpoint Inhibitors for Cervical Cancer

Since 2015, clinical trials on various checkpoint inhibitors have been conducted for cervical cancer.

4.1. PD-1/PD-l1 Inhibitor

KEYNOTE-028 (phase Ib study) and KEYNOTE-158 (phase II study), which investigated pembrolizumab in recurrent and unresectable cervical cancers, were conducted. In KEYNOTE-028, pembrolizumab 10 mg/kg was given every 2 weeks. Twenty-four patients participated, and the overall response rate (ORR) was 17%, 6-month progression-free survival (PFS) was 13%, and 6-month OS was 66.7%. Moreover, Grade 4 adverse events were not observed [21]. Based on these results, KEYNOTE-158 was conducted. In KEYNOTE-158, pembrolizumab 200 mg/kg was given every 3 weeks. The ORR was 12.2%. Clinical response was observed only in PD-L1 positive cases. The drug effects were dependent of PD-L1 expression in this population [22]. Based on these results, the FDA approved pembrolizumab with PD-L1 IHC 22C3 PharmDx as a companion diagnostic in recurrent and unresectable advanced cervical cancer in June 2018. Moreover, CheckMate 358 (phase I–II study) using nivolumab was conducted. In this trial, nivolumab 240 mg/kg was given every 2 weeks in virus-related tumors, including cervical cancer. The ORR was 26.3%, and the disease control rate was 70.8%. For adverse events, Grade 3/4 hyponatremia and diarrhea were observed [23]. Based on the results of these studies, pembrolizumab and nivolumab appeared useful in recurrent and unresectable advanced cervical cancers, though a longer observation period is necessary in the future. (Table 1)

Key targets for immunotherapy



O´Donnell Nature 2019

CONCLUSIONS & FUTURE PROSPECTS

ICI activity in frequent tumors (not melanoma, NSCLC, etc) seems restricted to certain subpopulations

Breast cancer: TNBC, TILS, PD-L1 IC+ by SP142 IC_A

BRCA tumors might be more immunogenic and suitable for ICI

Gastrointestinal tumors and miscellanea: MSI/MMR+ (agnostic of cancer site)

Prostate and cervical cancer, limited activity of ICI as single Tx

Many biomarkers under intense scrutiny (TMB, gene signatures…)

Hundreds of clinical trials using combos (intralesional therapies, radiotherapy, targeted therapies, vaccines…) searching the Achilles heel for every single tumor