At Long Last: Immunologic Approaches to Treatment of GI Cancers

Richard M. Goldberg MD
Director, WVU Cancer Institute

Disclosures

- Funded research:
  - Bayer
  - Merck
  - Sanofi
- Consulting and lectures:
  - Merck
  - Merck KGA
  - Taiho

Pretest

- Which molecular marker(s) are essential to determine whether a patient should be treated with a PD-1 inhibitor?
  1. IHC staining for PD-1 expression on tumor cells
  2. IHC staining for PD-1 expression on tumor infiltrating lymphocytes
  3. IHC staining for mismatch repair proteins on tumor cells
  4. Both 2 and 3
  5. All of the above

Pretest

- Treatment with a PD-1 inhibitor has been associated with each of the following toxicities except:

1. Cardiomyopathy
2. Neutropenia
3. Hypothyroidism
4. New onset diabetes
5. Nausea, vomiting and diarrhea

Pretest

- Treatment with a PD-1 Inhibitor has led to responses in which of the following tumor types:

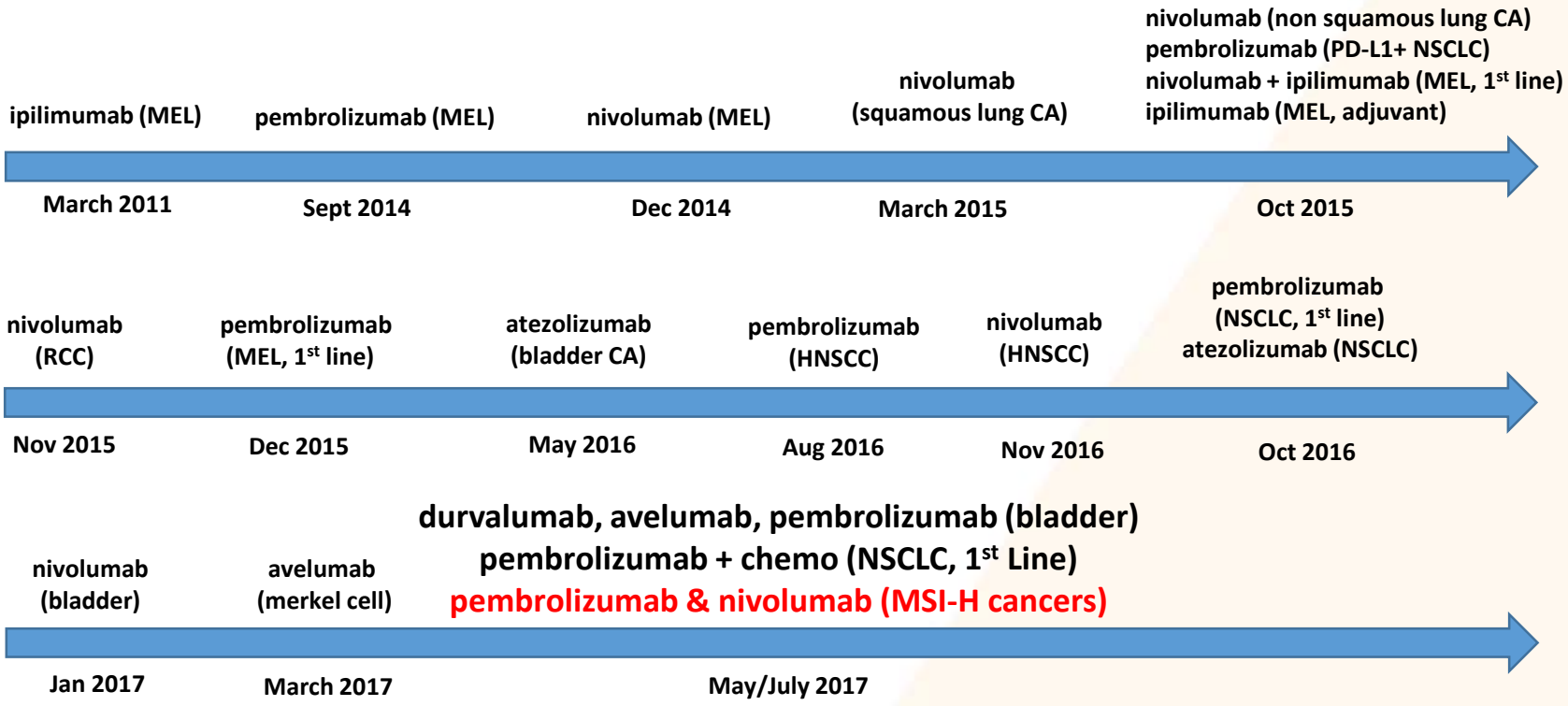
1. Colorectal cancer
2. Pancreatic cancer
3. Sarcomas
4. Anal cancers
5. All of the above

Today's Topics

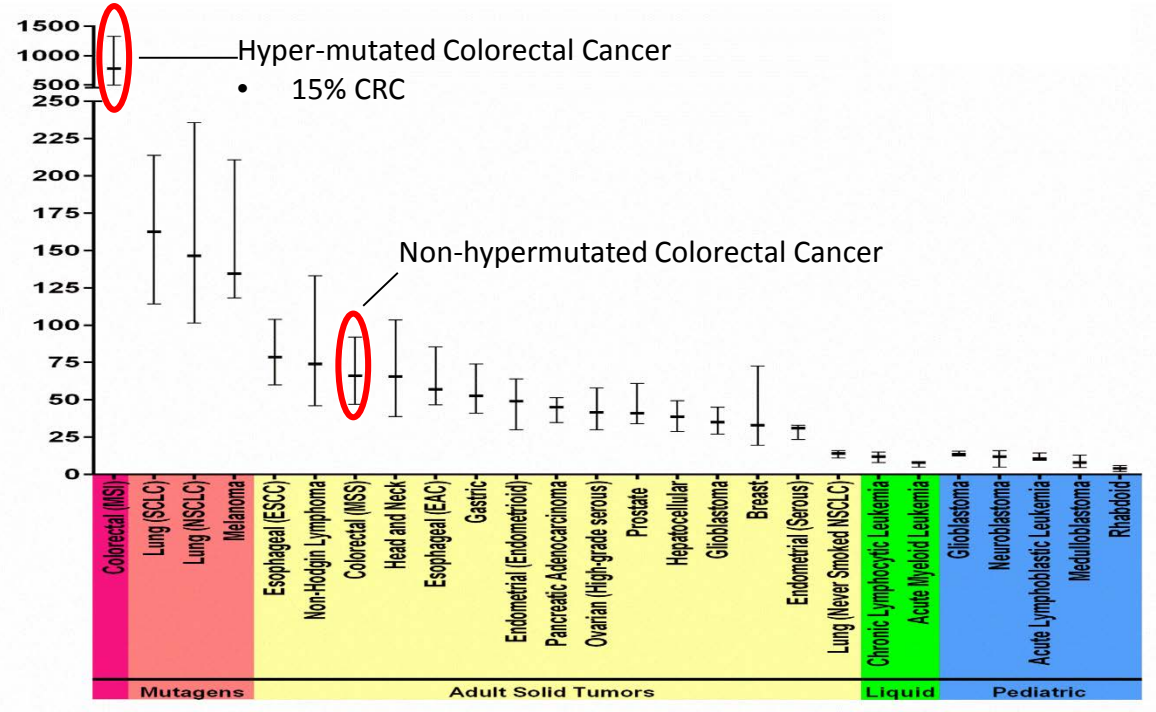
- Background
- Gastric Cancer
- Colorectal Cancer
- MSI-H tumors regardless of histology & site of origin
- MSS tumors
- Anal Cancer
- Next steps

The Hottest Area in Cancer Drug Development

FDA Approvals Timeline for Immuno-Oncology Agents for Solid Tumors



Mutational Burden



Courtesy: Luis Diaz

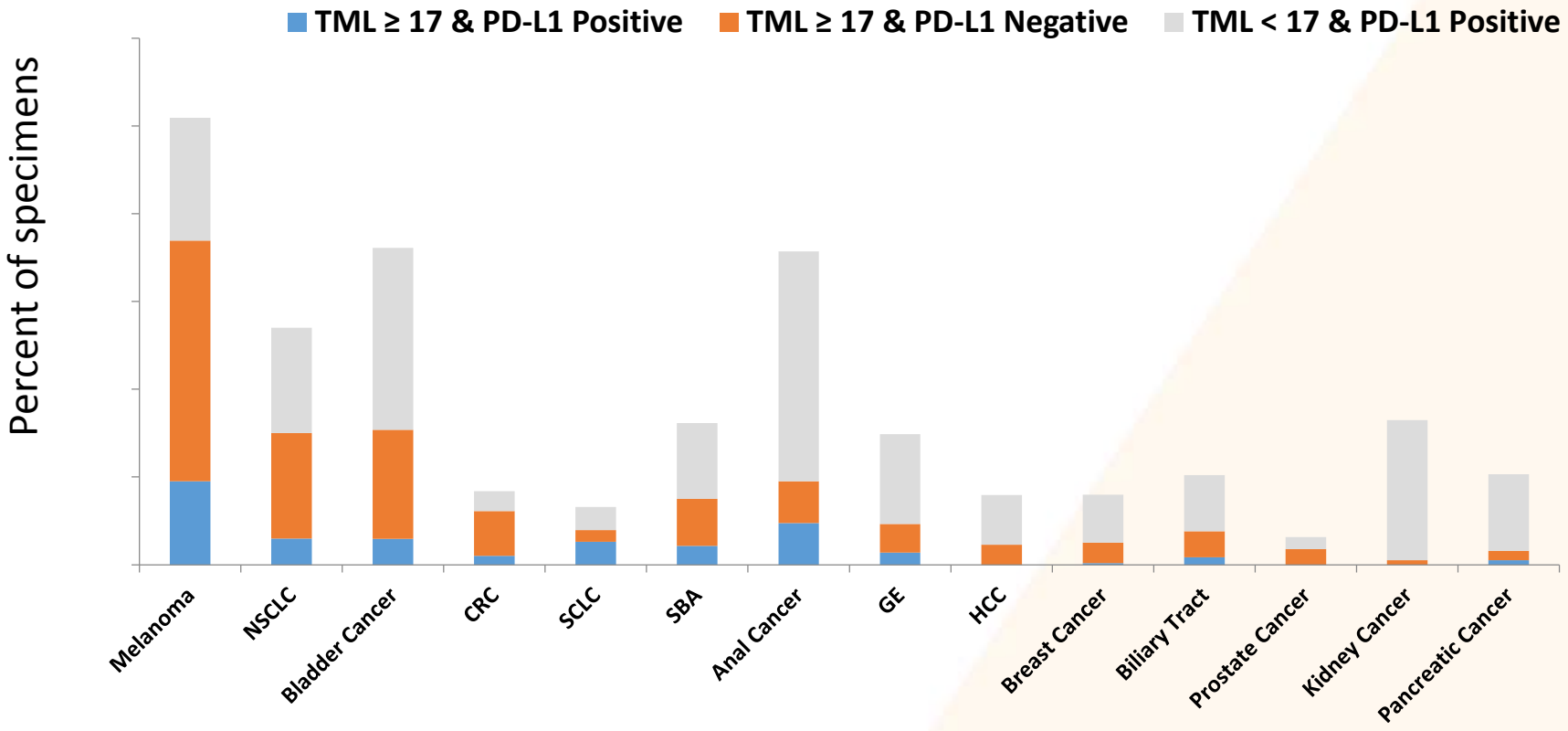
Characterization of Tumor Mutation Load (TML) in Solid Tumors

[1]Mohamed E. Salem, [2]Joanne Xiu, [3]Heinz-Josef Lenz, [1]Michael B. Atkins, [4]Philip Agop Philip, [5]Jimmy J. Hwang, [2]Zoran Gatalica, [2]Nianqing Xiao, [1]Geoffrey Thomas Gibney, [6]Wafik S. ElDeiry, [5]Antoinette R. Tan, [5]Edward S. Kim, [4]Anthony Frank Shields, [5]Derek Raghavan, and [1]John Marshall

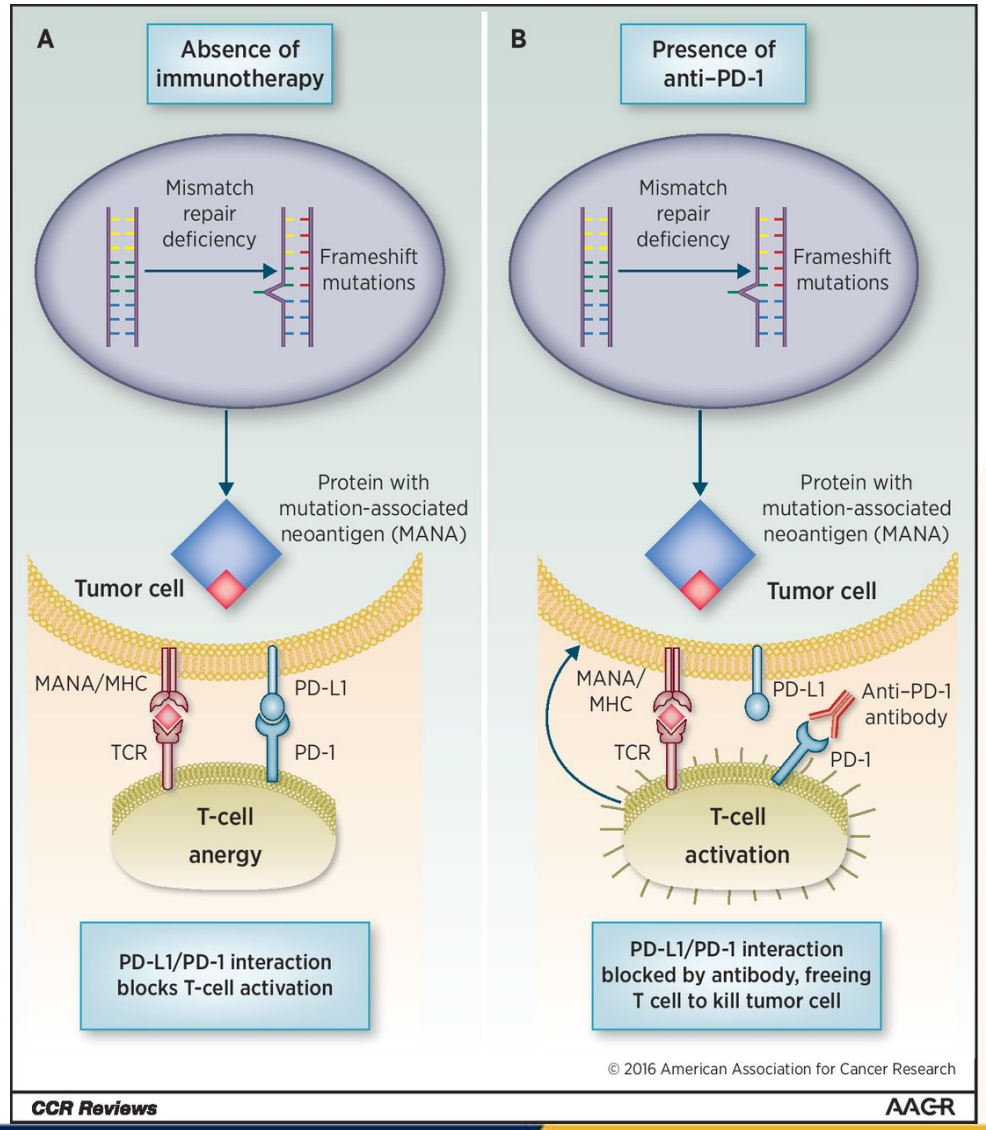
[1]Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC • [2]Caris Life Sciences, Phoenix, AZ • [3]USC Norris Comprehensive Cancer Center, Los Angeles, CA • [4]Karmanos Cancer Institute, Detroit, MI • [5]Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC • [6]Fox Chase Cancer Center, Philadelphia, PA

In Collaboration with Caris

Combination of TML and PD-L1 expression

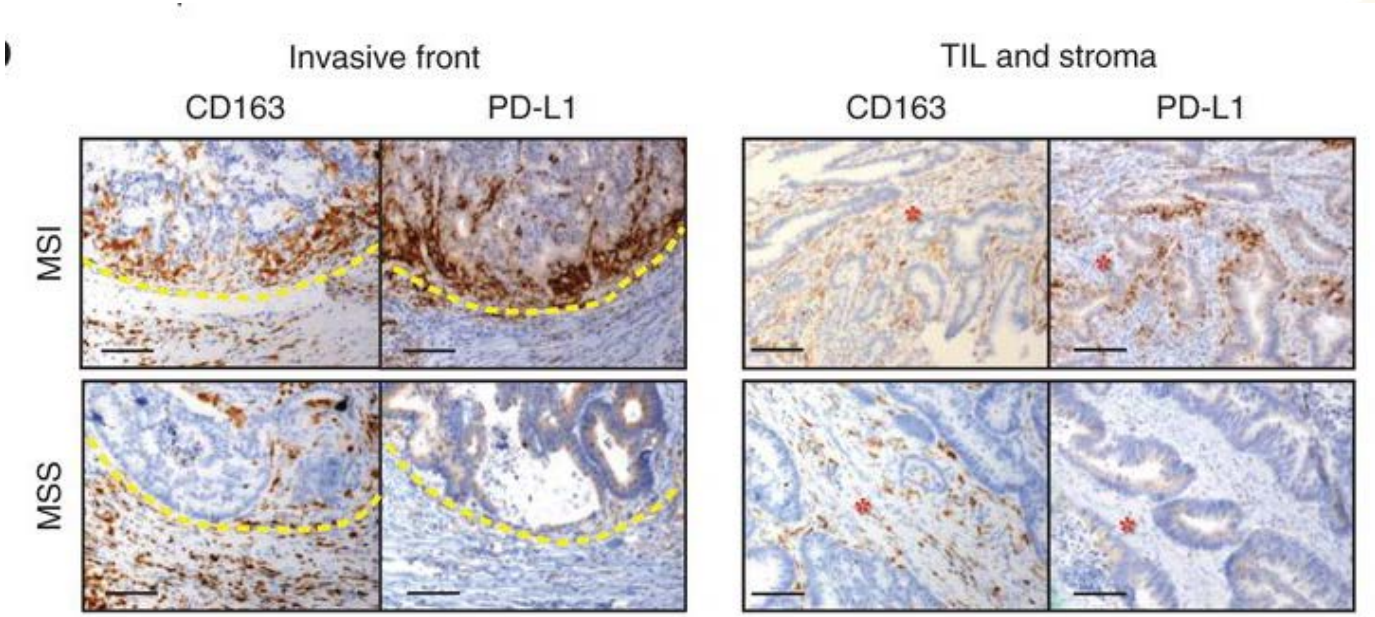


Neoantigens



Jonathan C. Dudley et al.
Clin Cancer Res 2016;22:813-820

PD-L1+ Tumor Infiltrating Myeloid Cells



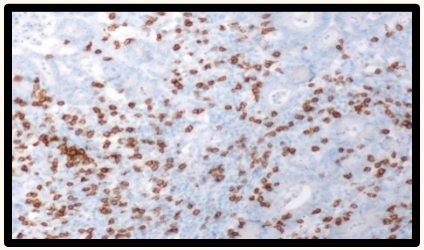
Cd163: myeloid cells

Nicolas J. Llosa et al. Cancer Discovery 2015;5:43-51

Microsatellite High (MSI-H, dMMR)
Cancers That Have a High Mutational Burden

- Missing proteins that repair DNA replication errors: MSH2, MSH6, MLH1, PMS2.
- dMMR tumors are infiltrated with T cells
- dMMR/MSI-H cancers harbor thousands of mutations (hypermutated phenotype).
- Mutations encode proteins that can become immune system targets: aka mismatch-associate neoantigens or MANAs.

Regardless of tumor histology



ACA with CD8 T Cells

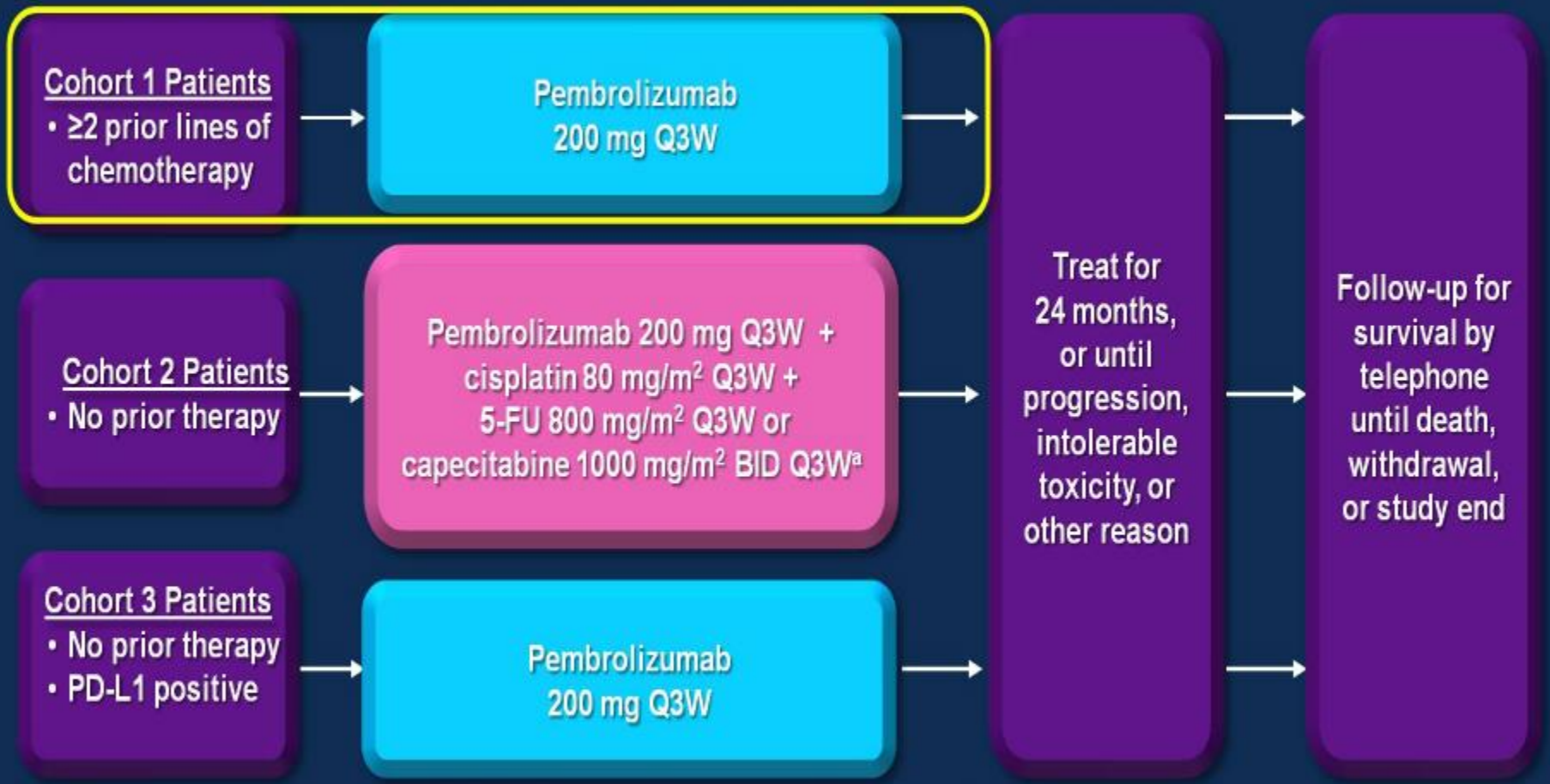
KEYNOTE-059 Cohort 1: Efficacy and Safety of Pembrolizumab Monotherapy in Patients With Previously Treated Advanced Gastric Cancer

Charles S. Fuchs,[1] Toshihiko Doi,[2] Raymond WJ Jang,[3] Kei Muro,[4] Taroh Satoh,[5] Manuela Machado,[6] Weijing Sun,[7] Shadia I. Jalal,[8] Manish Shah,[9] Jean-Phillipe Metges,[10] Marcelo Garrido,[11] Talia Golan,[12] Mario Mandala,[13] Zev A. Wainberg,[14] Daniel V.T. Catenacci,[15] Yung-Jue Bang,[16] Jared Lunceford,[17] Mary Savage,[17] Jiangdian Wang,[17] Minori Koshiji,[17] Rita P. Dalal,[17] Harry H. Yoon[18]

[1]Yale Cancer Center, New Haven, CT, USA; [2]National Cancer Center East; Chiba, Kashiwa, Japan; [3]Princess Margaret Cancer Center, Toronto, ON, Canada; [4]Aichi Cancer Center Hospital, Nagoya, Aichi, Japan; [5]Graduate School of Medicine, Osaka University, Suita, Osaka, Japan; [6]Portuguese Institute of Oncology, Porto, Portugal; [7]University of Pittsburgh, Pittsburgh, PA, USA; [8]Indiana University School of Medicine, Indianapolis, IN, USA; [9]Weill Cornell Medical College, New York Presbyterian Hospital, New York, NY, USA; [10]Centre Hospitalier Regional Universitaire (CHRU) de Brest - Hopital Morvan, Brest, CEDEX, France; [11]Pontificia Universidad Católica de Chile, Santiago, Chile; [12]Sheba Medical Center at Tel Hashomer, Ramat Gan, Israel; [13]ASST Papa Giovanni XXIII, Bergamo, Italy; [14]Ronald Reagan UCLA Medical Center, Los Angeles, CA, USA; [15]University of Chicago Medicine, Chicago, IL, USA; [16]Seoul National University Hospital, Seoul, South Korea; [17]Merck & Co., Inc., Kenilworth, NJ; [18]Mayo Clinic, Rochester, MN, USA

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

KEYNOTE-059 (NCT02335411): Phase 2 Multicohort Study of Pembrolizumab for G/GEJ Adenocarcinoma



Response assessment by RECIST v1.1: first scan at 9 weeks after cycle 1, every 6 weeks for first year, followed by every 9 weeks

[a]Capecitabine was administered *only in* Japan

Baseline Disease Characteristics

Characteristic, n (%)	N = 259
ECOG PS	
0	107 (41.3)
1	151 (58.3)
Location of primary tumor	
Gastric	125 (48.3)
GEJ	133 (51.4)
Number of prior therapies	
2	134 (51.7)
3	75 (29.0)
≥4	50 (19.3)

Response in All Patients

Response[a]	N = 259	
	%	95% CI
ORR (CR + PR)	11.6	8.0-16.1
CR	2.3	0.9-5.0
PR	9.3	6.0-13.5
SD	16.2	11.9-21.3
PD	56.0	49.7-62.1
DCR[b]	27.0	21.7-32.9

- Median (range) follow-up: 5.8 months (0.5-21.6)

[a]Only confirmed responses were included
[b]CR + PR + SD≥2 months
Data cutoff: January 16, 2017

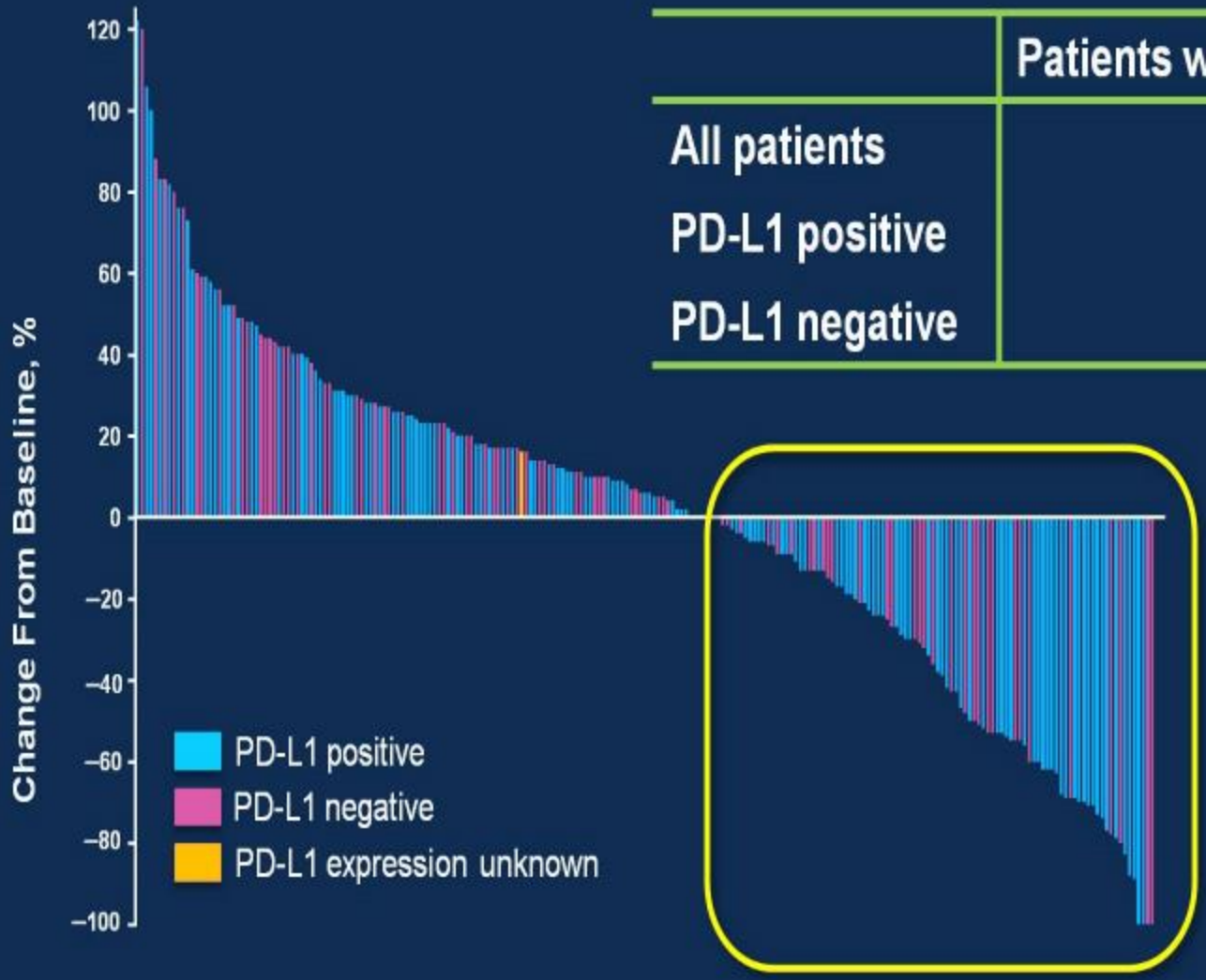
Response by PD-L1 Expression

Response[a]	PD-L1 Positive (n = 148)		PD-L1 Negative (n = 109)	
	%	95% CI	%	95% CI
ORR	15.5	10.1-22.4	6.4	2.6-12.8
CR	2.0	0.4-5.8	2.8	0.6-7.8
PR	13.5	8.5-20.1	3.7	1.0-9.1
DCR[b]	33.1	25.6-41.3	19.3	12.3-27.9

[a]Only confirmed responses were included
[b]CR + PR + SD≥2 months
Data cutoff: January 16, 2017

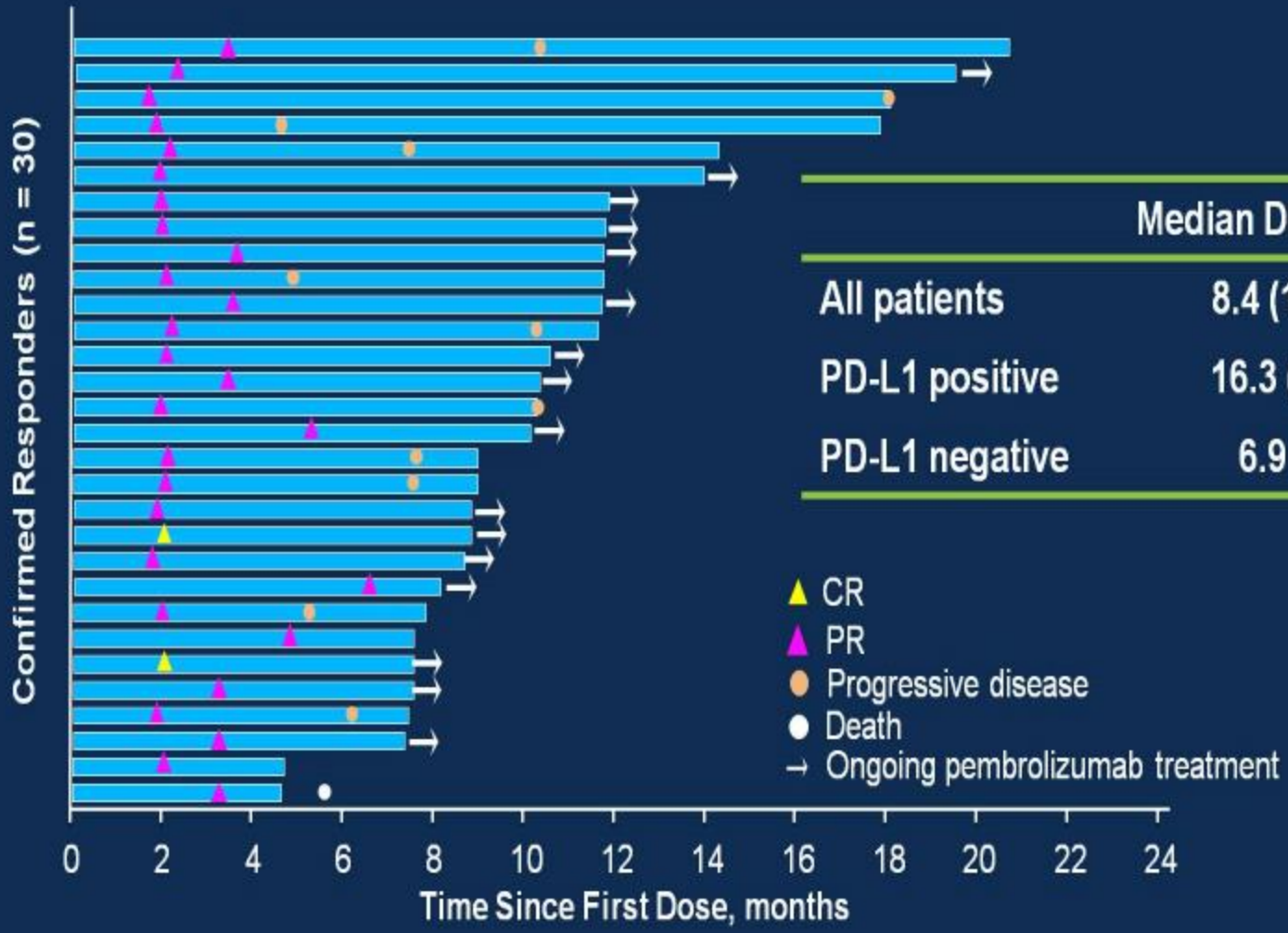
Maximum Percentage Change From Baseline in Target Lesion Size[a]

	Patients with reduction, %
All patients	42.4
PD-L1 positive	47.3
PD-L1 negative	36.3



[a]Only patients with measurable disease per RECIST v1.1 by central review at baseline who had ≥1 postbaseline assessment were included (n = 223)
Data cutoff: January 16, 2017

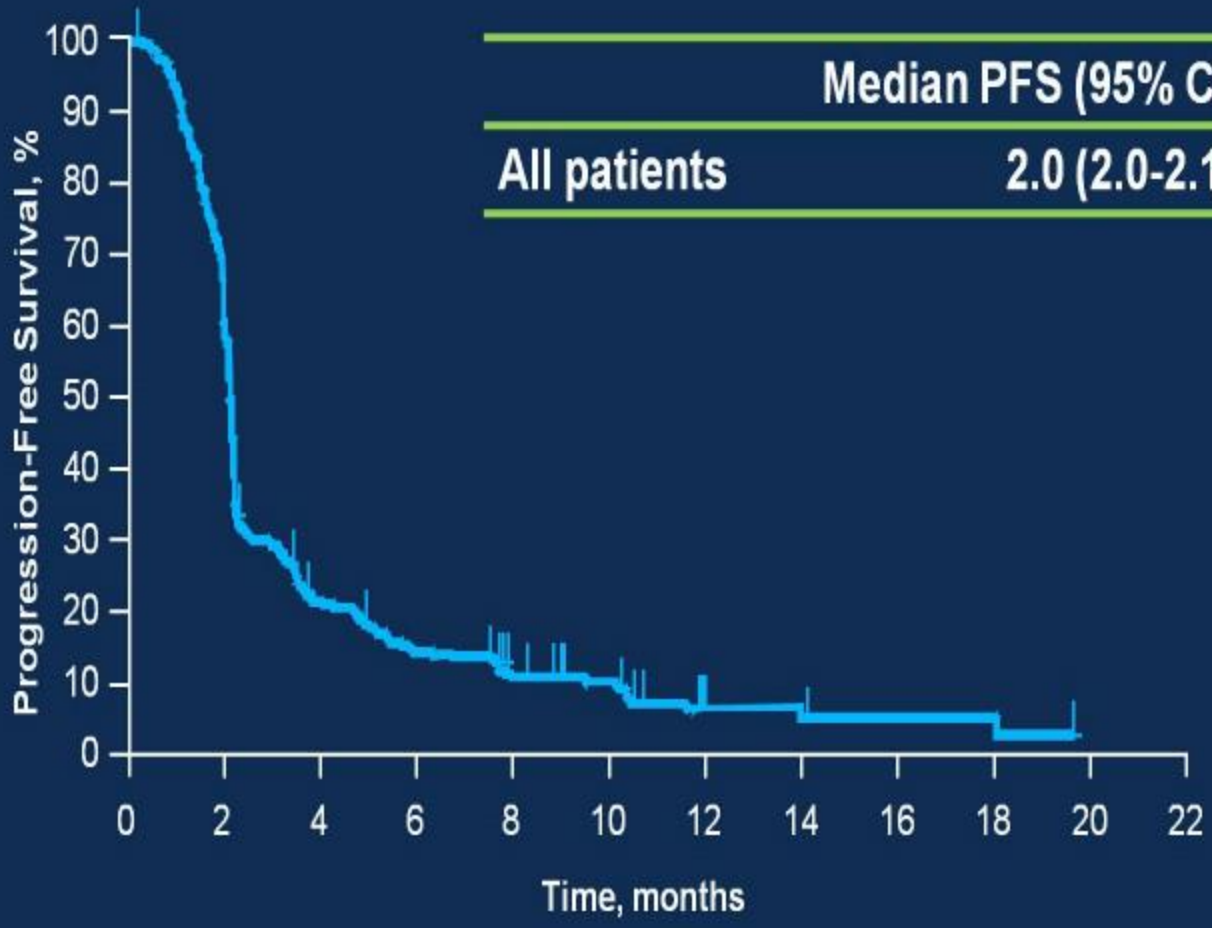
Treatment Exposure[a] and Duration of Response



	Median DOR (95% CI), mos
All patients	8.4 (1.6+[b] to 17.3+)
PD-L1 positive	16.3 (1.6+ to 17.3+)
PD-L1 negative	6.9 (2.4 to 7.0+)

[a]Patients with measurable disease per RECIST v1.1 by central review at baseline who had ≥1 postbaseline assessment (n = 30). Bar length indicates time to last imaging assessment.
[b]No progressive disease at last disease assessment. Data cutoff: January 16, 2017.

PFS in All Patients



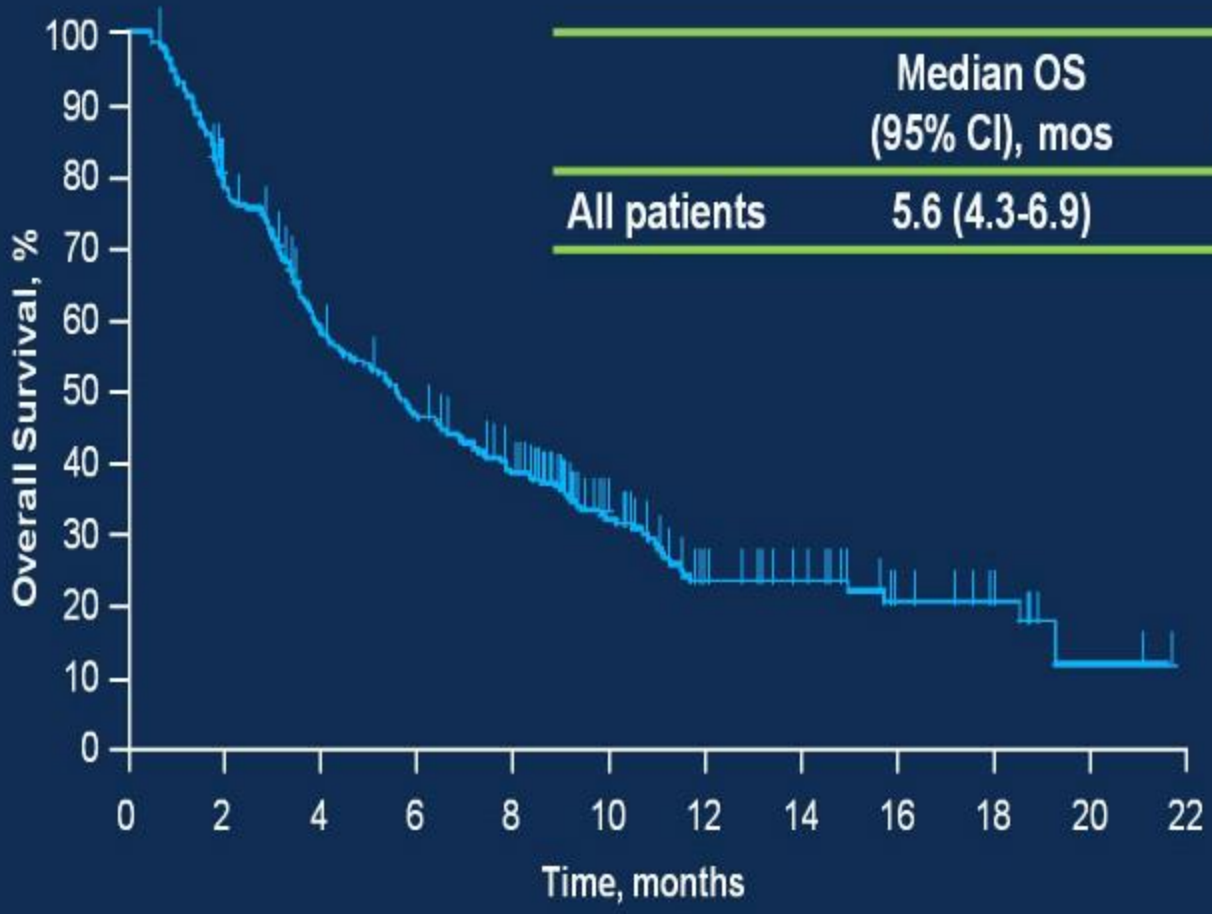
	Median PFS (95% CI), months
All patients	2.0 (2.0-2.1)

Numbers at risk

259	136	51	34	22	17	4	2	2	2	0	0

Data cutoff: January 16, 2017

OS in All Patients



	Median OS (95% CI), mos	12-month OS rate, %
All patients	5.6 (4.3-6.9)	23.4

Numbers at risk

259	199	144	112	87	51	27	22	12	7	2	0

Response by MSI Status (n = 174)

4.0% of patients were MSI-High

Response[a]	MSI-High (n = 7)		Non–MSI-High (n = 167)	
	%	95% CI	%	95% CI
ORR	57.1	18.4-90.1	9.0	5.1-14.4
CR	14.3	0.4-57.9	2.4	0.7-6.0
PR	42.9	9.9-81.6	6.6	3.3-11.5
DCR[b]	71.4	29.0-96.3	22.2	16.1-29.2

[a]Only confirmed responses were included
[b]CR + PR + SD≥2 months
Data cutoff: January 16, 2017

Nivolumab ± Ipilimumab in Patients With Advanced/Metastatic Chemotherapy-Refractory Gastric, Esophageal, or Gastroesophageal Junction Cancer: CheckMate 032 Study

Yelena Y. Janjigian,[1] Patrick A. Ott,[2] Emiliano Calvo,[3] Joseph W. Kim,[4] Paolo A. Ascierto,[5] Padmanee Sharma,[6] Katriina Peltola,[7] Dirk Jaeger,[8] Jeffrey Evans,[9] Filippo de Braud,[10] Ian Chau,[11] Marina Tschaika,[12] Christopher T. Harbison,[12] Weiguo Cai,[12] Johanna Bendell,[13] Dung T. Le[14]

[1]Gastrointestinal Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; [2]Dana-Farber Cancer Institute, Boston, MA; [3]START Madrid, Centro Integral Oncológico Clara Campal, Madrid, Spain; [4]Yale Cancer Center, New Haven, CT; [5]Istituto Nazionale Tumori IRCCS, Naples, Italy; [6]The University of Texas MD Anderson Cancer Center, Houston, TX; [7]Comprehensive Cancer Center, Helsinki University Hospital, Helsinki, Finland; [8]National Center for Tumor Diseases, University Hospitals Heidelberg, Heidelberg, Germany; [9]Beatson West of Scotland Cancer Centre, University of Glasgow, Glasgow, UK; [10]Fondazione IRCCS Istituto Tumori Milano, University of Milan, Milan, Italy; [11]Royal Marsden Hospital, London and Surrey, UK; [12]Bristol-Myers Squibb, Princeton, NJ; [13]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; [14]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD

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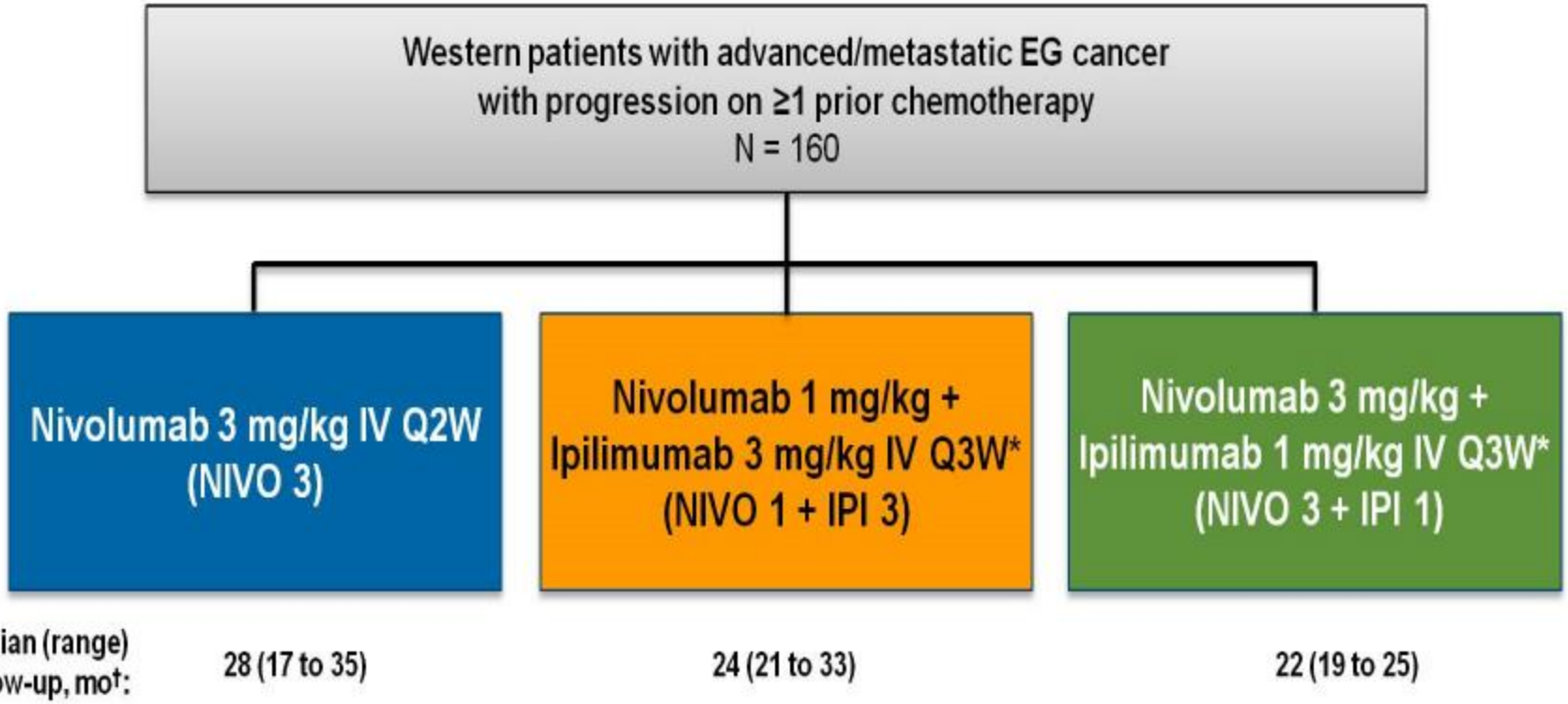
Checkmate 032 EG Cohort



DOR, duration of response; EG, esophagogastric (including gastric/esophageal/gastroesophageal junction cancer); TTR, time to response.

* Nivolumab + ipilimumab administered for 4 cycles followed by nivolumab 3 mg/kg IV Q2W.

† Time from first dose to data cut-off; follow-up was shorter for patients who died prior to data cut-off.

Baseline Characteristics

Patients, n (%)	NIVO 3 n = 59	NIVO 1 + IPI 3 n = 49	NIVO 3 + IPI 1 n = 52
Age, median (range), years	60 (29 to 80)	53 (27 to 77)	58 (19 to 81)
≥65 years	17 (29)	10 (20)	17 (33)
Male	45 (76)	34 (69)	45 (87)
Race			
White	56 (95)	46 (94)	50 (96)
Black	3 (5)	1 (2)	1 (2)
Asian/other	0	2 (4)	1 (2)
Primary site			
Gastric	19 (32)	22 (45)	18 (35)
GEJ/esophageal	40 (68)	27 (55)	34 (65)
Number of prior regimens			
0	0	1 (2)	0
1	10 (17)	6 (12)	16 (31)
2	**20 (34)**	**19 (39)**	**16 (31)**
3	**19 (32)**	**11 (22)**	**13 (25)**
>3	**10 (17)**	**12 (24)**	**7 (13)**
PD-L1 tumor expression, n/N (%)*			
≥1%	16/42 (38)	10/42 (24)	13/43 (30)
<1%	**26/42 (62)**	**32/42 (76)**	**30/43 (70)**

* PD-L1 tumor expression rates reported according to the number of patients with quantifiable samples. PD-L1 was quantifiable in 71%, 86%, and 83% of patients in the NIVO 3, NIVO 1 + IPI 3, and NIVO 3 + IPI 1 treatment groups, respectively.

Objective Response

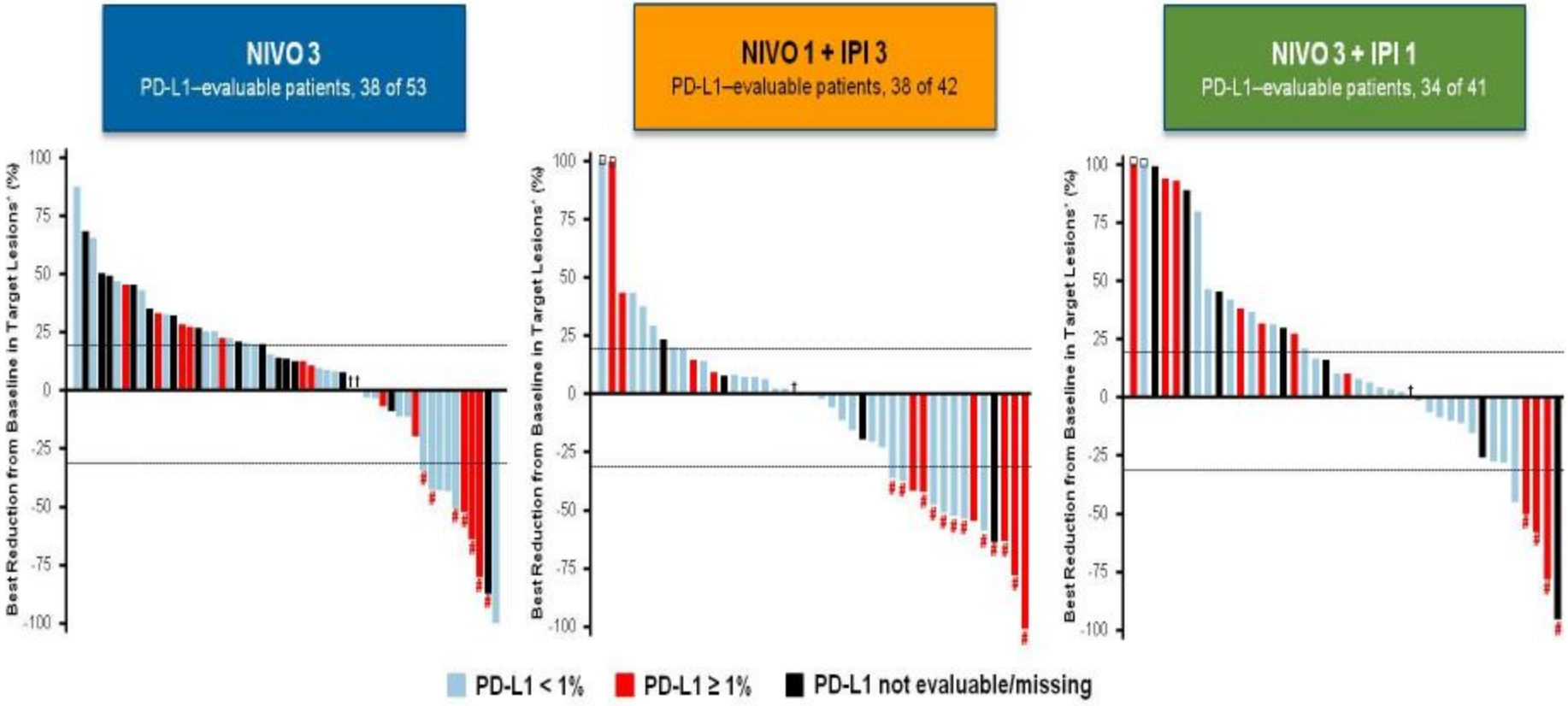
	NIVO 3 n = 59	NIVO 1 + IPI 3 n = 49	NIVO 3 + IPI 1 n = 52
ORR, n (%)*	**7 (12)**	**12 (24)**	**4 (8)**
[95% CI]	[5, 23]	[13, 39]	[2, 19]
BOR, n (%)*			
Complete response	1 (2)	1 (2)	0
Partial response	6 (10)	11 (22)	4 (8)
Stable disease	12 (20)	8 (16)	15 (29)
Progressive disease	34 (58)	23 (47)	24 (46)
Not evaluable	6 (10)	6 (12)	9 (17)
DCR, n (%)†	19 (32)	20 (41)	19 (37)
Median TTR (range), months	1.6 (1.2 to 4.0)	2.7 (1.2 to 14.5)	2.6 (1.3 to 2.8)
Median DOR (95% CI), months	7.1 (3.0, 13.2)	7.9 (2.8, NE)	NR (2.5, NE)

BOR, best objective response; DCR, disease control rate; NR, not reached, NE, not estimable.

* Investigator review.

† Patients with a BOR of complete response, partial response, or stable disease.

Best Reduction in Target Lesions



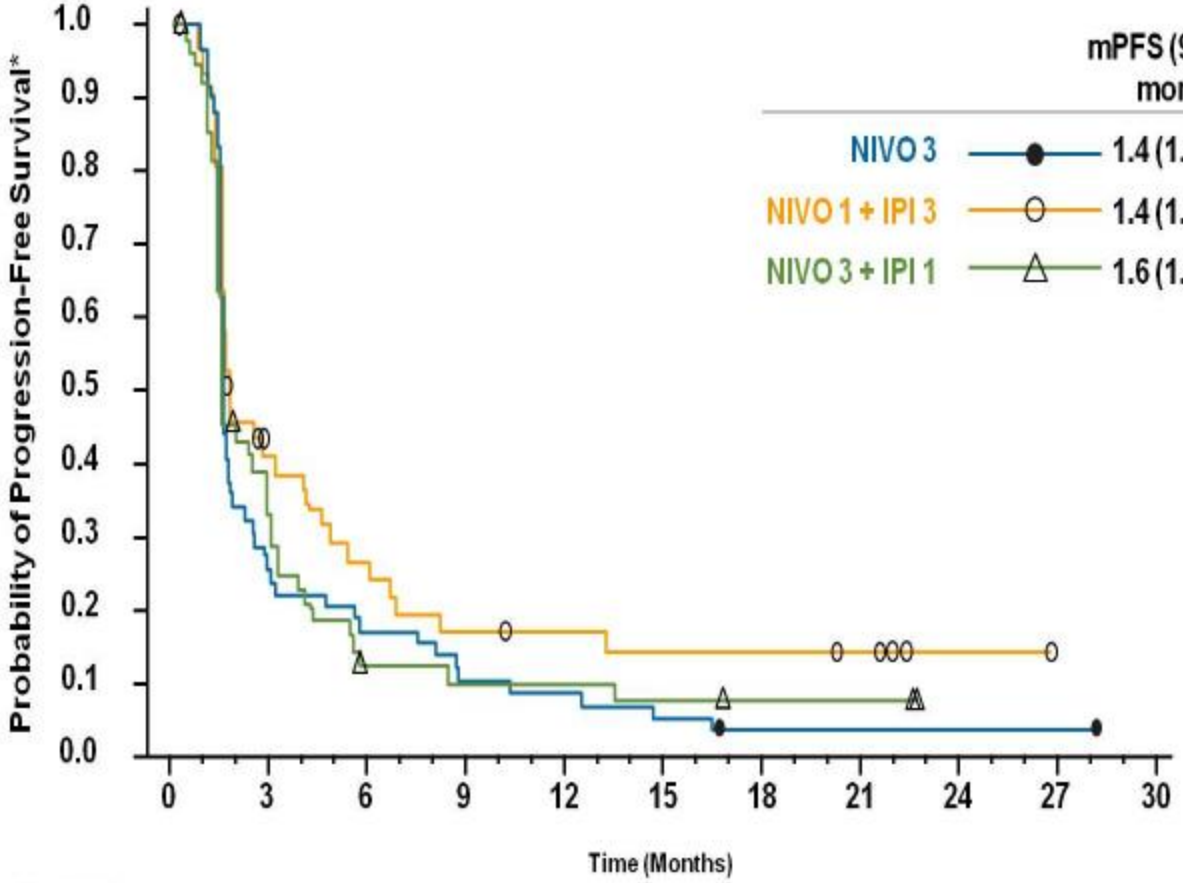
* Investigator review.

\# Patients with confirmed response (complete or partial response).

† Patients with 0% best reduction in target lesion, including 3 patients with PD-L1 ≥1% (NIVO 3, n=2; NIVO 3 + IPI 1, n=1) and 1 patient with PD-L1 <1% (NIVO 1 + IPI 3).

□ change truncated to 100%

Progression-Free Survival



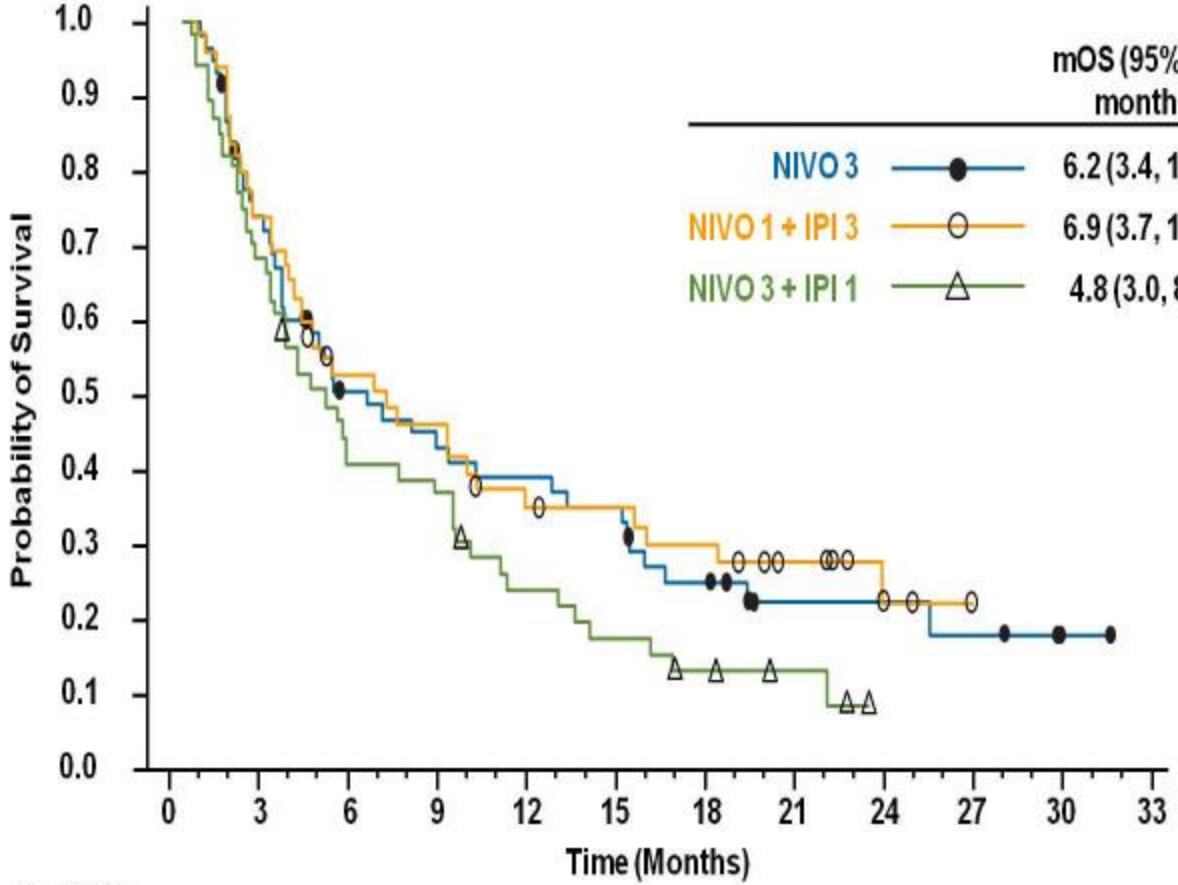
	mPFS (95% CI), months	6-month PFS rate, %	12-month PFS rate, %
NIVO 3	1.4 (1.2, 1.5)	17	8
NIVO 1 + IPI 3	1.4 (1.2, 3.8)	24	17
NIVO 3 + IPI 1	1.6 (1.4, 2.6)	12	10

No. at Risk:											
NIVO 3	59	13	10	6	5	3	1	1	1	1	0
NIVO 1 + IPI 3	49	16	10	7	6	5	5	4	1	0	0
NIVO 3 + IPI 1	52	13	5	4	4	3	2	2	0	0	0

mPFS, median PFS

* Investigator review.

Overall Survival



	mOS (95% CI), months	12-month OS rate, %	18-month OS rate, %
NIVO 3	6.2 (3.4, 12.4)	39	25
NIVO 1 + IPI 3	6.9 (3.7, 11.5)	35	28
NIVO 3 + IPI 1	4.8 (3.0, 8.4)	24	13

No. at Risk:

NIVO 3	59	40	26	21	20	15	11	5	5	4	1	0
NIVO 1 + IPI 3	49	35	24	19	14	14	11	8	3	0	0	0
NIVO 3 + IPI 1	52	33	20	18	11	8	4	3	0	0	0	0

mOS, median OS.

Treatment-Related Adverse Events

Patients, n (%)	NIVO 3 n = 59		NIVO 1 + IPI 3 n = 49		NIVO 3 + IPI 1 n = 52	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Any TRAE	41 (69)	10 (17)	41 (84)	23 (47)	39 (75)	14 (27)
Serious TRAEs	**6 (10)**	**3 (5)**	**21 (43)**	**17 (35)**	**13 (25)**	**9 (17)**
TRAEs leading to treatment discontinuation	2 (3)	2 (3)	10 (20)	10 (20)	7 (13)	5 (10)
TRAEs in ≥15% of patients in any treatment arm						
ALT increased	5 (8)	2 (3)	8 (16)	7 (14)	5 (10)	2 (4)
AST increased	7 (12)	3 (5)	8 (16)	5 (10)	2 (4)	1 (2)
Decreased appetite	9 (15)	0	5 (10)	0	3 (6)	0
Diarrhea	9 (15)	1 (2)	15 (31)	7 (14)	5 (10)	1 (2)
Fatigue	20 (34)	1 (2)	14 (29)	3 (6)	10 (19)	0
Pruritus	10 (17)	0	9 (18)	1 (2)	12 (23)	0
Rash	5 (8)	0	10 (20)	0	8 (15)	0

- One grade 5 TRAE was reported (tumor lysis syndrome in a patient treated with NIVO 3 + IPI 1)

TRAE, treatment-related adverse event.

Two High Impact Publications
NEJM and Science

Team: Hopkins, NCI, OSU, Providence Cancer Center in Portland OR, Stanford, UPMC, WVU, Swim Across America, and Merck

PD-1 blockade in tumors with mismatch-repair deficiency

Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, Skora AD, Luber BS, Azad NS, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Duffy SM, **Goldberg RM**, de la Chapelle A, Koshiji M, Bhaijee F, Huebner T, Hruban RH, Wood LD, Cuka N, Pardoll DM, Papadopoulos N, Kinzler KW, Zhou S, Cornish TC, Taube JM, Anders RA, Eshleman JR, Vogelstein B, Diaz LA Jr.
N Engl J Med. 2015 Jun25;372(26)2509-20. Epub 2015 May 30. PMID: 26028255.

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

Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, Lu S, Kemberling H, Wilt C, Luber BS, Wong F, Azad NS, Rucki AA, Laheru D, Donehower R, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Greten TF, Duffy AG, Ciombor KK, Eyring AD, Lam BH, Joe A, Kang SP, Holdhoff M, Danilova L, Cope L, Meyer C, Zhou S, **Goldberg RM**, Armstrong DK, Bever KM, Fader AN, Taube J, Housseau F, Spetzler D, Xiao N, Pardoll DM, Papadopoulos N, Kinzler KW, Eshleman JR, Vogelstein B, Anders RA, Diaz LA Jr.
Science 2017;357(6349):409-413. Epub 2017 June 8. PMID: 28596308.

Keynote-016: Study Cohorts

Colorectal Cancers

Cohort A
Deficient in Mismatch Repair (n=28)

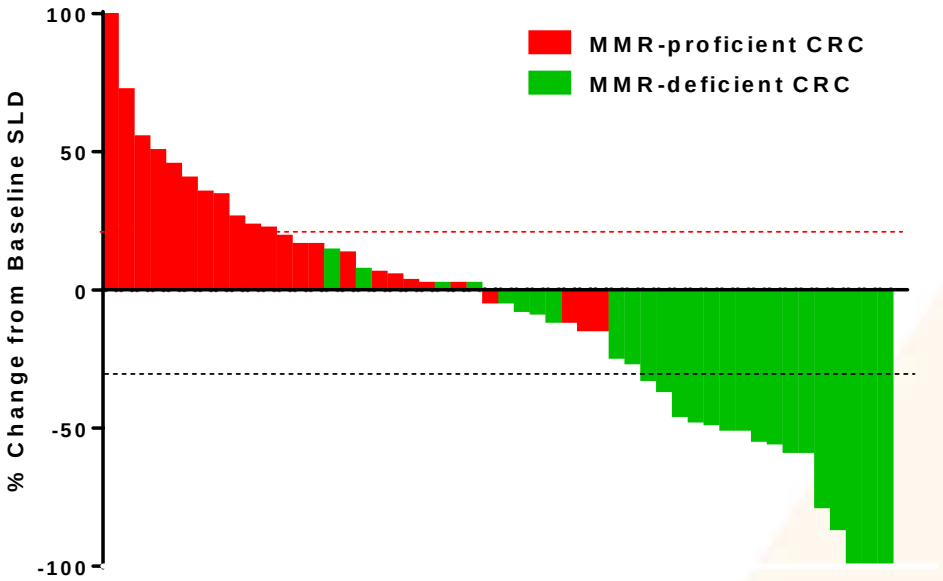
Cohort B
Proficient in Mismatch Repair (n=25)

Non-Colorectal Cancers

Cohort C
Deficient in Mismatch Repair (n=30)

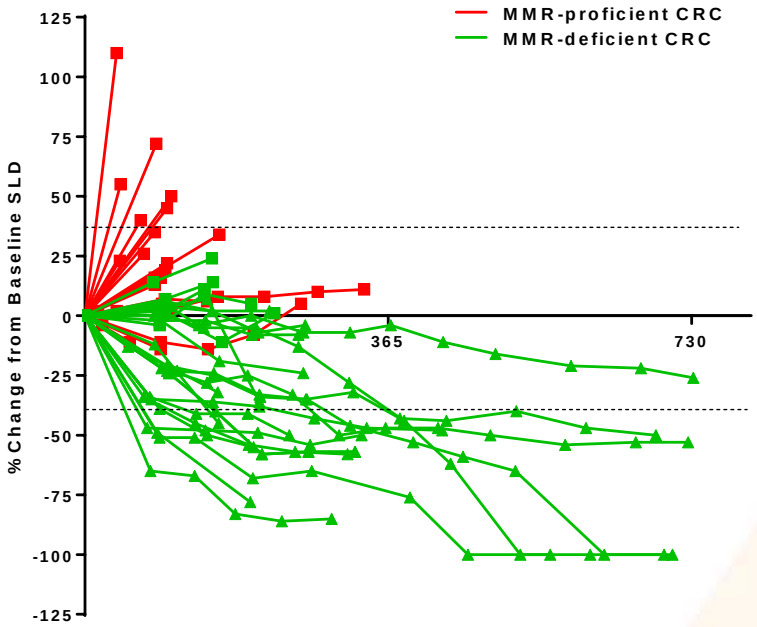
- Anti-PD1 (Pembrolizumab) – 10 mg/kg every 2 weeks

Colorectal Cancer: Best Radiographic Responses



No PRs or CRs in MMR-proficient CRC

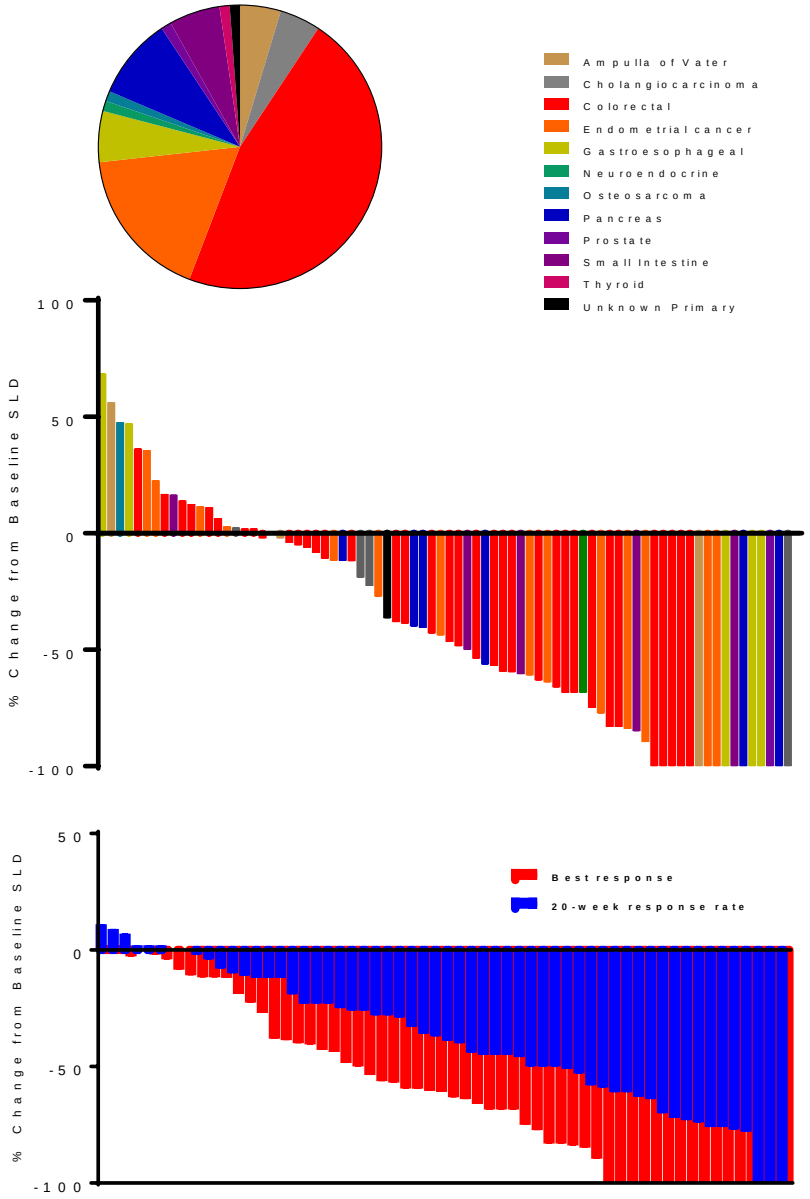
Colorectal Cancer: Radiographic Responses



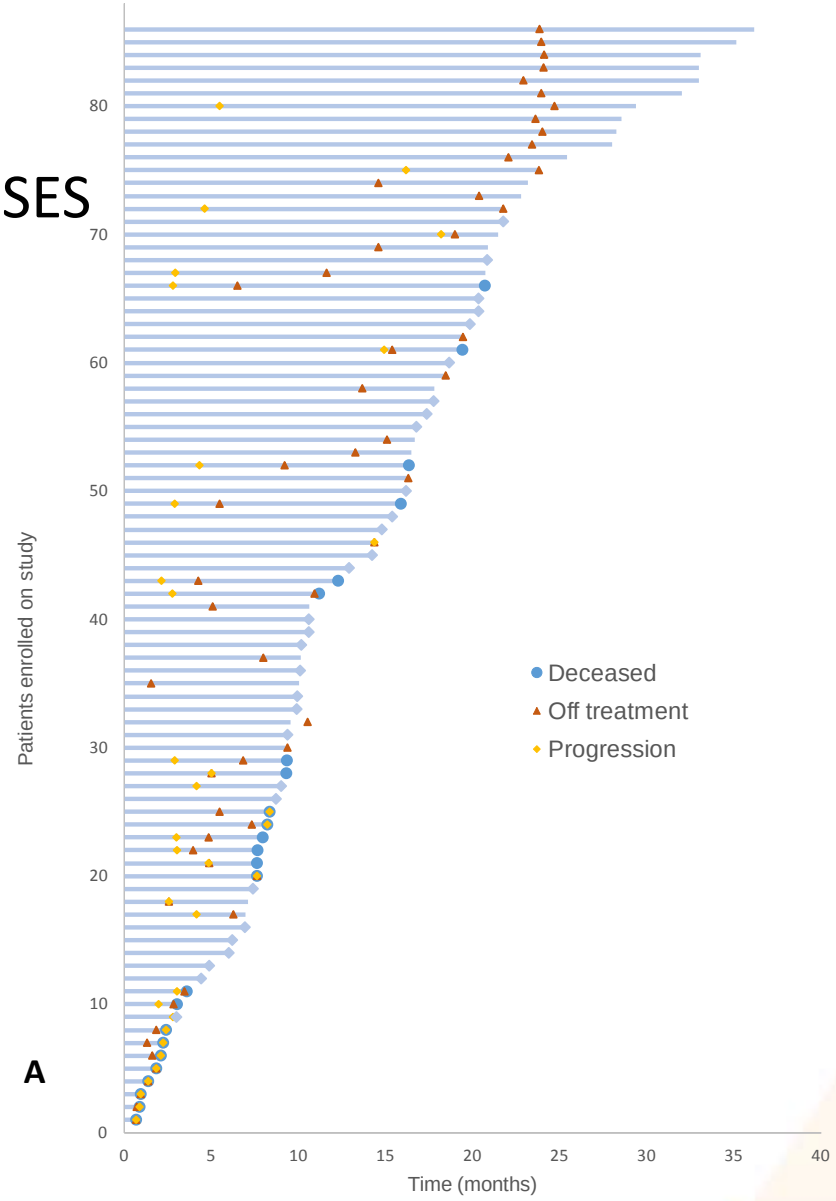
Response By Tumor Type

	N	response rate n (%)	DOR range (months)
CRC	90	32(36%)	(1.6+, 22.7+)
Non-CRC	59	27(46%)	(1.9+, 22.1+)
Endometrial	14	5 (36%)	(4.2+, 17.3+)
Biliary	11	3 (27%)	(11.6+, 19.6+)
Gastric or GE junction	9	5 (56%)	(5.8+, 22.1+)
Pancreatic	6	5 (83%)	(2.6+, 9.2+)
Small intestinal	8	3 (38%)	(1.9+, 9.1+)
Breast	2	PR, PR	(7.6, 15.9)
Prostate	2	PR, SD	9.8+
Bladder	1	NE	
Esophageal	1	PR	18.2+
Sarcoma	1	PD	
Thyroid	1	NE	
Retroperitoneal	1	PR	7.5+
Small cell lung	1	CR	8.9+

RESPONSES

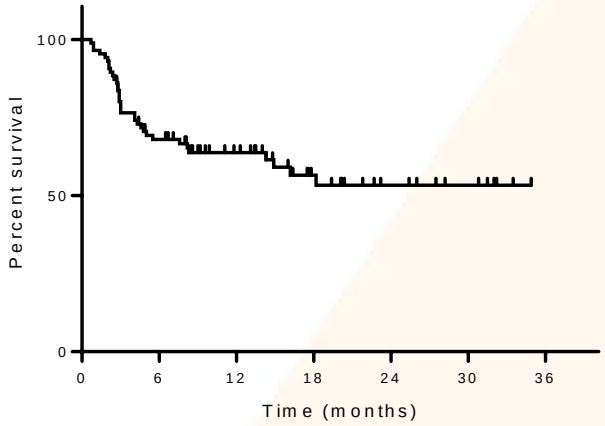

Ampulla of Vater
Cholangiocarcinoma
Colorectal
Endometrial cancer
Gastroesophageal
Neuroendocrine
Osteosarcoma
Pancreas
Prostate
Small Intestine
Thyroid
Unknown Primary
% Change from Baseline SLD
100
50
0
-50
-100
% Change from Baseline SLD
50
0
-50
-100
Best response
20-week response rate

RESPONSES

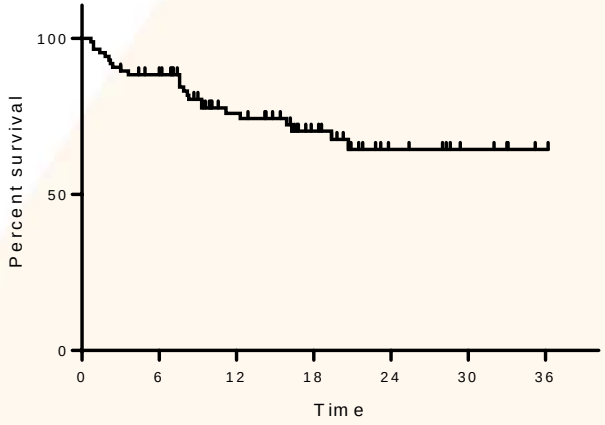


A

B

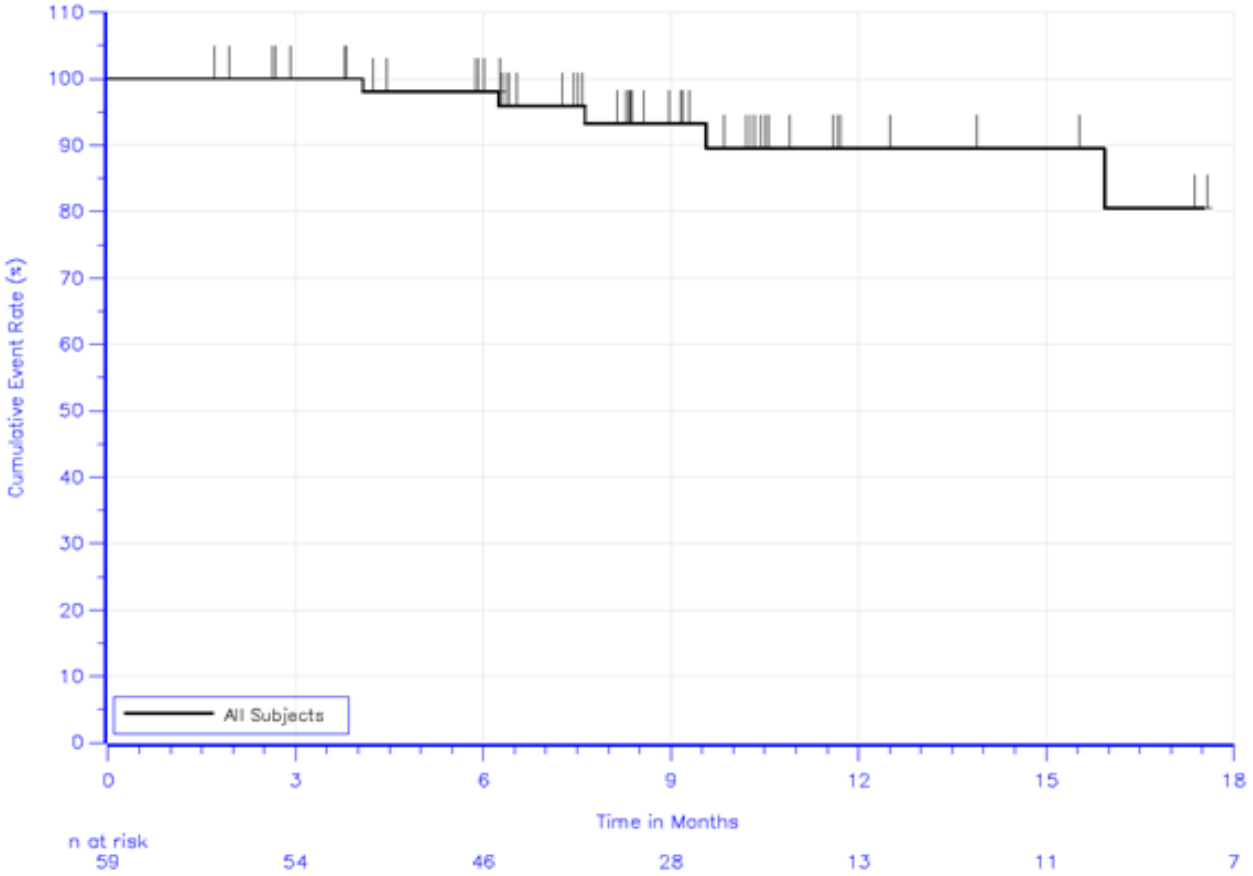


C

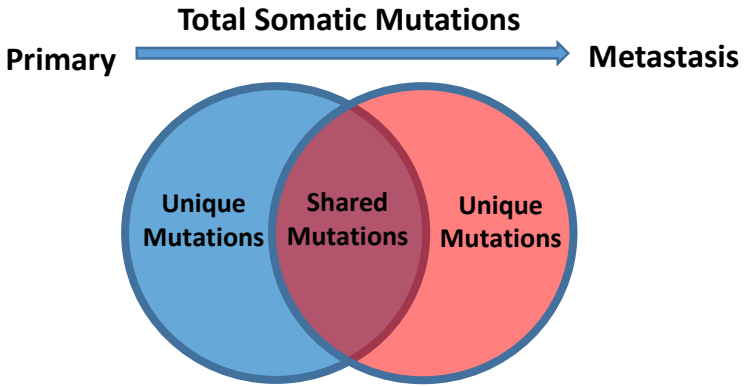


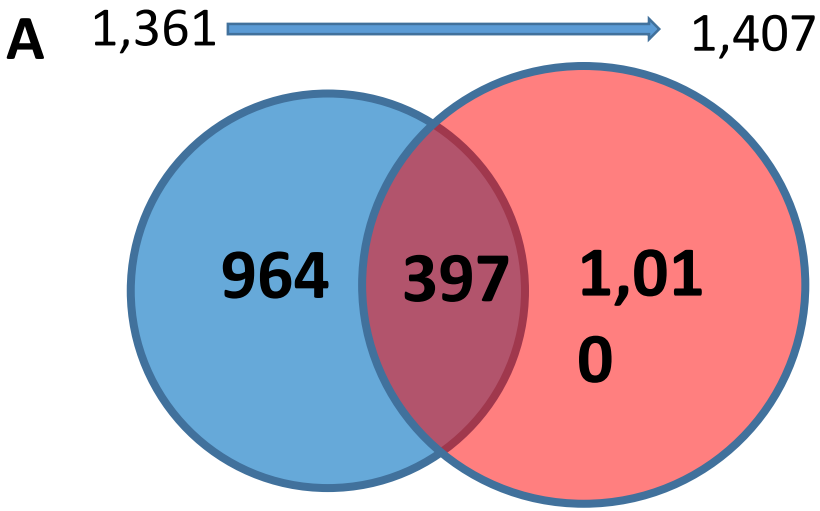
Duration of Response

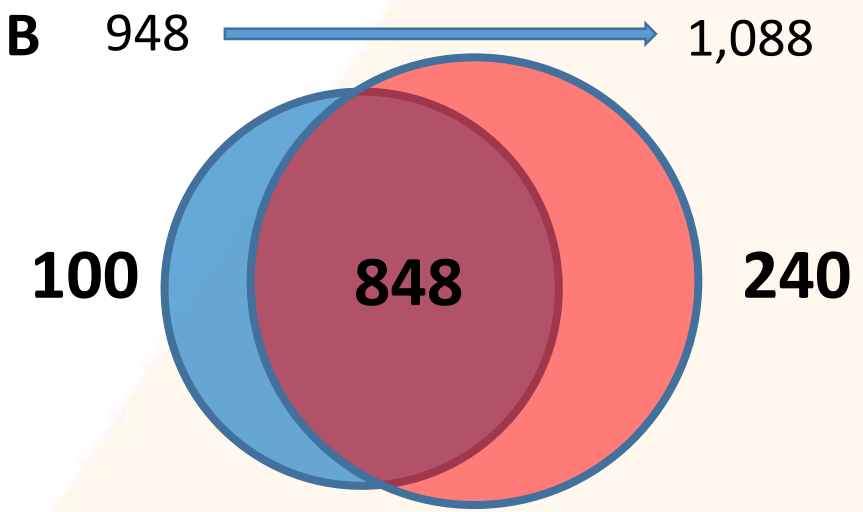
Kaplan-Meier Estimates of Response Duration in Subjects with Confirmed Response Based on IRC Assessment per RECIST 1.1 (ASaT Population in sBLA)



Median DOR (mos): Not reached (1.6+ - 22.7+)

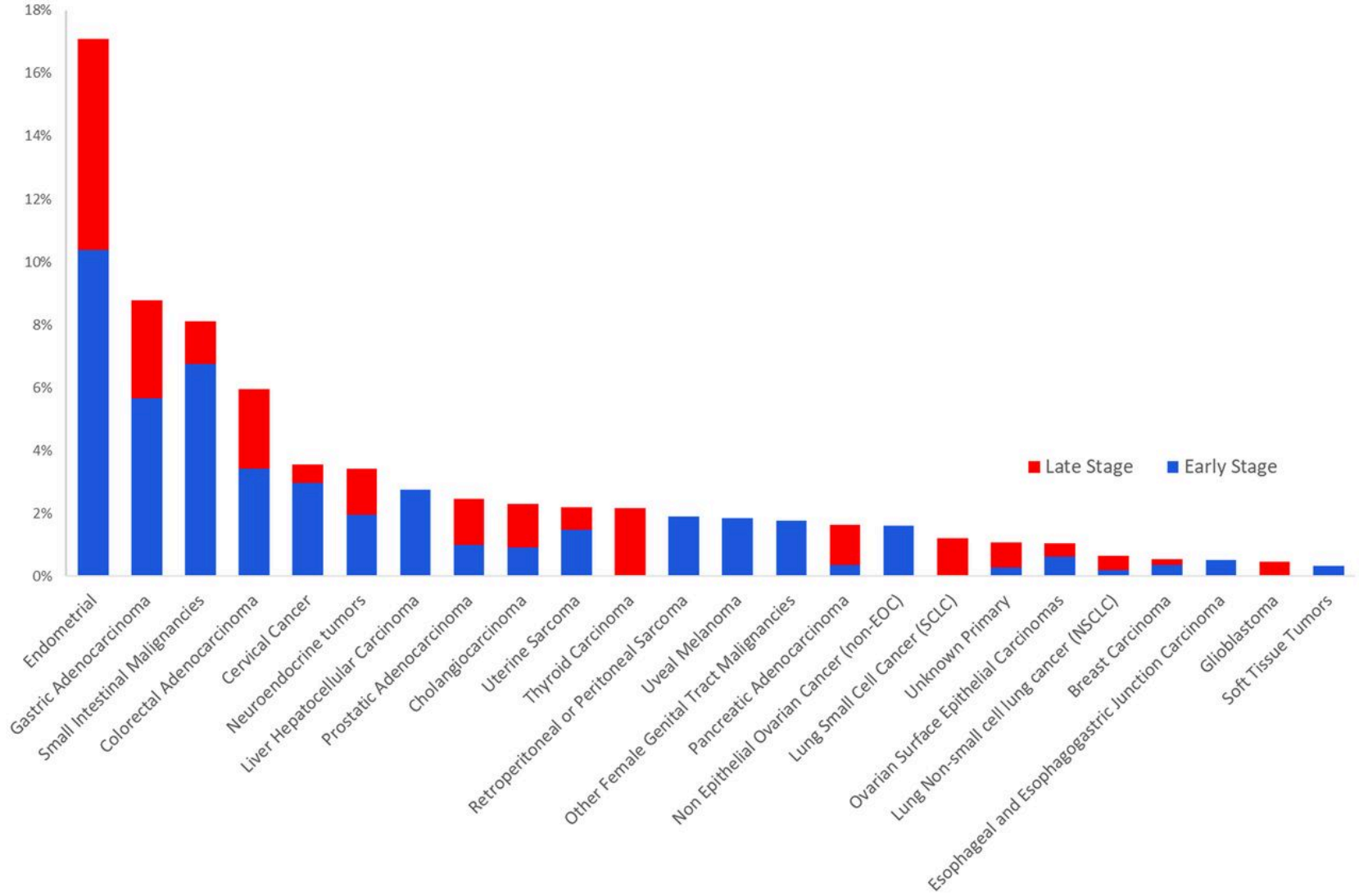






Dung T. Le et al. Science 2017;science.aan6733

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



A New Paradigm in FDA Approval That is Agnostic to Histology and Primary Site: Pembrolizumab Approved for MSI-H or Mismatch Repair Deficient Tumors

- for the treatment of adult and pediatric patients with unresectable or metastatic,
  microsatellite instability-high (MSI-H) or mismatch repair deficient
  - solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or
  - colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan

- pembrolizumab 200mg every 3 weeks for adults and 2mg/kg (up to 200mg) every 3 weeks for children

T cells on the lookout for neoantigens

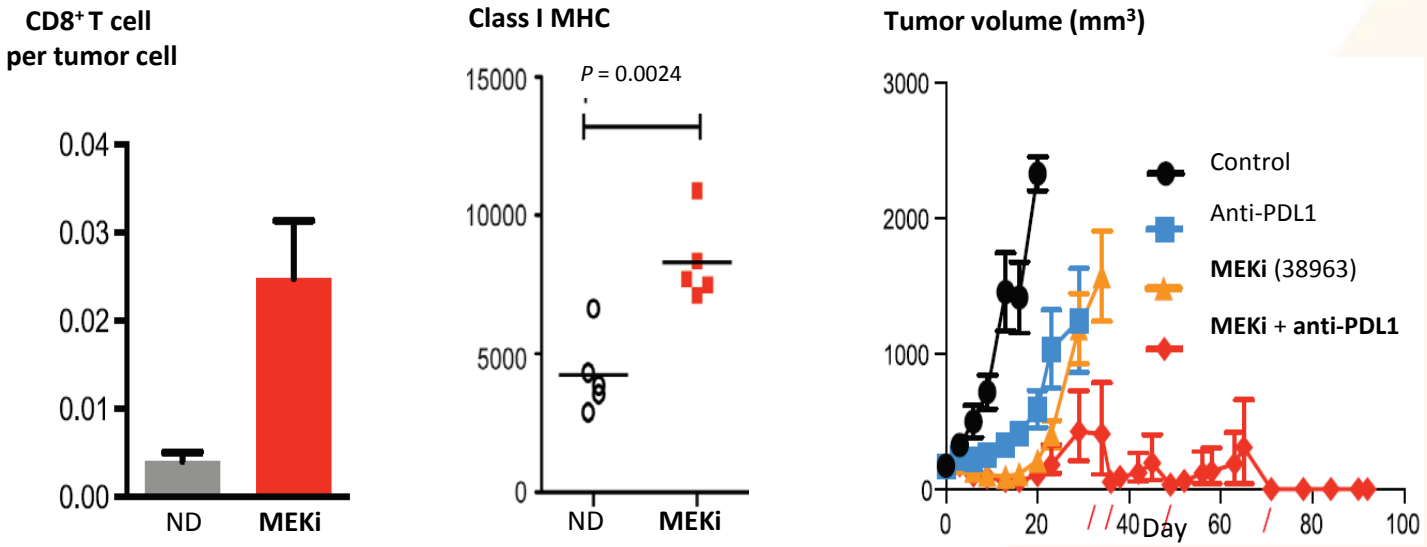
Clinical activity and safety of cobimetinib and atezolizumab in colorectal cancer

Johanna Bendell,[1] Tae Won Kim,[2] Boon Cher Goh,[3] Jeffrey Wallin,[4] Do-Youn Oh,[5] Sae-Won Han,[5] Carrie Lee,[6] Matthew D. Hellmann,[7] Jayesh Desai,[8] Jeremy Lewin,[9] Benjamin J. Solomon,[10] Laura Q. Chow,[11] Wilson H. Miller Jr,[12] Justin Gainor,[13] Keith Flaherty,[13] Jeffrey Infante,[1] Meghna Das Thakur,[4] Paul Foster,[4] Edward Cha,[4] Yung-Jue Bang[5]

[1]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; [2]Asan Medical Center, Seoul, South Korea; [3]Cancer Science Institute of Singapore, National University of Singapore, Singapore; [4]Genentech, Inc., South San Francisco, CA; [5]Seoul National University Hospital, Seoul, South Korea; [6]UNC Lineberger Comprehensive Cancer Center, University of North Carolina – Chapel Hill, North Carolina; [7]Memorial Sloan Kettering Cancer Center, New York, NY; [8]Royal Melbourne Hospital, University of Melbourne, Melbourne, VIC, Australia; [9]Princess Margaret Cancer Center, University Health Network, Toronto, ON, Canada; [10]Peter MacCallum Cancer Center, Melbourne, VIC, Australia; [11]University of Washington, Seattle, WA; [12]Segal Cancer Center and Jewish General Hospital, McGill University, Montreal, QC, Canada; [13]Massachusetts General Hospital, Boston, MA

PD-L1 and MEK Inhibition: A Rational Combination

- MEK inhibition alone can result in **intratumoral T-cell accumulation** and **MHC I upregulation**, and synergizes with an anti-PDL1 agent to promote **durable tumor regression**[1]



- To examine the possible benefits of MEK inhibition with an anti-PDL1 agent, we evaluated cobimetinib + atezolizumab in patients with advanced solid tumors

MHC, major histocompatibility complex; ND, no drug (vehicle alone).
CT26 (KRASmt) CRC models. 1. Ebert et al. *Immunity* 2016.

Efficacy: Confirmed Objective Response

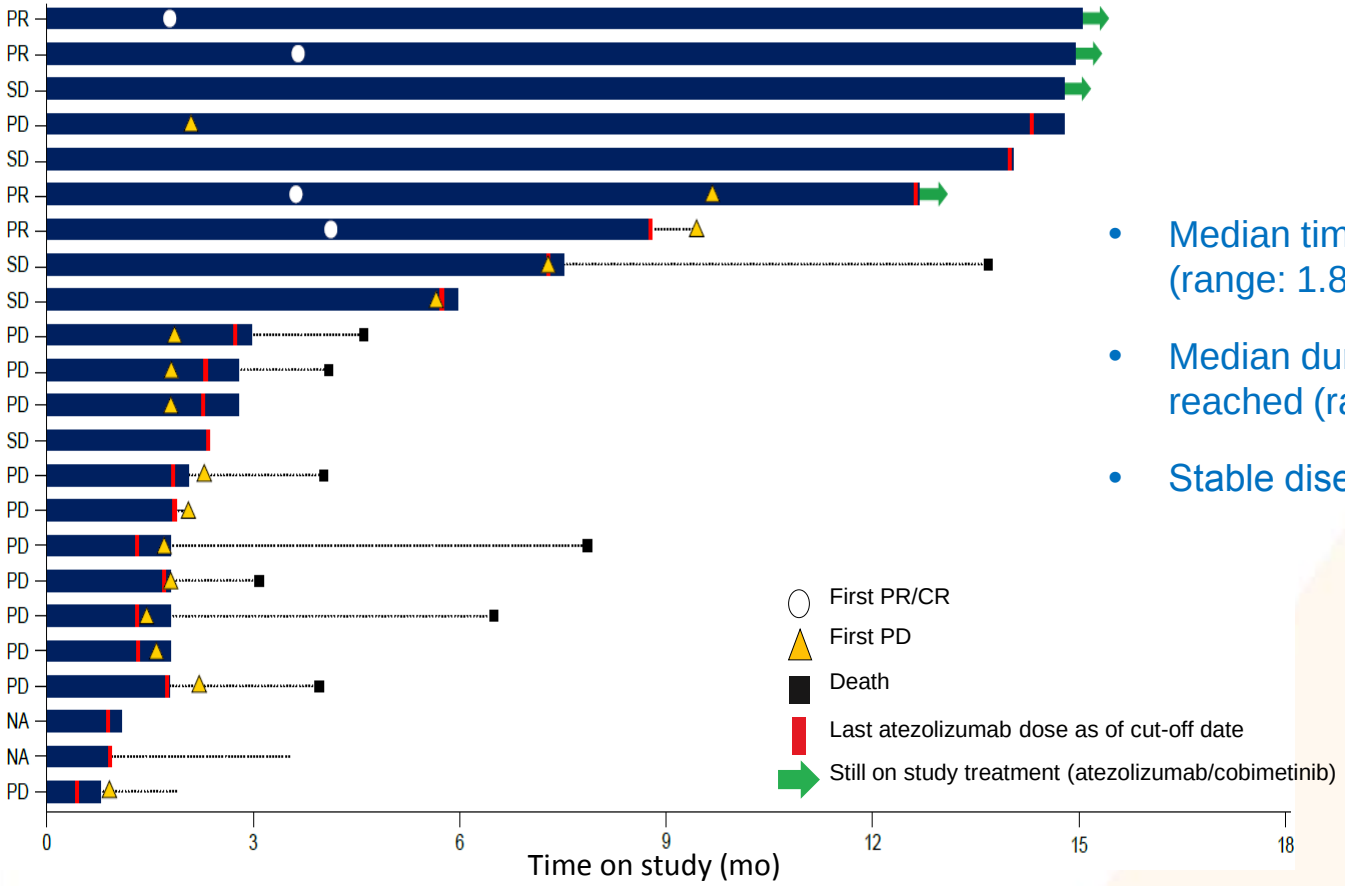
Confirmed Response per RECIST v1.1	*KRAS* mutant CRC Cohort (n = 20)	All CRC Patients (N = 23)
ORR (95% CI)	20% (5.7, 43.7)	17% (5.0, 38.8)
PR	20%	17%
SD	20%	22%
PD	50%	52%
NE	10%	9%

- Response did not correlate with PD-L1 status: IC0 (n = 2), IC1 (n = 1) and IC3 (n = 1)

NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Bendell J, et al. Cobimetinib and atezolizumab in CRC. ASCO 2016

Efficacy: Duration of Treatment and Response



- Median time to first response was 3.7 mo (range: 1.8 to 4.1 mo)
- Median duration of response was not reached (range: 5.4 to 11.1+ mo)
- Stable disease can be durable (≥ 6 mo)

Efficacy-evaluable patients. Data cut-off February 12, 2016.

NCI9673: A Multi-Institutional ETCTN Phase II Study of Nivolumab in Refractory Metastatic Squamous Cell Carcinoma of the Anal Canal

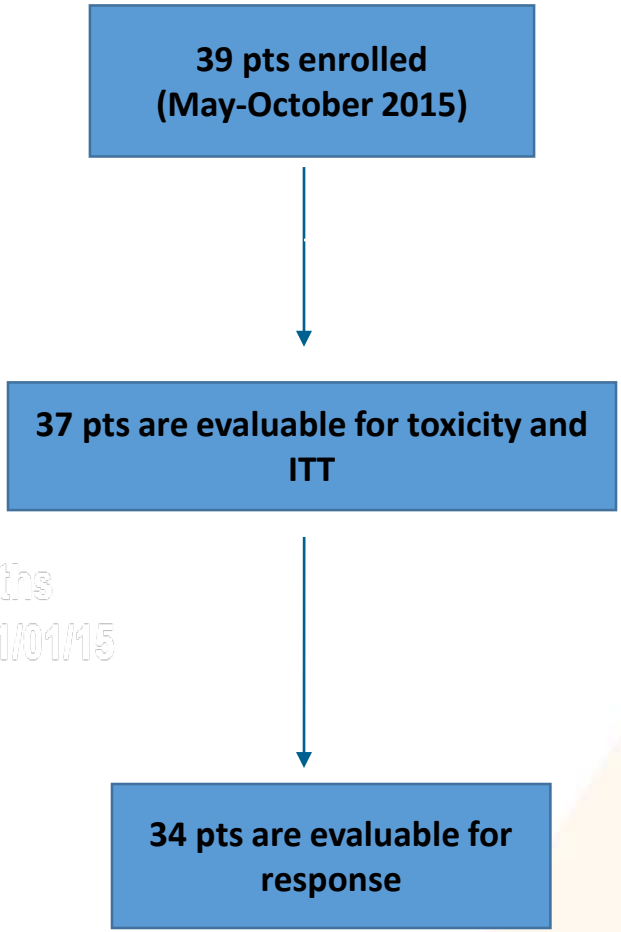
V. Morris[1], K. Ciombor[2], M.E. Salem[3], H. Nimeiri[4], S. Iqbal[5], P. Singh[6], B. Polite[7],

D. Deming[8], E. Chan[9], J.L. Wade[10], T.S. Bekaii-Saab[2], H.E. Uronis[11], M.G. Pasia[1], G. Bland[1],

R.A. Wolff[1], A. Ohinata[1], C. Ohaji[1], J.E. Rogers[1], P. Sharma[1], **C. Eng[1]**

[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]The Ohio State University Comprehensive Cancer Center, Arthur G. James Cancer Hospital, Columbus, OH; [3]Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC; [4]Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL; [5]University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, CA; [6]Washington University, Siteman Cancer Center, St. Louis, MO; [7]The University of Chicago, Chicago, IL; [8]University of Wisconsin Hospitals and Clinics, Madison, WI; [9]Vanderbilt University Medical Center, Nashville, TN; [10]Cancer Care Center of Decatur, Decatur, IL; [11]Duke University Medical Center, Durham, NC

NCI9673: Consort Diagram



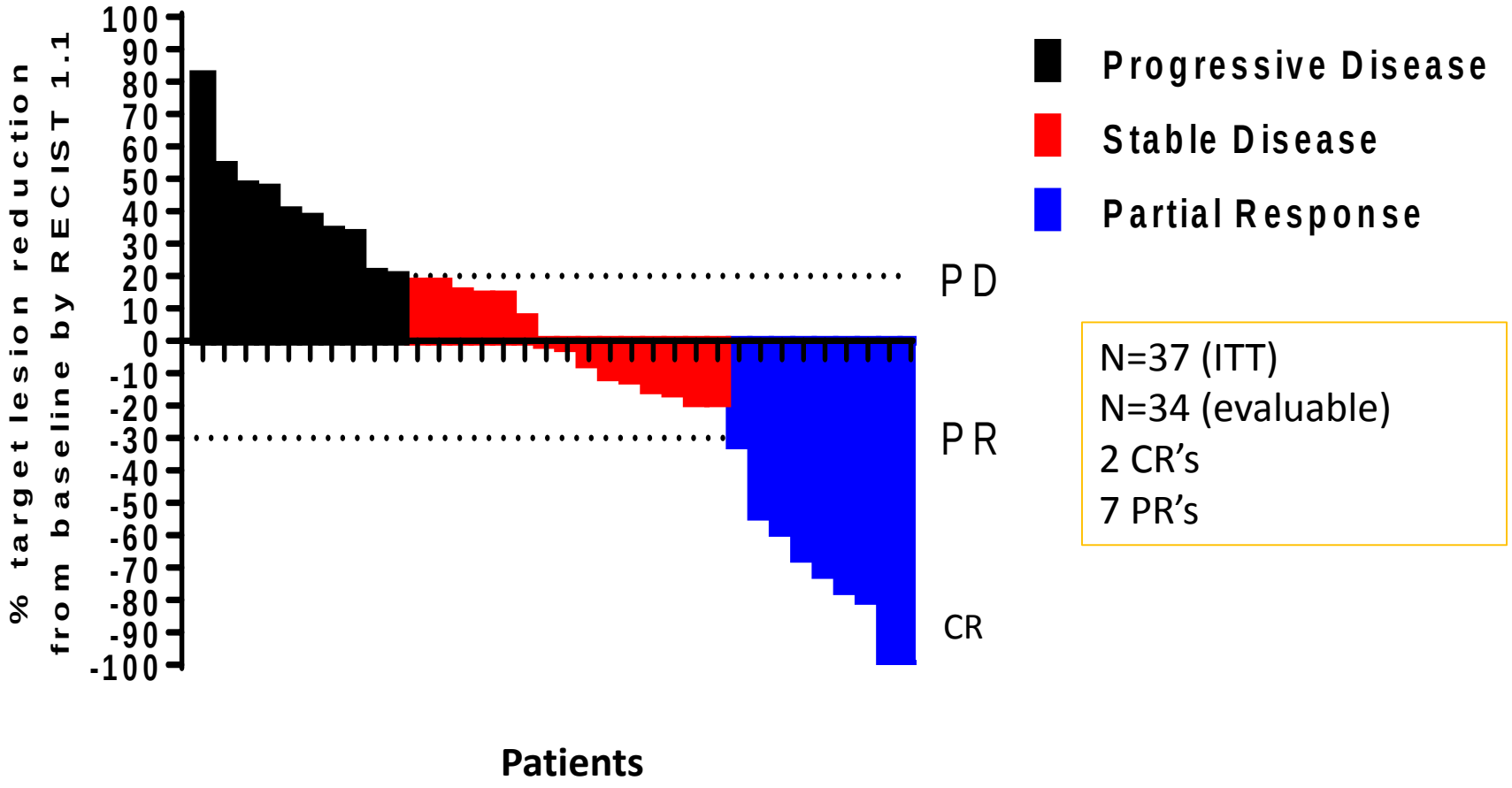
- 2 patients were screen failures

- 1 patient was determined to be ineligible
- 1 patient received palliative XRT*
- 1 patient had an acute infection**

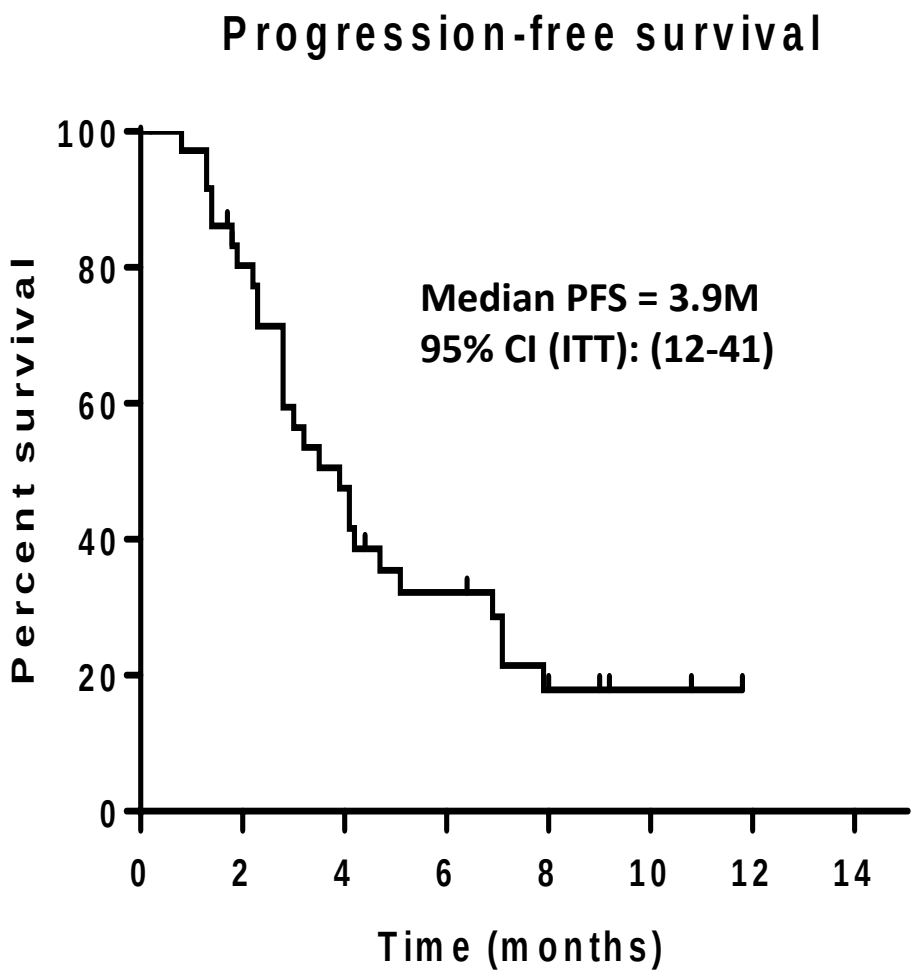
- Rapid enrollment in < 6 months
- Closed to enrollment as of 11/01/15

*both within < 1 week of enrollment; **not treatment-related

NCI9673: Primary Endpoint of Response Rate



Secondary Endpoint:



Next Steps

- in MSI-H tumors
  - FOLFOX + a PD-1 inhibitor
    - In first line therapy
    - As adjuvant therapy
- In MSS tumors
  - Coupling with other IO agents
    - Nivo + ipi
- Exploring the importance of PD-1 expression
- Understanding
  - PD-1 vs PD-L1
  - Utility of different agents with the same targets

Post-test

- Which molecular marker(s) are essential to determine whether a patient should be treated with a PD-1 inhibitor?
  1. IHC staining for PD-1 expression on tumor cells
  2. IHC staining for PD-1 expression on tumor infiltrating lymphocytes
  3. IHC staining for mismatch repair proteins on tumor cells
  4. Both 2 and 3
  5. All of the above

Post-test

- Treatment with a PD-1 inhibitor has been associated with which of the following toxicities except:

1. Cardiomyopathy
2. Neutropenia
3. Hypothyroidism
4. New onset diabetes
5. Nausea, vomiting and diarrhea

Post-test

- Treatment with a PD-1 Inhibitor has led to responses in which of the following tumor types:

1. Colorectal cancer
2. Pancreatic cancer
3. Sarcomas
4. Anal cancers
5. All of the above

Questions?