Immunotherapy in GI Malignancies

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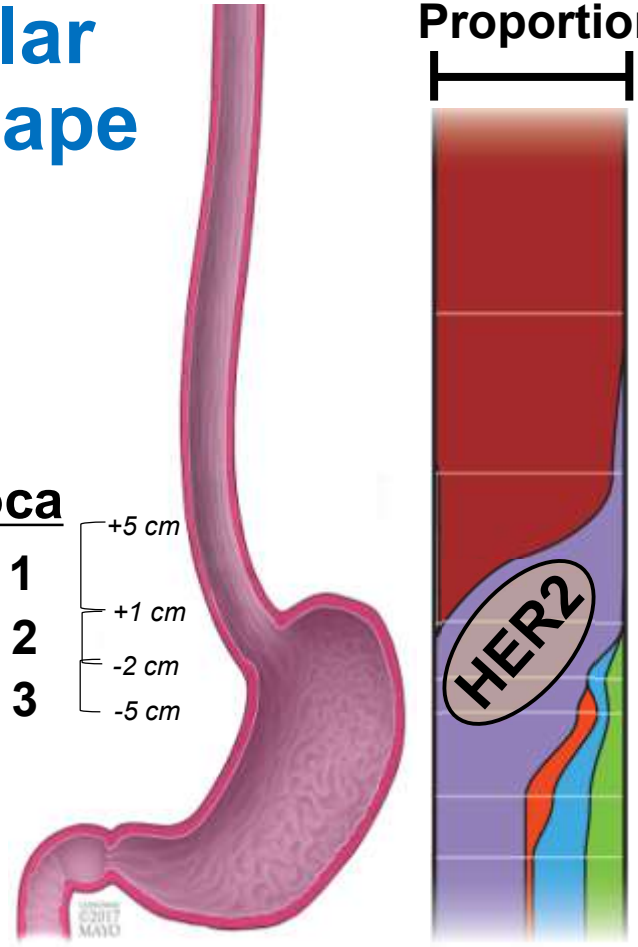
FDA Approval of IO Agents in GI Cancers

	1st Line	2nd Line	3rd Line	Comments
Esophageal SCC		Pembro for CPS ≥10		
Gastroesophageal ACA			Pembro for CPS ≥1	Nivo approved in Asia based on ATTRACTION-2
Pancreas Ca				
Hepatocellular Ca	(Atezolizumab+ BEV)	Pembrolizumab Nivolumab		Pembro and Nivo approval based on non-randomized studies
Biliary Ca				
Colorectal Ca			Nivo and Pembro for MSI-H/ MMR-D	
Anal SCC				
MSI-H/ MMR-D Ca			Pembrolizumab	Tumor-entity independent approval

Molecular Landscape

TCGA,
Nature 2017



ESCC (enriched in PD-L1)
CIN, chrom. instability (*eg,* HER2)
MSI, microsatellite instability
EBV, Epstein Barr Virus
GS, genomically stable

Esoph SCC signature

GEJ adenoca

Siewert 1
Siewert 2
Siewert 3

+5 cm
+1 cm
-2 cm
-5 cm

Siewert refers to tumors involving GEJ; distances are location of tumor center relative to anatomic GEJ

CIN

MSI ..... Yes

EBV ..... Promising

GS

Vulnerable to anti-PD-1 therapy

TCGA Nature 2014; Salem et al The Oncologist 2018;
Panda A et al. JNCI 2018

IO in Esophageal Cancer – Keynote 180

- Phase 2 single arm pembrolizumab
- N=121, 3+ prior lines of therapy
- 52% SCC
- **48% PD-L1 CPS score ≥10**

Response rate (%)	
All pts (n=121)	9.9
ACA (n=58)	5.2
SCC (n=63)	14.3
PD-L1 CPS ≥10 (n=58)	13.8
PD-L1 CPS <10 (n=63)	6.3

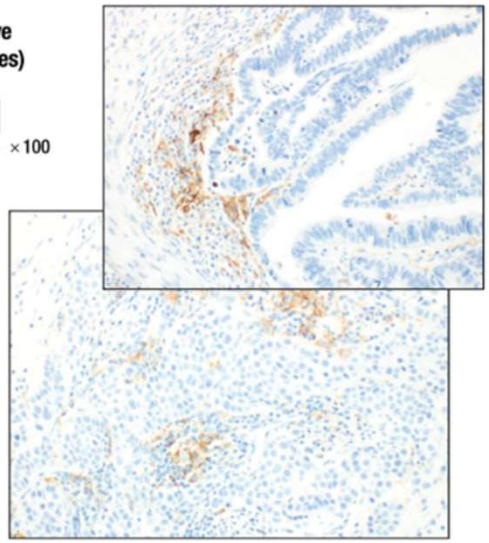
SCC + CPS + (n=35) RR 20%

. CPS: Evaluating the numerator. Identifying PD-L1-positive tumor-associated immune cells (lymphocytes and macrophages)

$$\text{CPS} = \frac{\text{\# of PD-L1-positive cells (tumor cells, lymphocytes, macrophages)}}{\text{Total \# of tumor cells}} \times 100$$

Element	Included in scoring
Immune cells	Membrane and/or cytoplasmic* staining (at any intensity) of mononuclear inflammatory cells (MICs) within tumor nests and adjacent supporting stroma: ■ Lymphocytes (including lymphocyte aggregates) ■ Macrophages Only MICs directly associated with the response to the tumor are scored.

*In MICs membrane and cytoplasmic staining are often indistinguishable due to high nuclear to cytoplasmic ratio. Therefore, membrane and/or cytoplasmic staining of MICs are included in the score.



Shah et al., JAMA Onc 2018

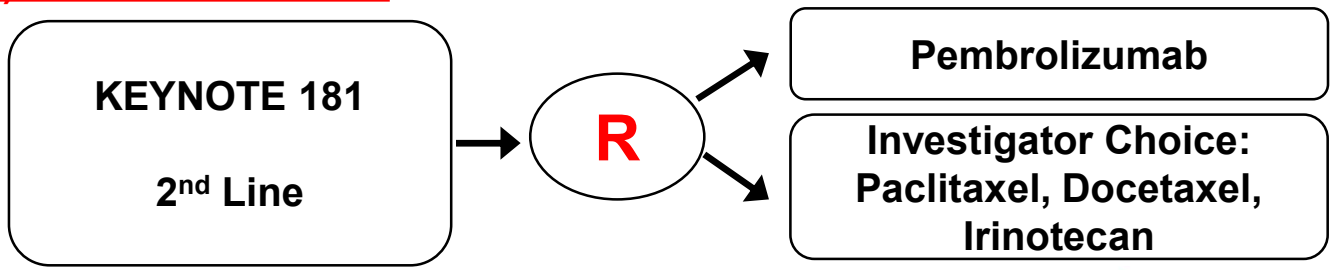
Phase III: Keynote-181

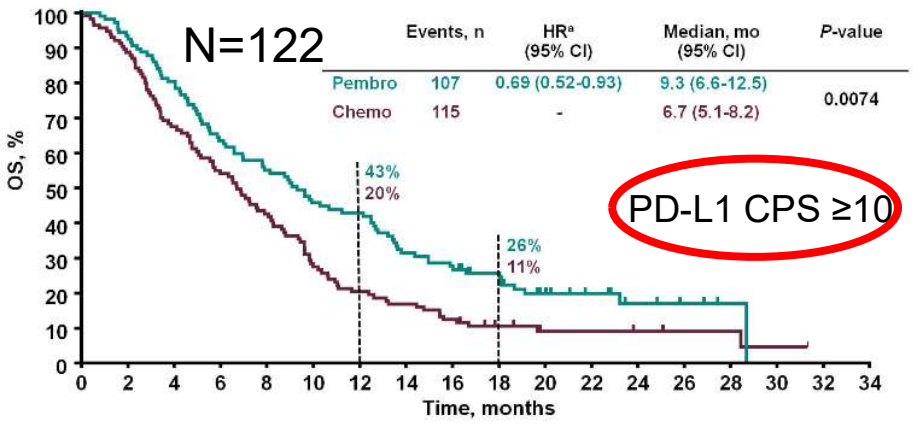
Overall alpha for study: one-sided alpha of 2.5%

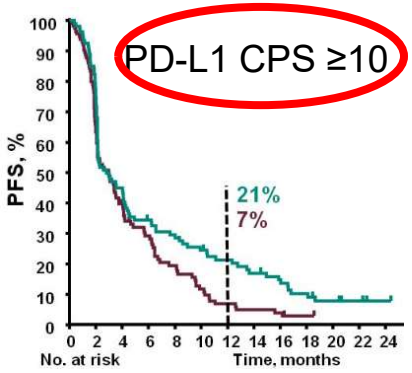
1. α 0.9% ($P \leq 0.0085$) for superiority of OS in PD-L1 CPS ≥10 **Positive**
2. α 0.8% ($P \leq 0.0077$) for superiority of OS in SCC **Negative**
3. α 0.8% ($P \leq 0.0077^{a}$) for superiority of OS in ITT **Negative**

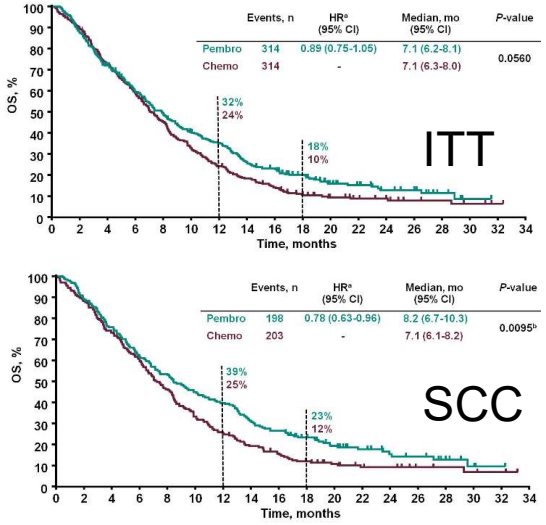
N=628, 2nd line esophageal/GEJ

- **122 (19%) w/ PD-L1 CPS ≥ 10**







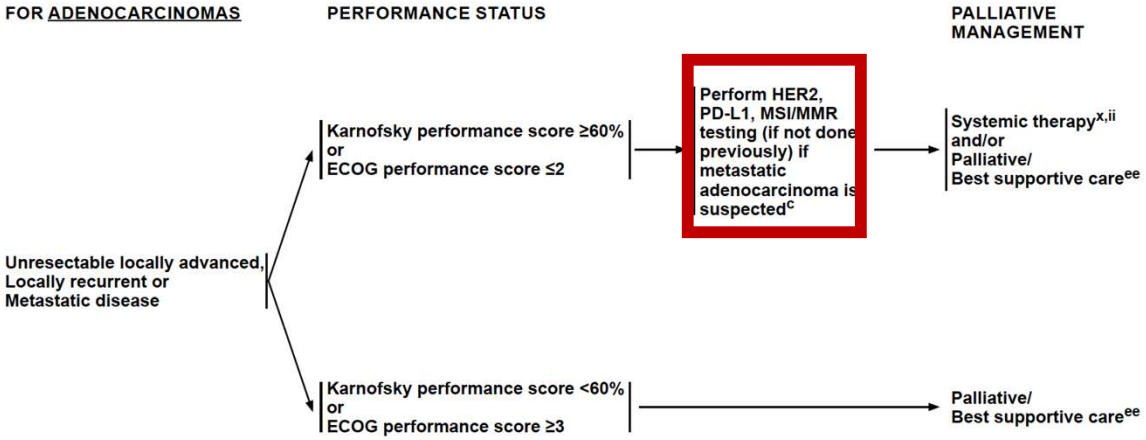


Kojima et al., ASCO GI 2019

Immunotherapy for Gastroesophageal Cancer

- **Pembrolizumab FDA approved 9/2017 for CPS PD-L1 >1 for gastric or GEJ ACA**
  - After 2 lines (including fluoropyrimidine and platinum + HER2 if appropriate)
  - PD-L1 IHC 22C3 pharmDx Kit (Dako)
  - Combined Positive Score (CPS) = PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by total number of tumor cells evaluated, multiplied by 100

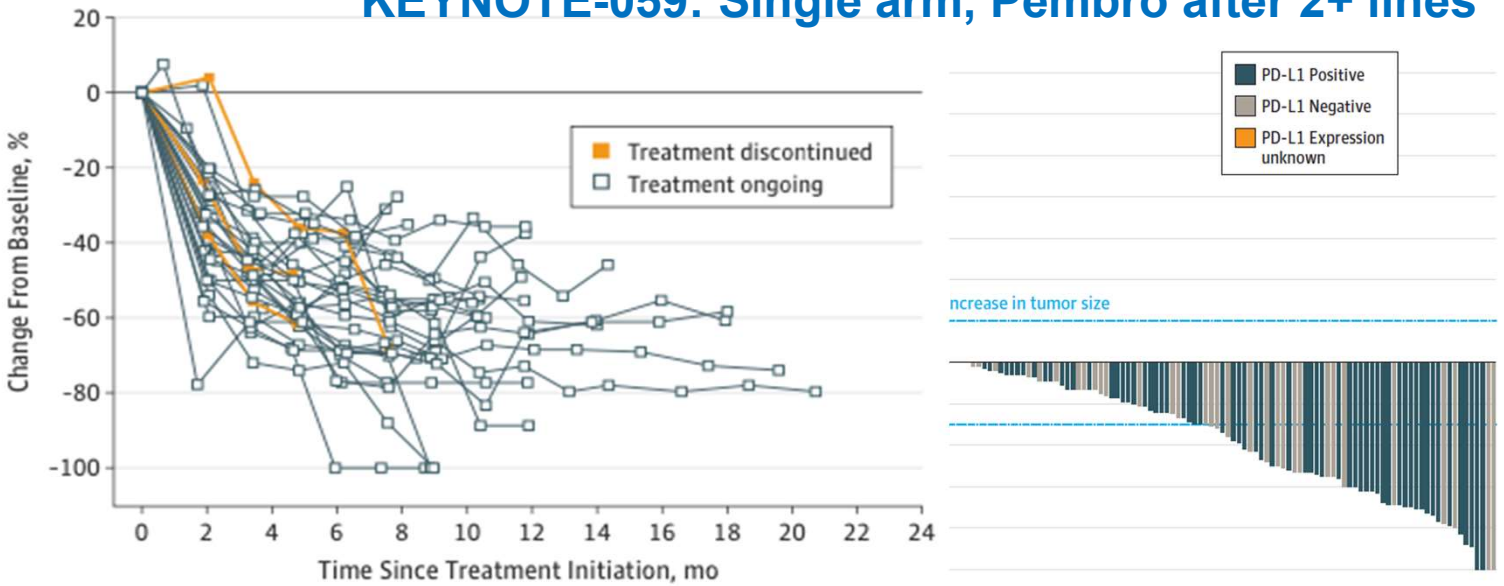
NCCN Guidelines:



Pembrolizumab
(for third-line or subsequent therapy for PD-L1-positive esophageal and EGJ adenocarcinoma)
Pembrolizumab 200 mg IV on Day 1
Cycled every 21 days[54]

Immunotherapy for Gastroesophageal Cancer

KEYNOTE-059: Single arm, Pembro after 2+ lines



Response rate (%)	
Overall	11.6
PD-L1+ / PD-L1-	15.5 / 6.4
MSI-H / MSS	57.1 / 9

FDA approval based upon: 143 patients PD-L1+ and MSS: RR 13.3%

7pts were MSI-H

Fuchs et al., JAMA Onc 2018

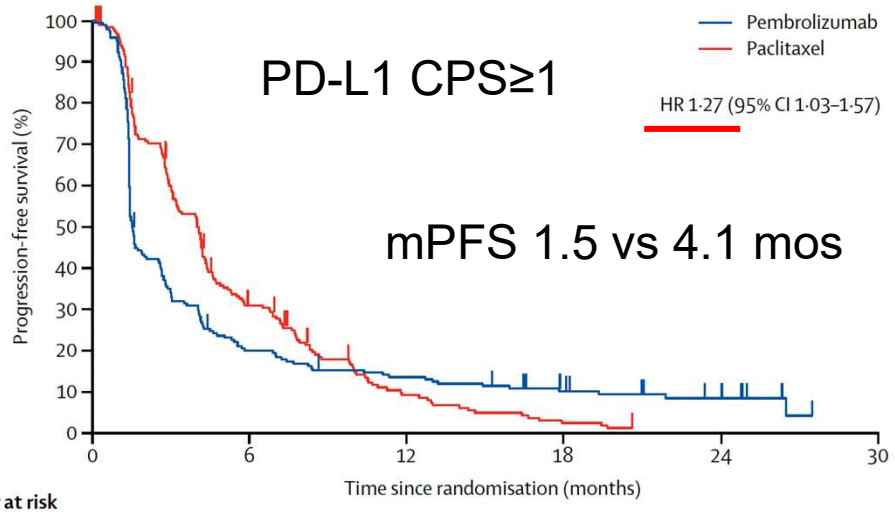
Negative Phase III: Keynote-061

N=592, 2nd line gastric/GEJ: Pembrolizumab vs. paclitaxel

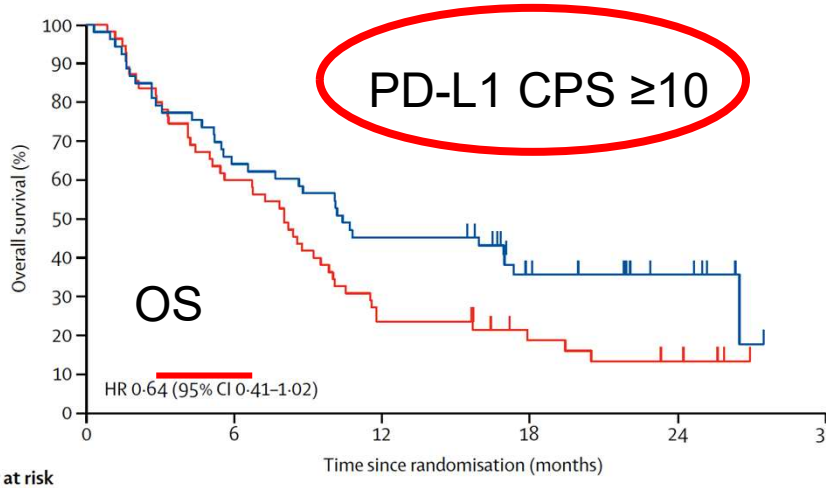
- 395 (66%) w/ PD-L1 CPS ≥ 1%
- **106 (18%) w/ PD-L1 CPS ≥ 10%**

Primary Endpoint: negative

mOS (HR 0.82, p=0.04):
Pembro 9.1 mos
Paclitaxel 8.3 mos



Number at risk (censored)						
Pembrolizumab	196 (0)	38 (2)	25 (3)	15 (7)	7 (12)	0 (19)
Paclitaxel	199 (0)	57 (9)	15 (14)	4 (14)	0 (15)	0 (15)



Number at risk (censored)						
Pembrolizumab	53 (0)	34 (0)	24 (0)	13 (7)	6 (14)	0 (
Paclitaxel	55 (0)	33 (0)	13 (0)	7 (4)	4 (5)	0 (

Shitara et al, Lancet 2018

Pembrolizumab With or Without Chemotherapy Versus Chemotherapy in Advanced G/GEJ Adenocarcinoma: The Phase 3, KEYNOTE-062 Study

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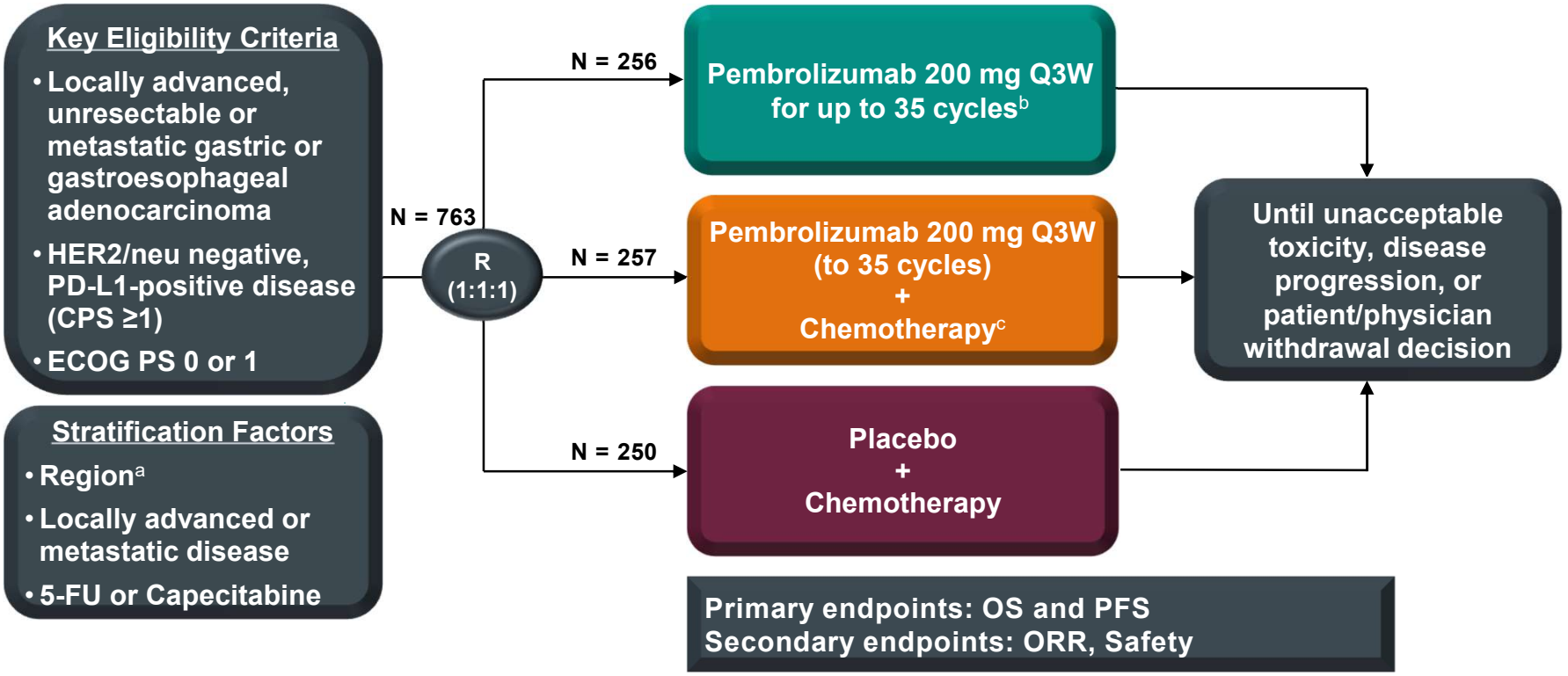
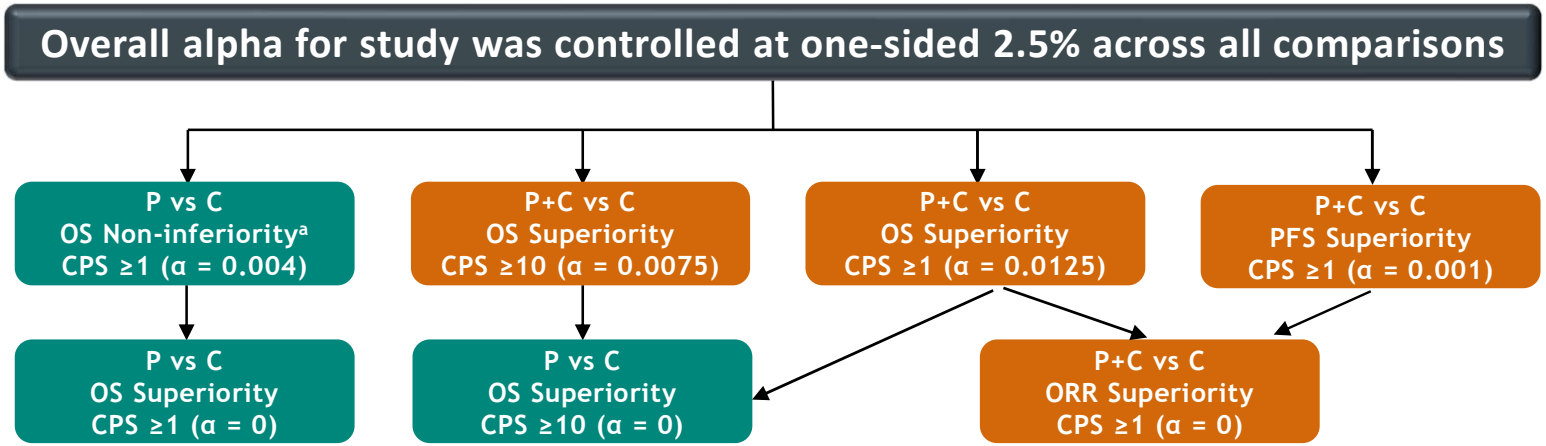
PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

KEYNOTE-062 Study Design (NCT02494583)



[a]EU/North America/Australia, Asia (South Korea, Hong Kong, Taiwan, Japan), Rest of World (including South America).
[b]Administration of pembrolizumab monotherapy was not blinded.
[c]Chemotherapy: Cisplatin 80 mg/m^2 Q3W + 5-FU 800 mg/m^2/d for 5 days Q3W or capecitabine BID d1-14 Q3W (Cisplatin may be capped at 6 cycles as per country guidelines).

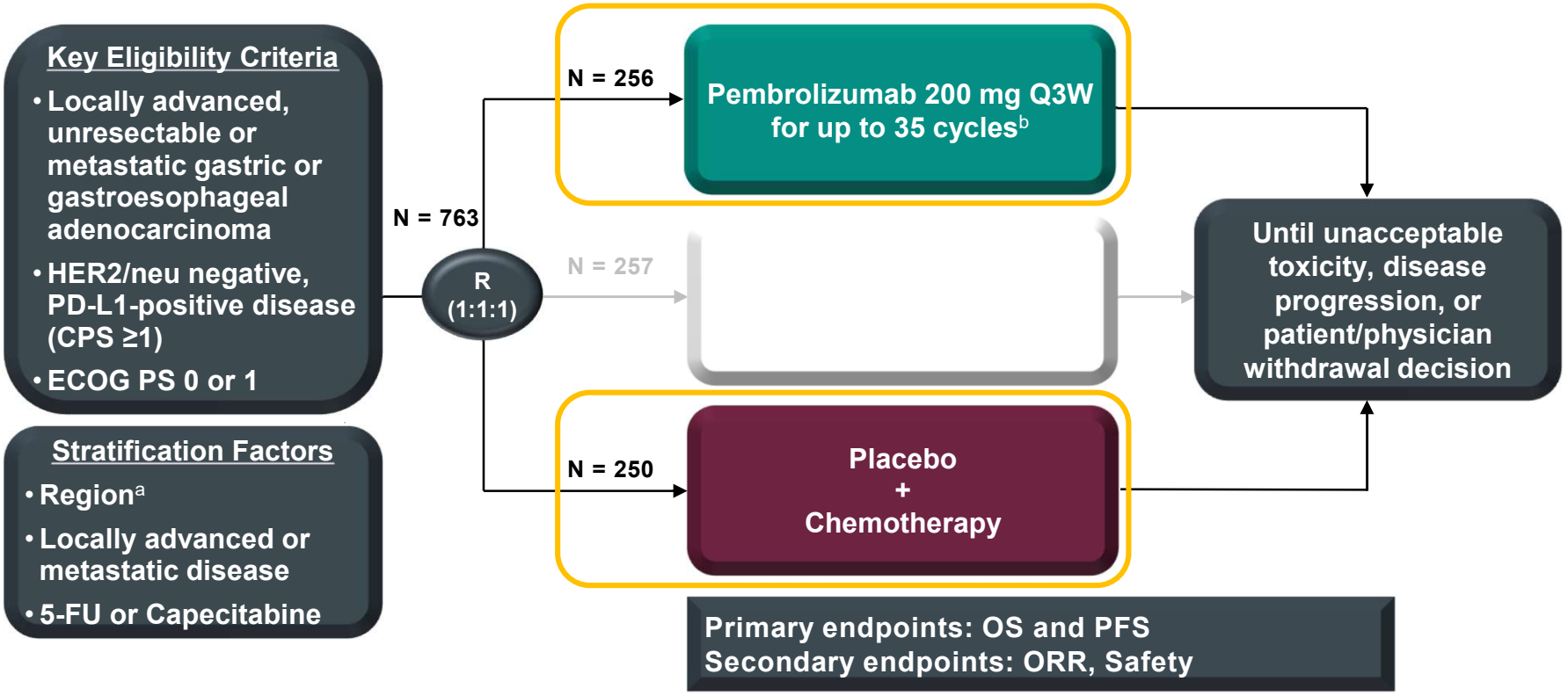
Statistical Considerations



- **Hypotheses in top row tested first and in parallel**
  - Remaining hypotheses tested only if preceding hypothesis was positive
  - Prespecified analysis plan allowed alpha passing from successful hypotheses
- **Final analysis: planned to occur ≥22 months after last patient was randomized and ~415 OS events observed in P+C and C treatment groups in patients with PD-L1 CPS ≥1**

[a]Alpha passed from non-inferiority to superiority test; Median follow-up, 11.3 months (range, 0.2-41.2); Data cutoff: March 26, 2019.

KEYNOTE-062: P vs C



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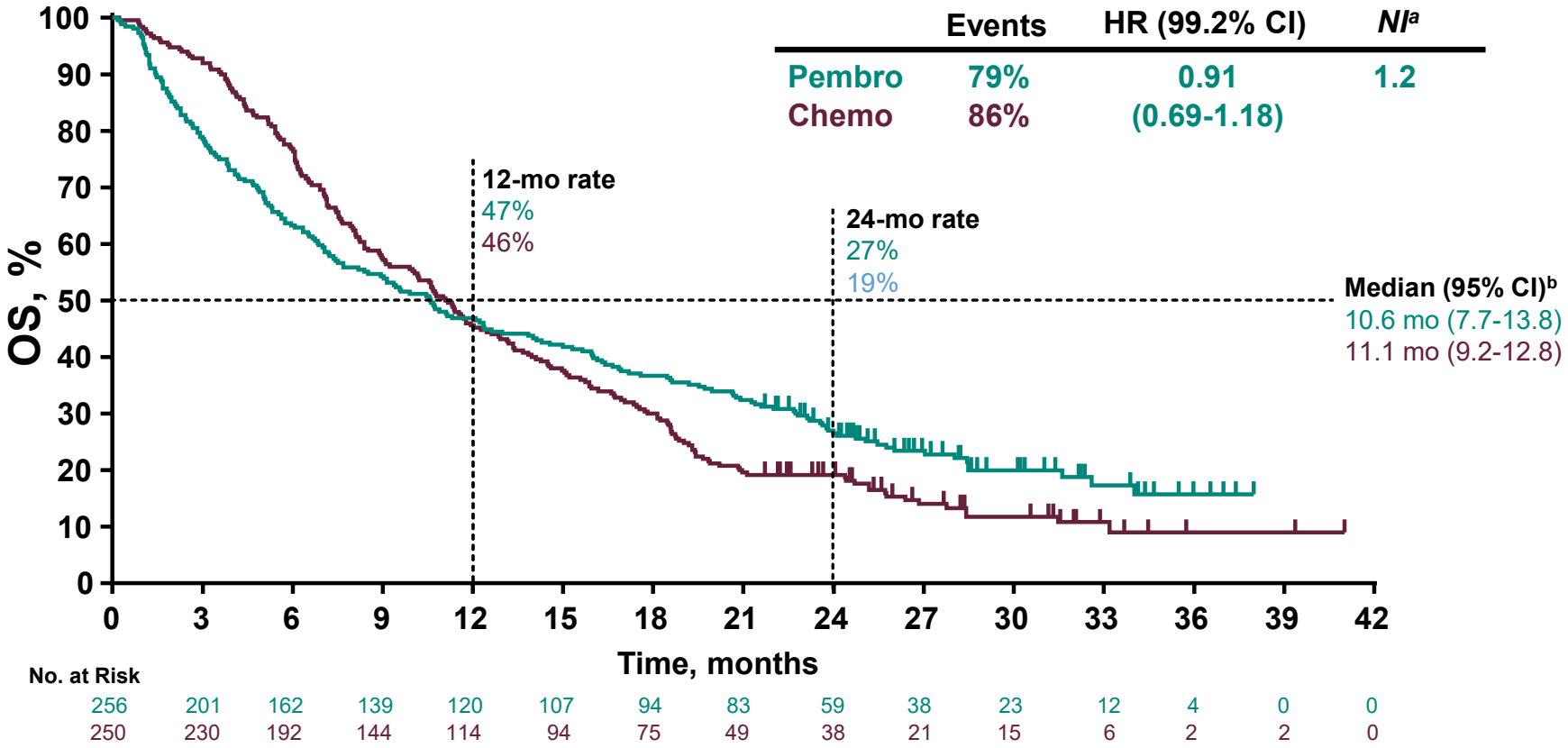
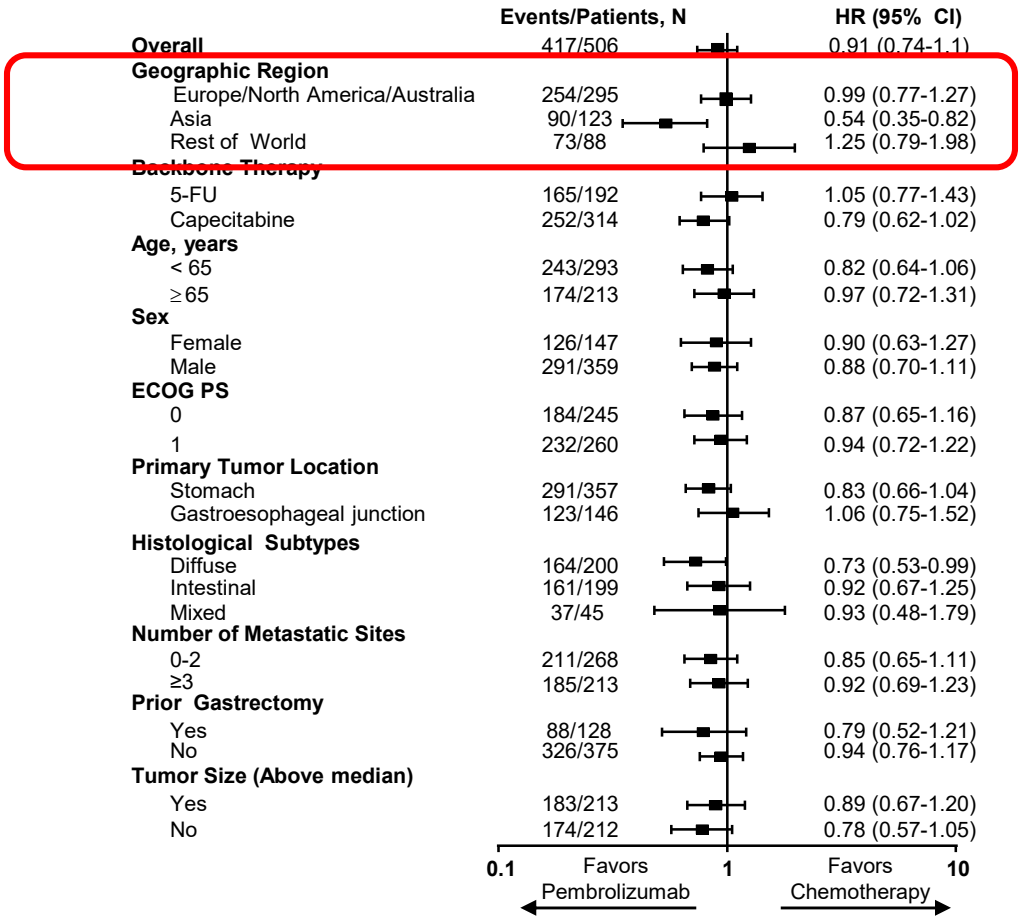
Overall Survival: P vs C (CPS ≥1)



[a]NI, non-inferiority margin; [b]HR (95% CI) = 0.91 (0.74-1.10), *P* = 0.162 for superiority of P vs C; Data cutoff: March 26, 2019.

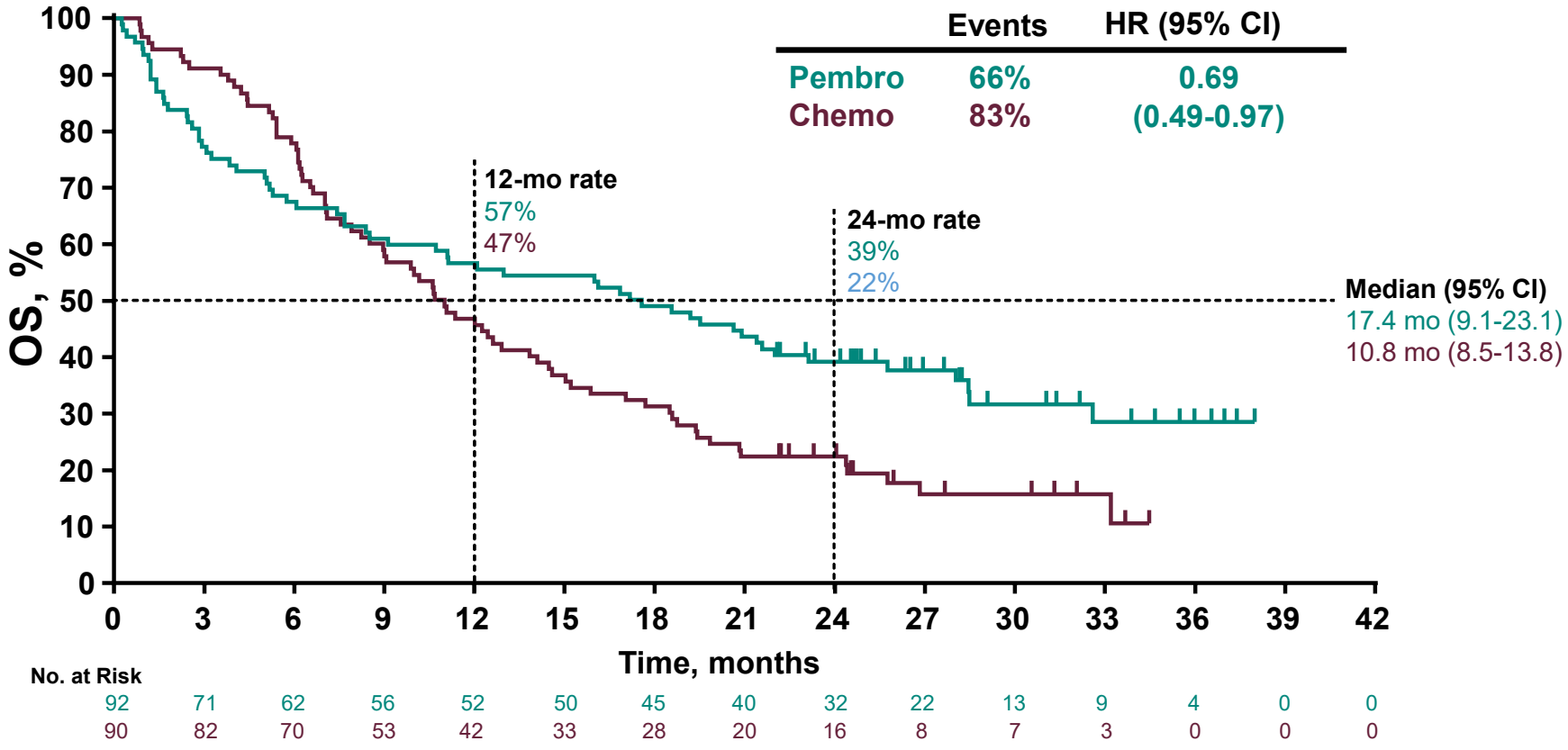
Overall Survival in Key Subgroups: P vs C

CPS ≥1



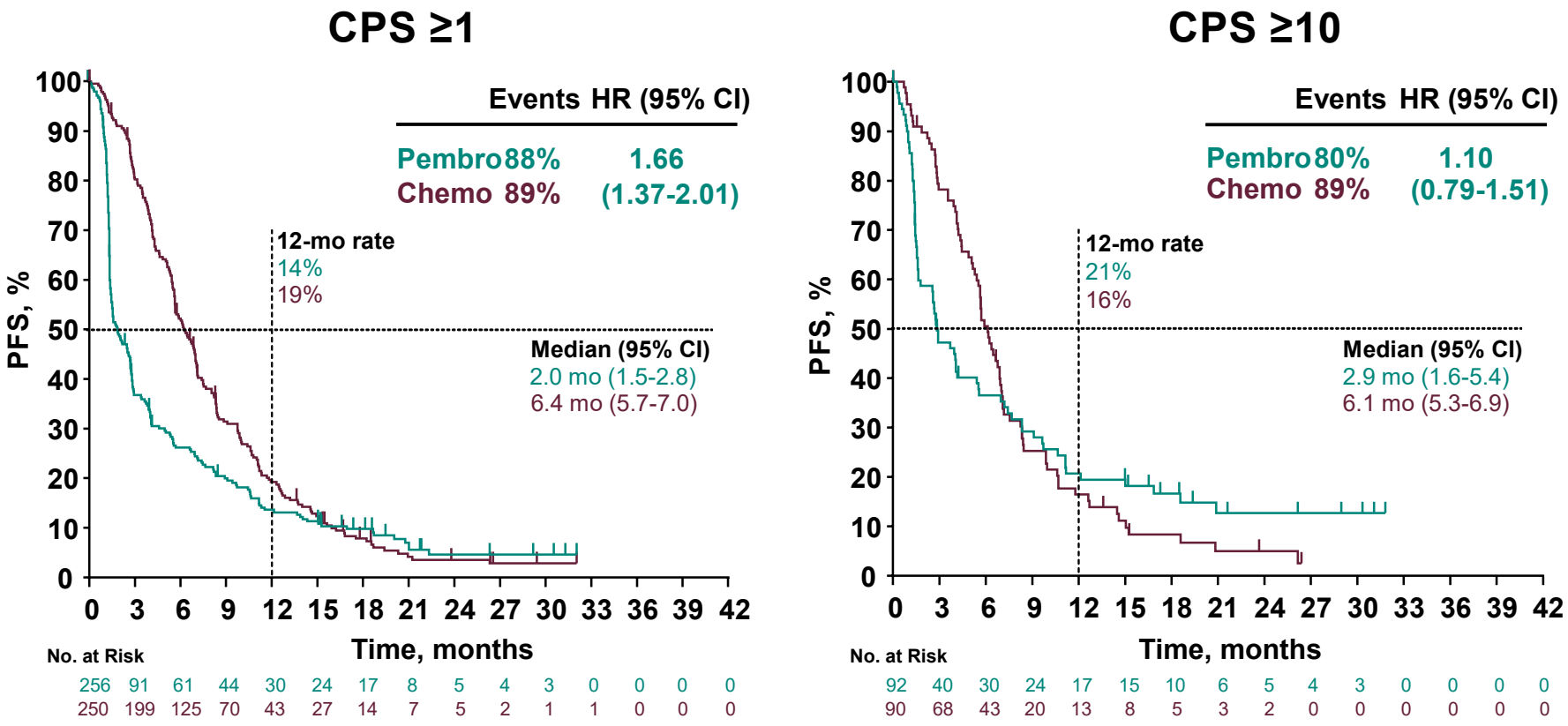
Data cutoff: March 26, 2019.

Overall Survival: P vs C (CPS ≥10)



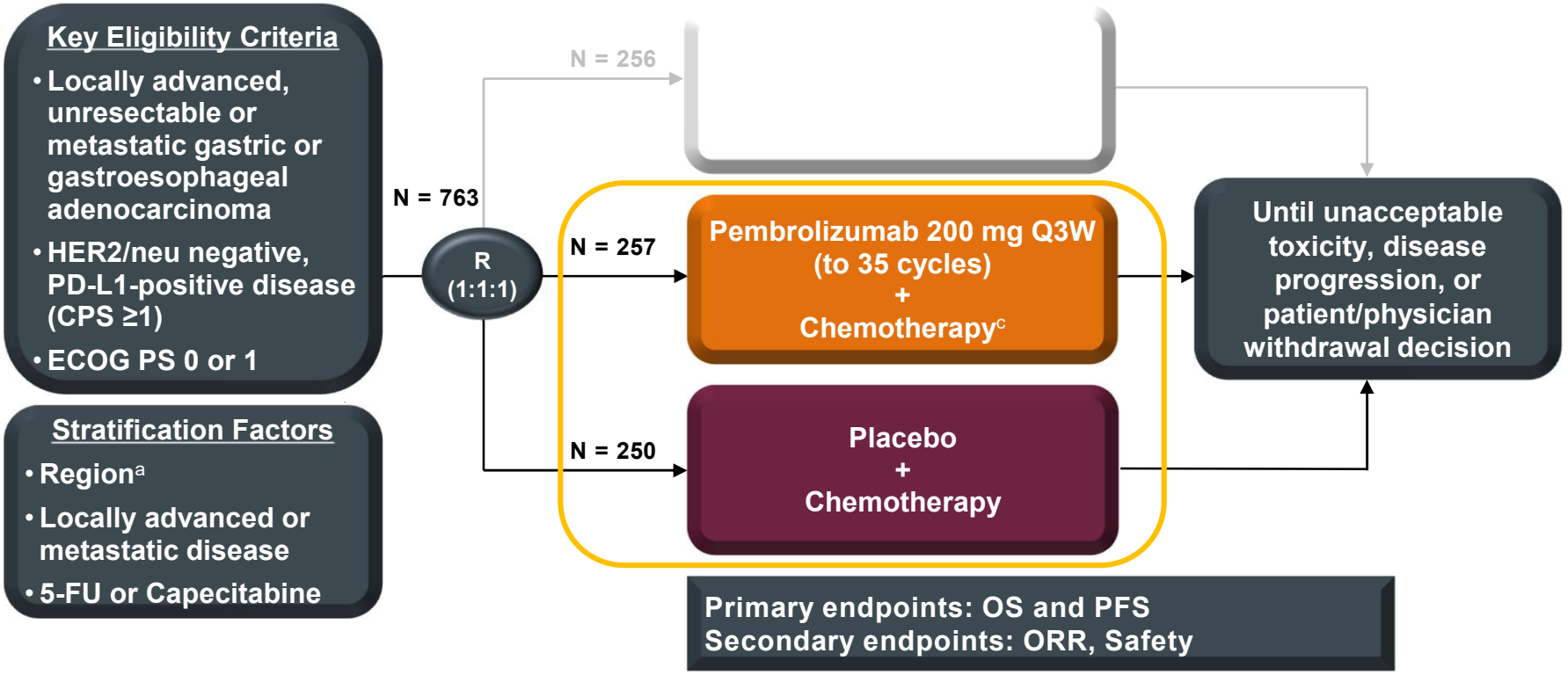
Data cutoff: March 26, 2019.

Progression-Free Survival: P vs C



PFS assessed per RECIST v1.1 by blinded independent central review (final analysis of PFS occurred at IA2); Data cutoff: Sept 28, 2018.

KEYNOTE-062: P+C vs C



[a]EU/North America/Australia, Asia (South Korea, Hong Kong, Taiwan, Japan), Rest of World (including South America).
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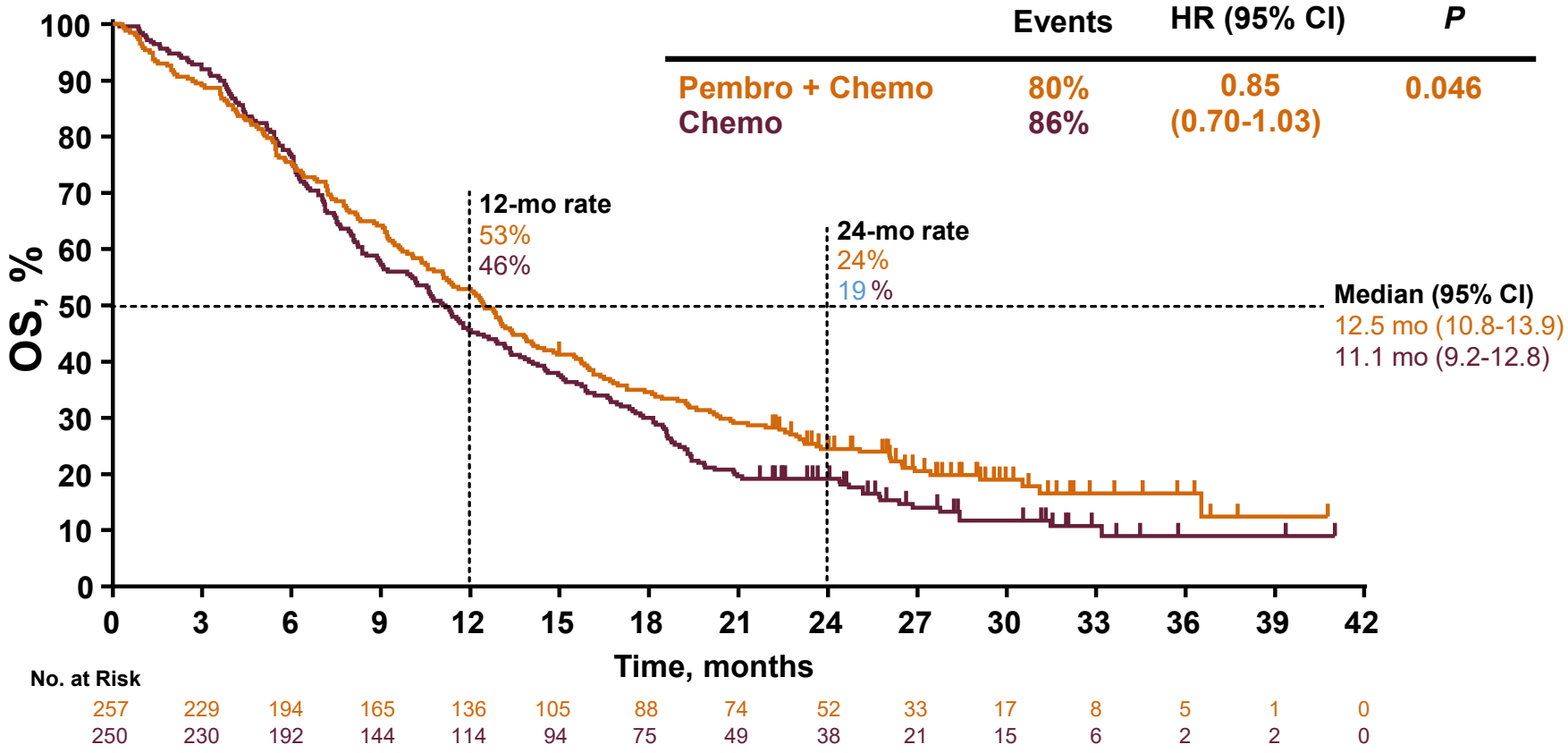
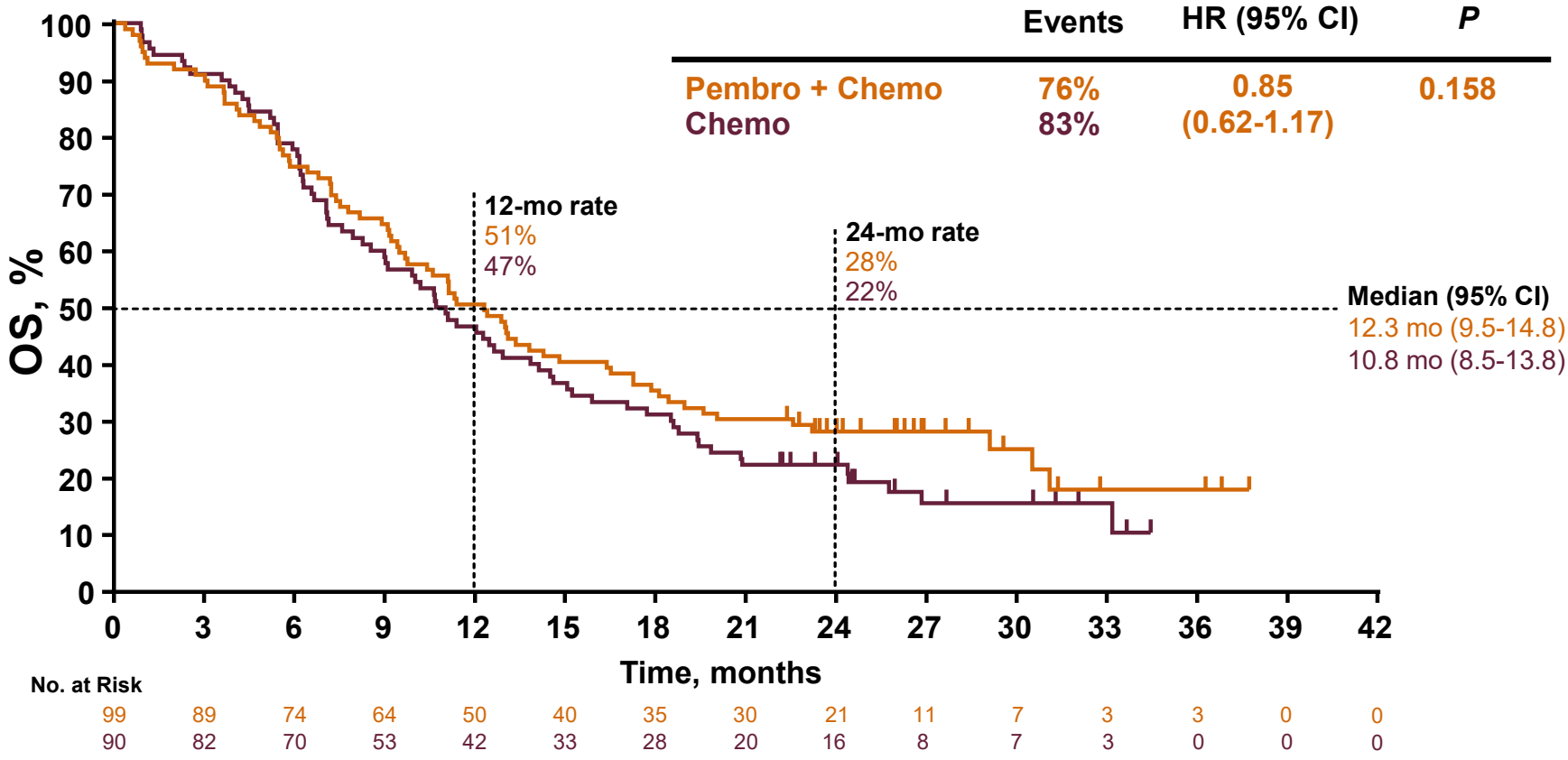
Overall Survival: P+C vs C (CPS ≥1)



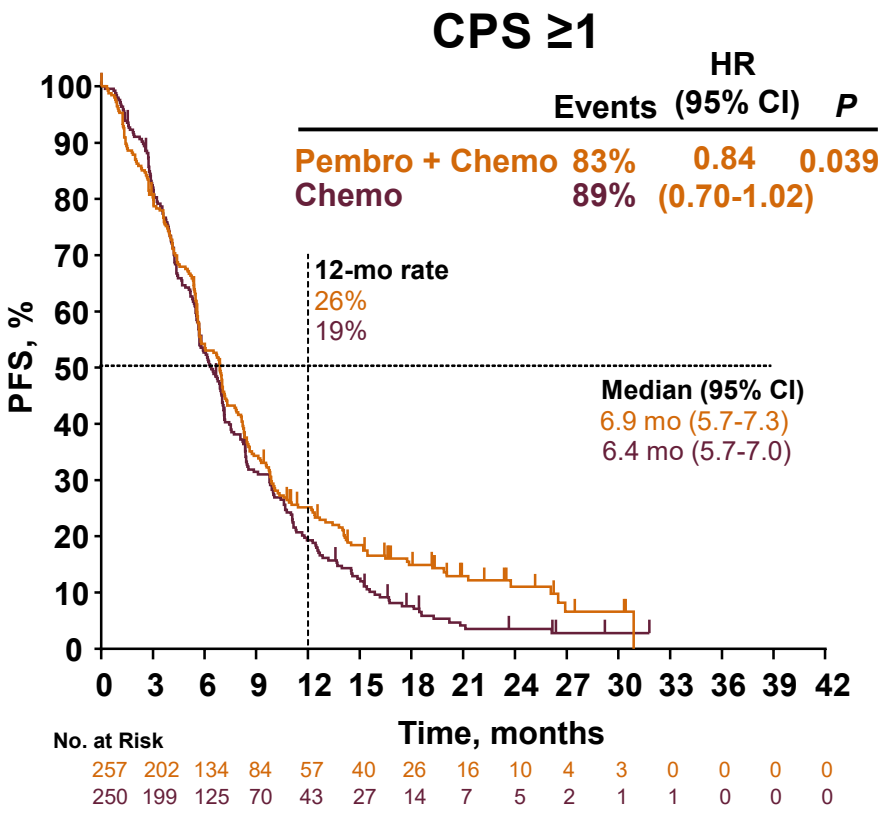
Data cutoff: March 26, 2019.

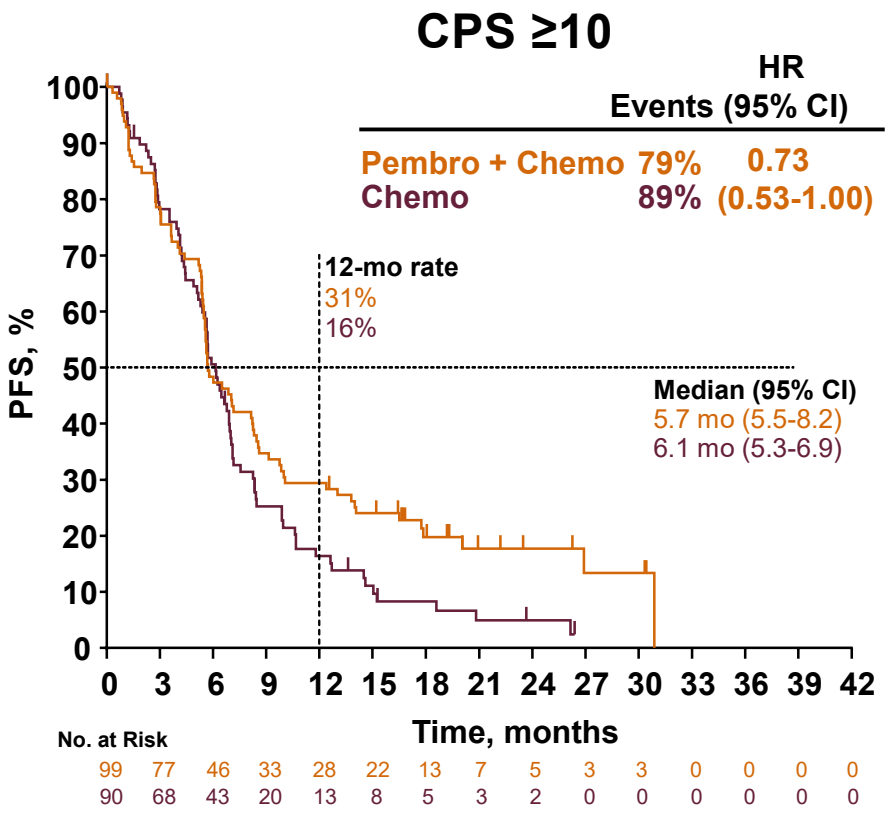
Overall Survival: P+C vs C (CPS ≥10)



Data cutoff: March 26, 2019.

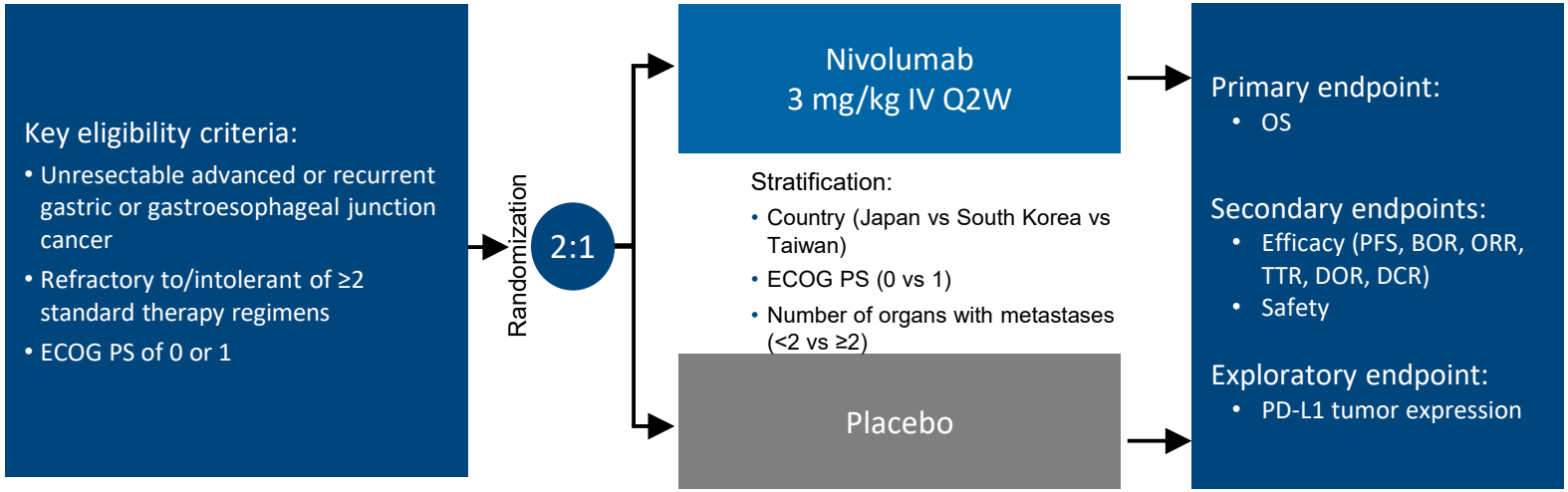
Progression-Free Survival: P+C vs C





PFS assessed per RECIST v1.1 by blinded independent central review (final analysis of PFS occurred at IA2); Data cutoff: Sept 28, 2018.

Phase 3 ATTRACTION-2: Nivolumab for GC after standard treatment

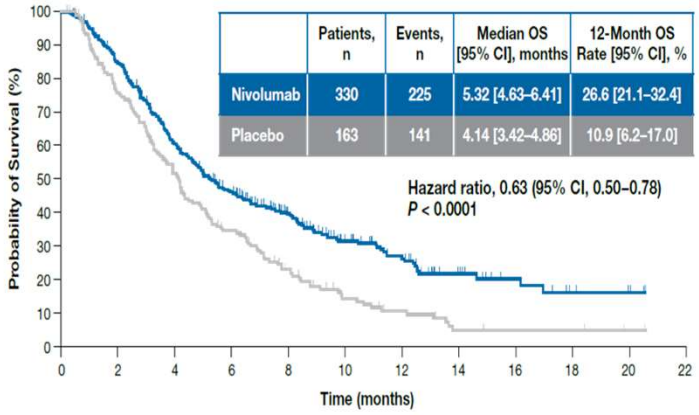


- Patients were permitted to continue treatment beyond initial RECIST v1.1–defined disease progression, as assessed by the investigator, if receiving clinical benefit and tolerating study drug
- Retrospective determination of tumor PD-L1 expression, defined as staining in ≥1% (or ≥5%) of tumor cells, was performed in a central laboratory using immunohistochemistry (28-8 pharmDx assay) for patients with available tumor samples

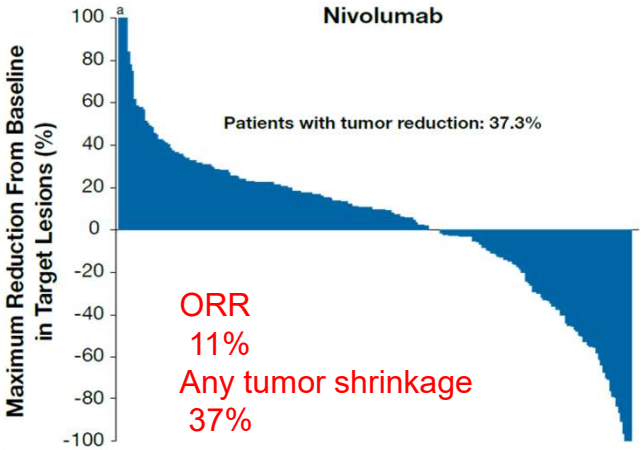
BOR, best overall response; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV; intravenous; ORR, objective response rate; PFS, progression-free survival; Q2W, every 2 weeks; RECIST, Response Evaluation Criteria In Solid Tumors; TTR, time to tumor response

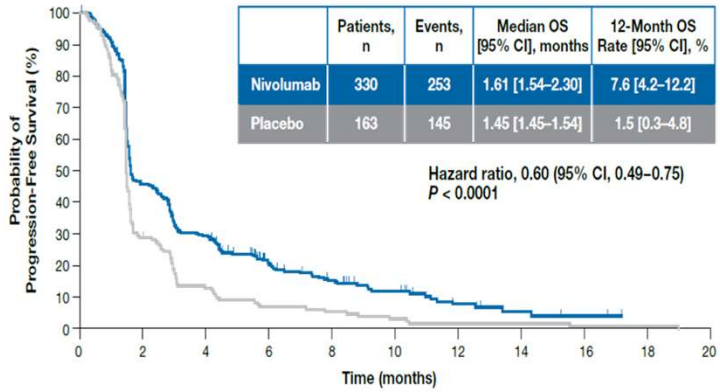
Kang YK et al. *Lancet* 2017 Dec 2;390(10111):2461-2471

Phase 3 ATTRACTION-2:
Nivolumab for GC after standard treatment



	Patients, n	Events, n	Median OS [95% CI], months	12-Month OS Rate [95% CI], %
Nivolumab	330	225	5.32 [4.63–6.41]	26.6 [21.1–32.4]
Placebo	163	141	4.14 [3.42–4.86]	10.9 [6.2–17.0]





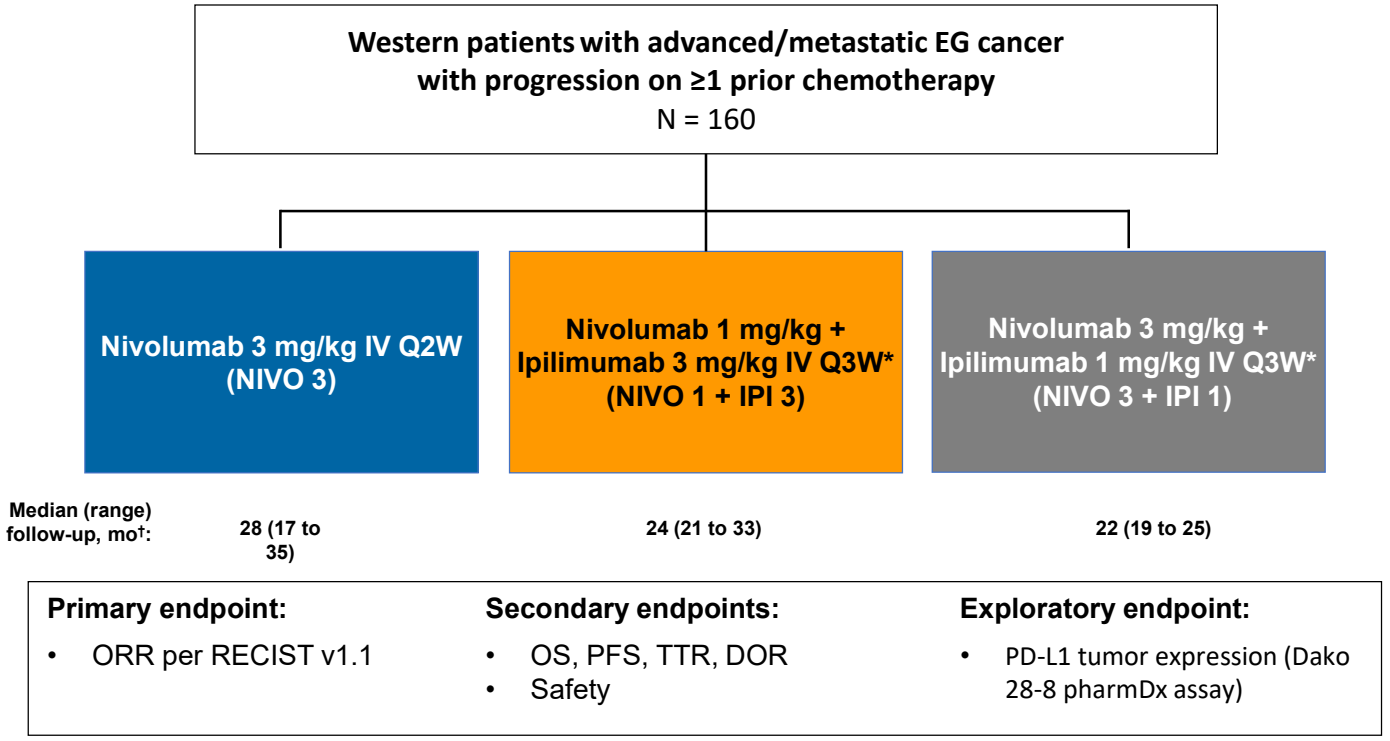
	Patients, n	Events, n	Median OS [95% CI], months	12-Month OS Rate [95% CI], %
Nivolumab	330	253	1.61 [1.54–2.30]	7.6 [4.2–12.2]
Placebo	163	145	1.45 [1.45–1.54]	1.5 [0.3–4.8]

Significant OS benefit in Asian pts
(mOS +1.2ms, 1y OS 26.6%, HR 0.63)

Well tolerated in pretreated GC pts
(d/c by AE 7% same with placebo)

Kang YK et al., Lancet 2017

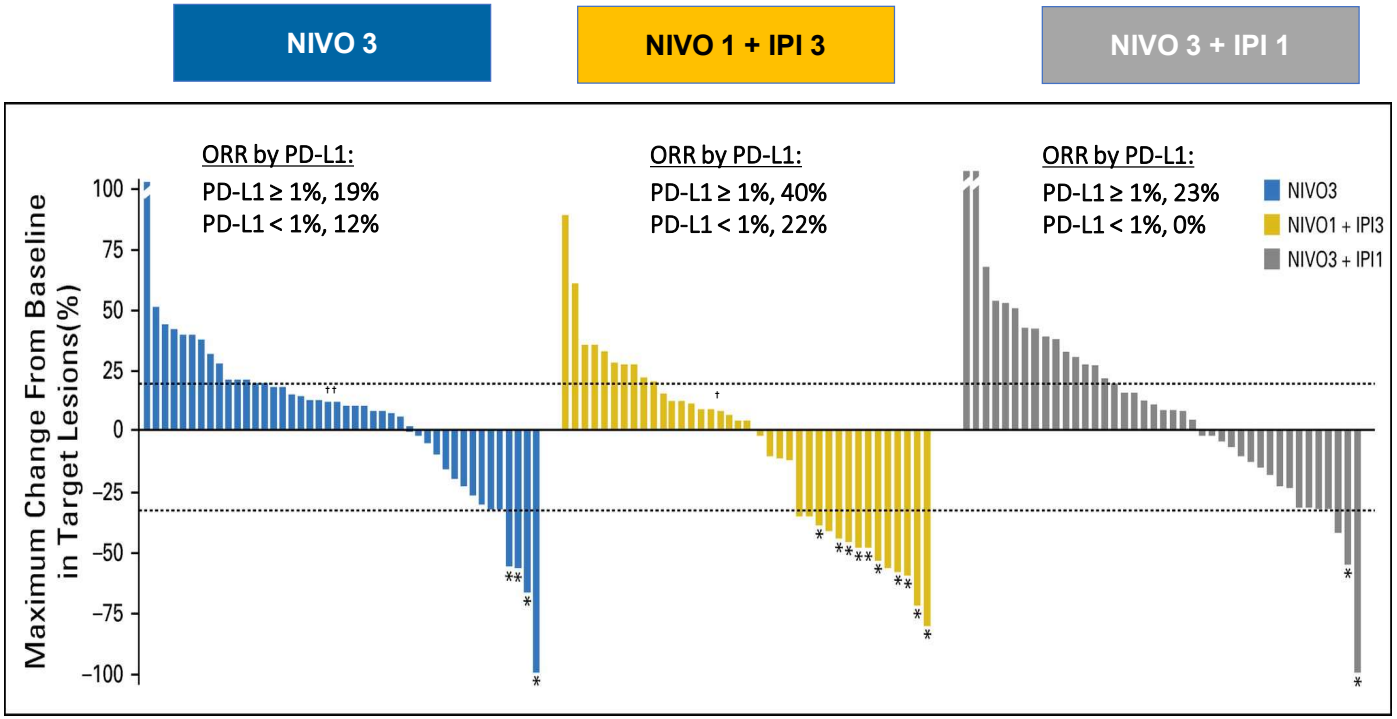
Nivolumab +/- IPI Checkmate 032 EG



DOR, duration of response; EG, esophagogastric (including gastric/esophageal/gastroesophageal junction cancer); TTR, time to response.
* Nivolumab + ipilimumab combination treatment administered for 4 cycles followed by nivolumab 3 mg/kg IV Q2W.
† Time from first dose to data cut-off.

Janjiigian et al., JCO 2018

Best Reduction in Target Lesions

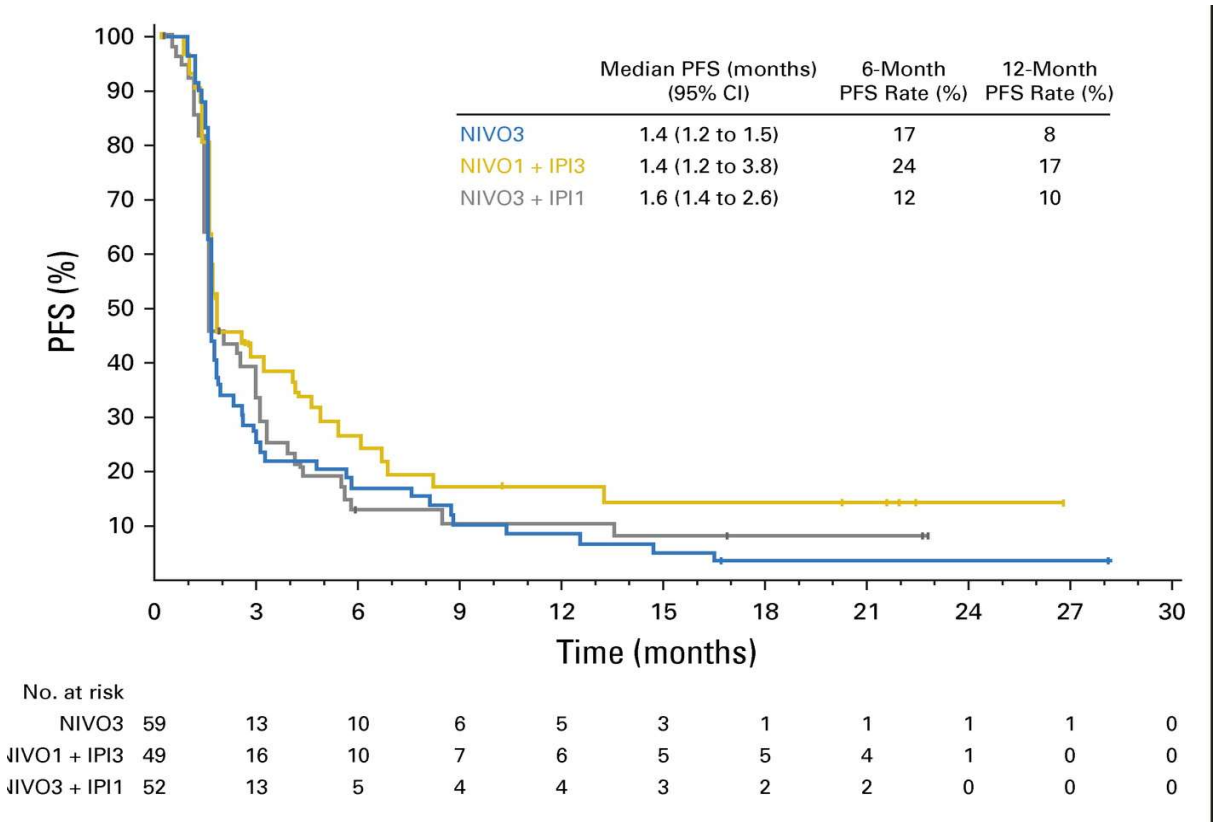


- **Responses were observed regardless of PD-L1 expression**

* Investigator review.
* Patients with confirmed response (complete or partial response).

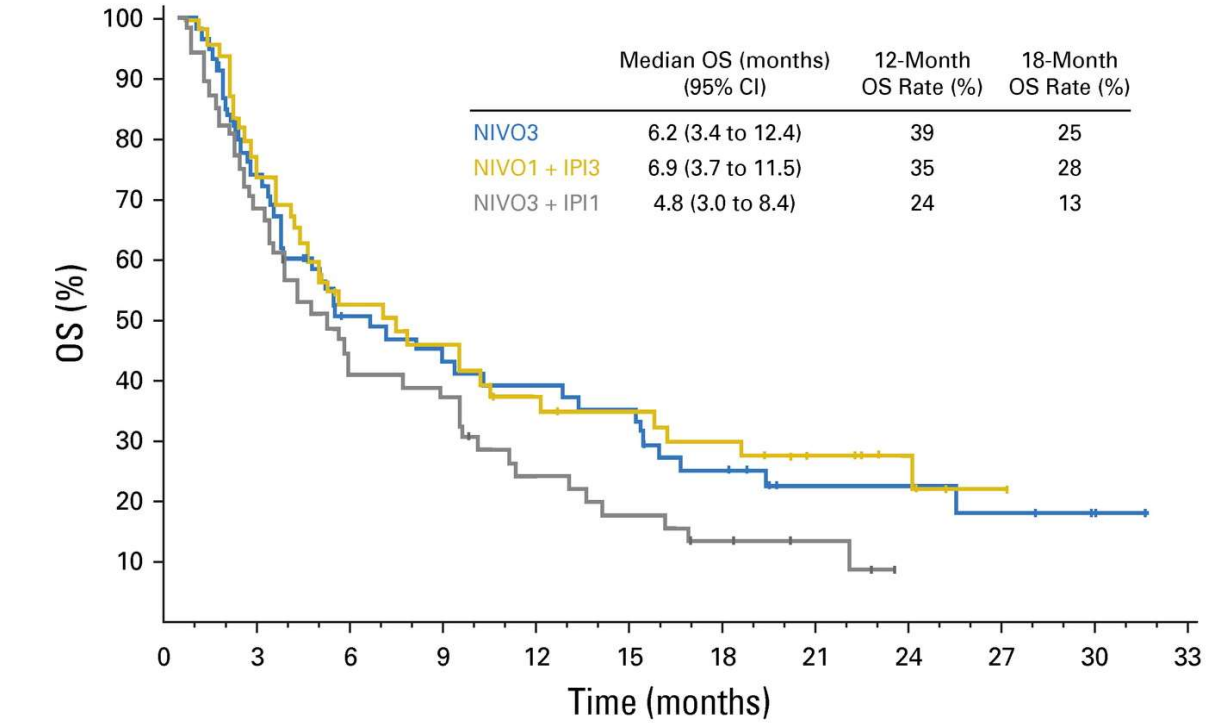
Janjiigian et al., JCO 2018

Progression-Free Survival



Janjiigian et al., JCO 2018

Overall Survival



	Median OS (months) (95% CI)	12-Month OS Rate (%)	18-Month OS Rate (%)
NIVO3	6.2 (3.4 to 12.4)	39	25
NIVO1 + IPI3	6.9 (3.7 to 11.5)	35	28
NIVO3 + IPI1	4.8 (3.0 to 8.4)	24	13

No. at risk												
NIVO3	59	40	26	21	20	15	11	5	5	4	1	0
NIVO1 + IPI3	49	35	24	19	14	14	11	8	3	0	0	0
NIVO3 + IPI1	52	33	20	18	11	8	4	3	0	0	0	0

Janjiigian et al., JCO 2018

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 (clinical deterioration and possible tumor lysis syndrome after 1 dose of NIVO 3 + IPI 1)**

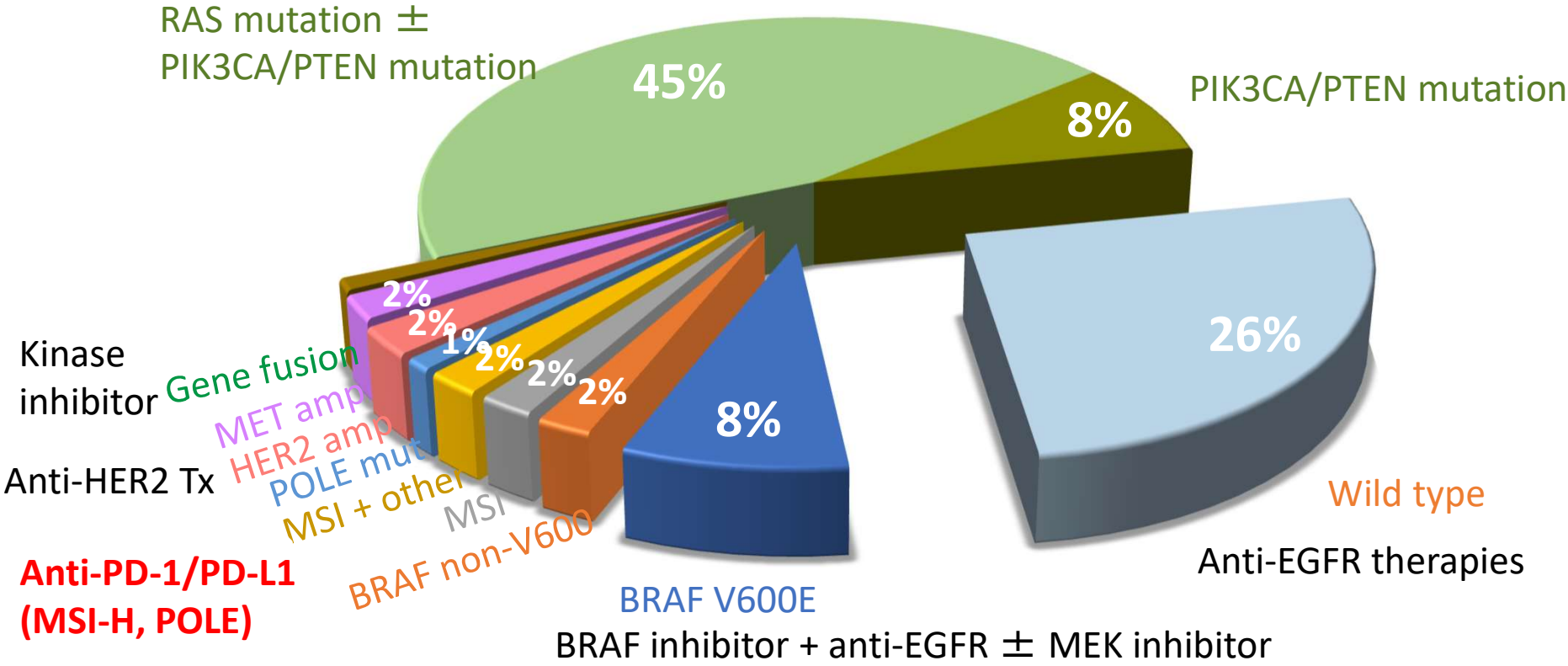
TRAE, treatment-related adverse event.

Janjiigian et al., JCO 2018

Ongoing Phase III Clinical Trials in Gastric and GEJ Adenocarcinoma

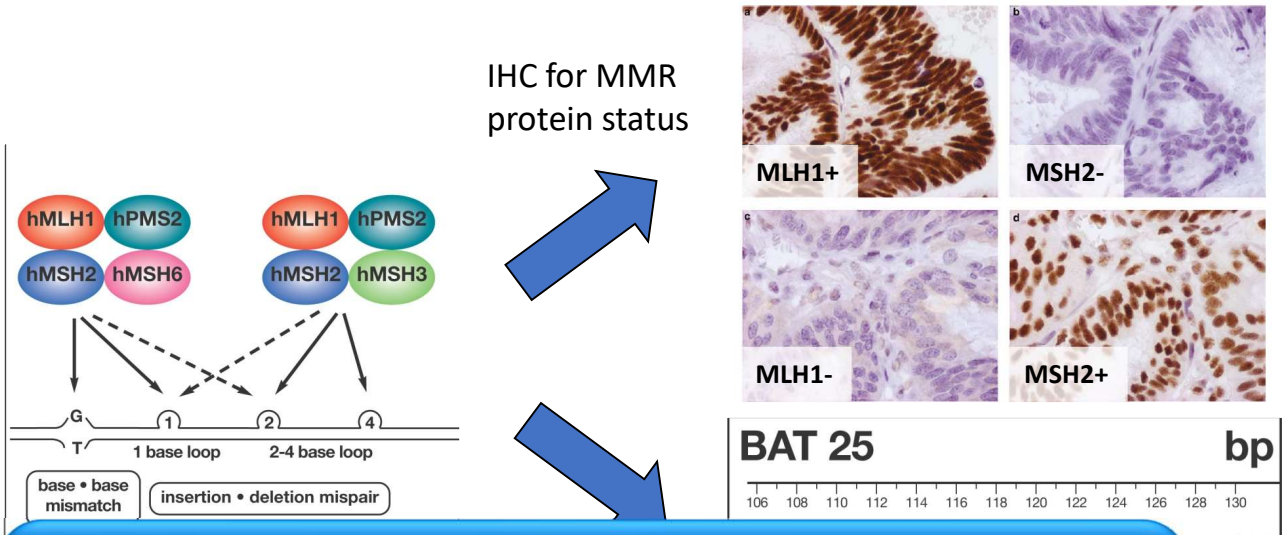
Study	Line	#	Endpoint	Selection	Intervention
Javelin Gastric 100	1st	666	OS + PFS		**ASCO GI 2020: negative**
Keynote 859	1st	780	OS		Pembrolizumab +Cis/5-FU or CAPOX vs. Cis/5-FU or CAPOX
Keynote 811	1st	732	OS + PFS	HER2+	Pembrolizumab + Trastuzumab + Cis/5-FU or CAPOX vs Trastuzumab + Cis/5-FU or CAPOX
CheckMate649	1st	2005	OS	PD-L1+	Nivolumab + CAPOX/FOLFOX vs. Nivolumab/Ipilimumab vs. CAPOX/FOLFOX
SHR-1210-III-311	1st	568	OS	PD-L1+	SHR-1210 (anti-PD1)/CAPOX vs CAPOX
Keynote-063	2nd	360	OS	PD-L1+	Pembrolizumab vs. Paclitaxel
Javelin Gastric 300	3rd	371	OS		Avelumab vs. Irinotecan or paclitaxel or BSC

Genomic Markers in CRC



Dienstmann. ASCO Ed Book. 2018.

Mismatch Repair Deficiency (MMR-D): Unique Biological Subgroup of Colon Cancer



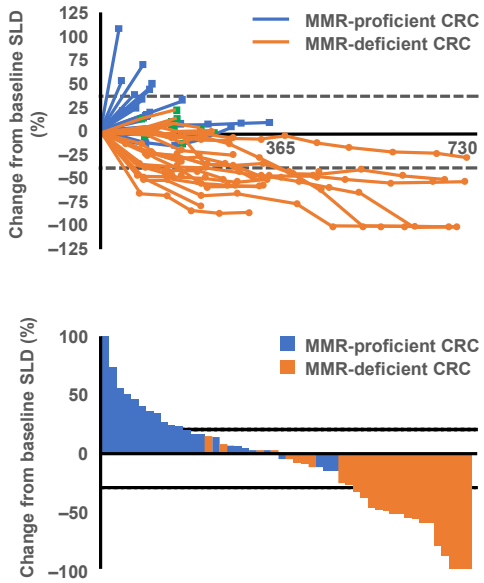
Thus, IHC for MMR proteins and PCR for MSI detect two manifestations of the same tumor biology:

- MMR-D is synonymous with MSI-H
- MMR-P is synonymous with MSI-L/MSS

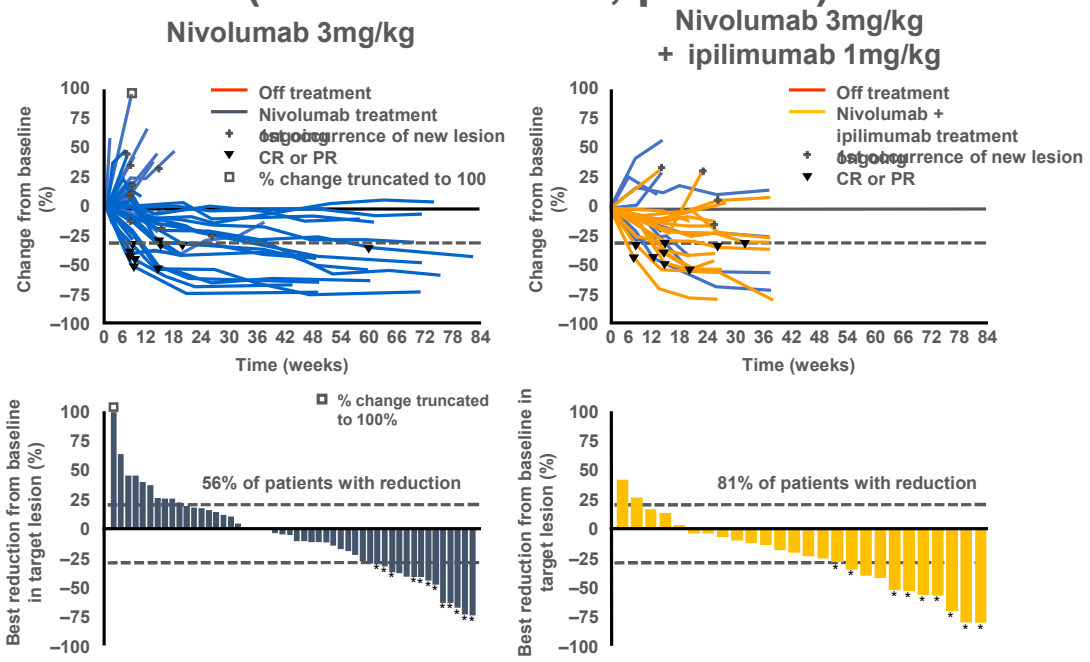
Imai and
Umetani
Rosen et a

MSI-high CRCs are responsive to PD-1 inhibitors

Pembrolizumab (KEYNOTE 016, phase II)[1,*]



Nivolumab ± ipilimumab (CheckMate-142, phase II)[2]

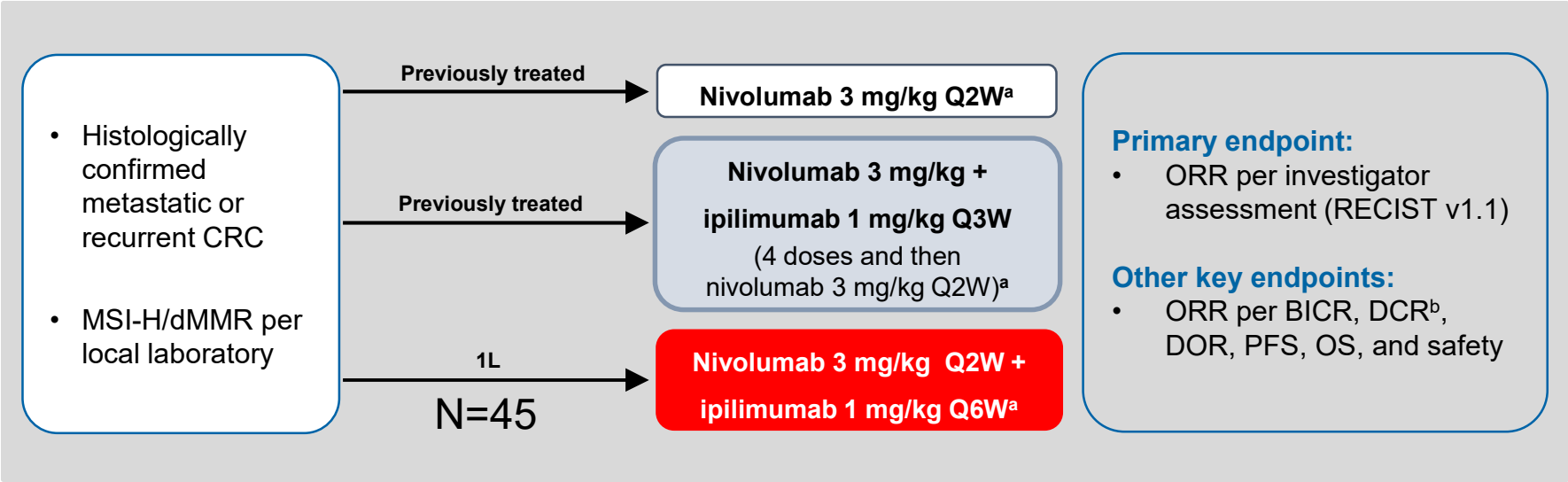


- ***Lynch Syndrome (yes/no/unknown): MMR-deficient CRC = 54/7/39; MMR-proficient CRC = 0/100/0**

1. Le et al. ASCO 2016; 2.Overman et al. ASCO 2016

CheckMate-142 Study Design

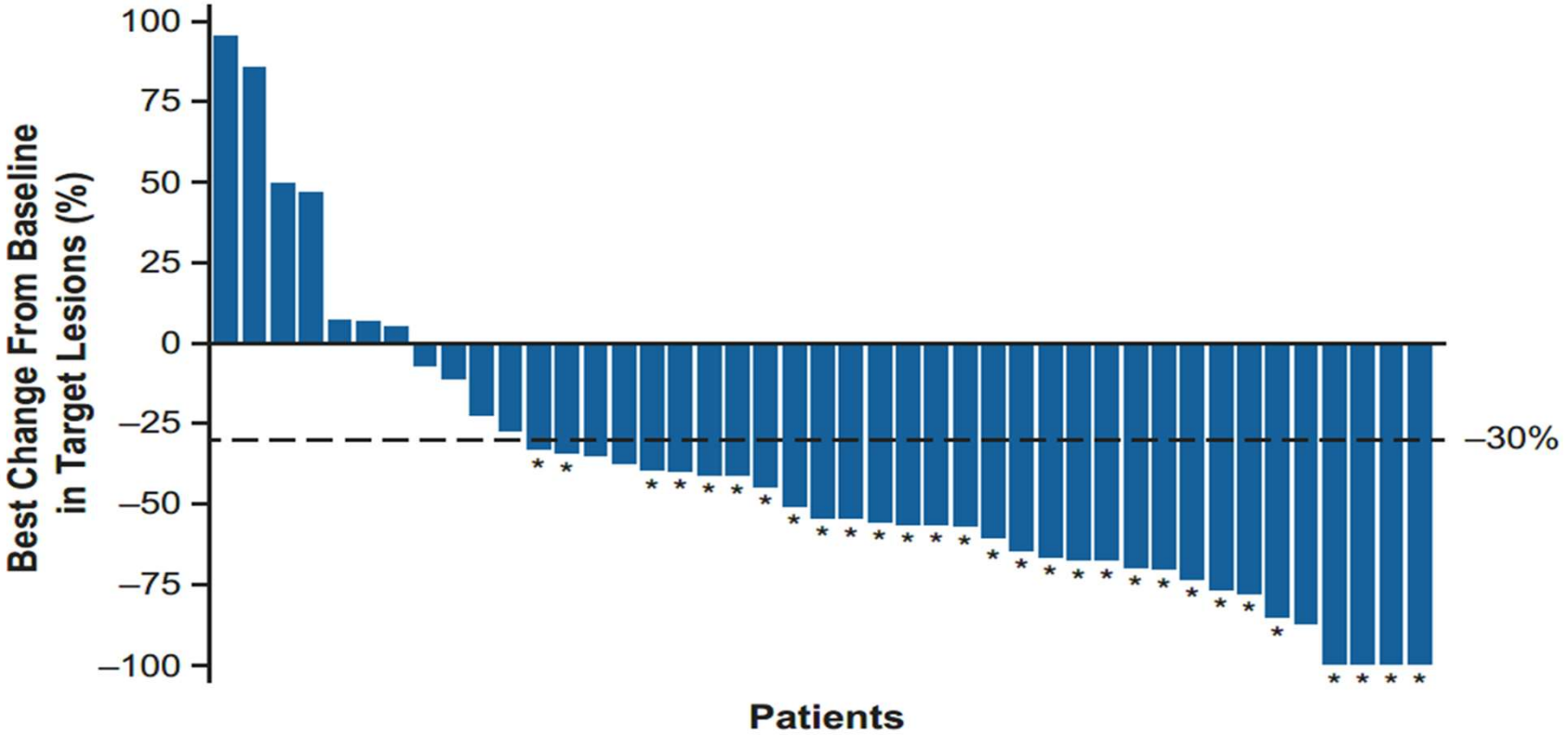
- CheckMate-142 is an ongoing, multi-cohort, nonrandomized phase 2 study evaluating the efficacy and safety of nivolumab-based therapies in patients with mCRC (NCT02060188)



[a]Until disease progression or discontinuation in patients receiving study therapy beyond progression, discontinuation due to toxicity, withdrawal of consent, or the study end; [b]Patients with a CR, PR, or SD for ≥12 weeks divided by the number of treated patients; [c]Time from first dose to data cutoff
BICR = blinded independent central review

Lenz et al., ESMO 2018, ASCO GI 2020

Best Reduction in Target Lesions

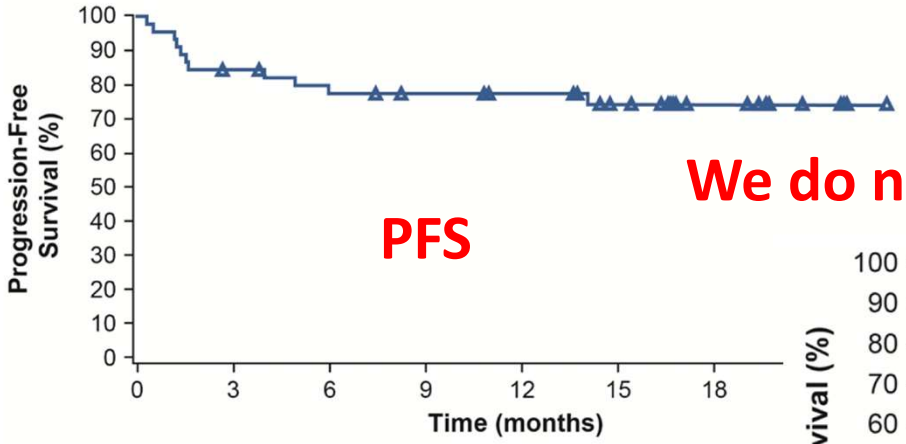


- 84% of patients had a reduction in tumor burden from baseline

*Confirmed response per investigator assessment
[a]Evaluable patients per investigator assessment

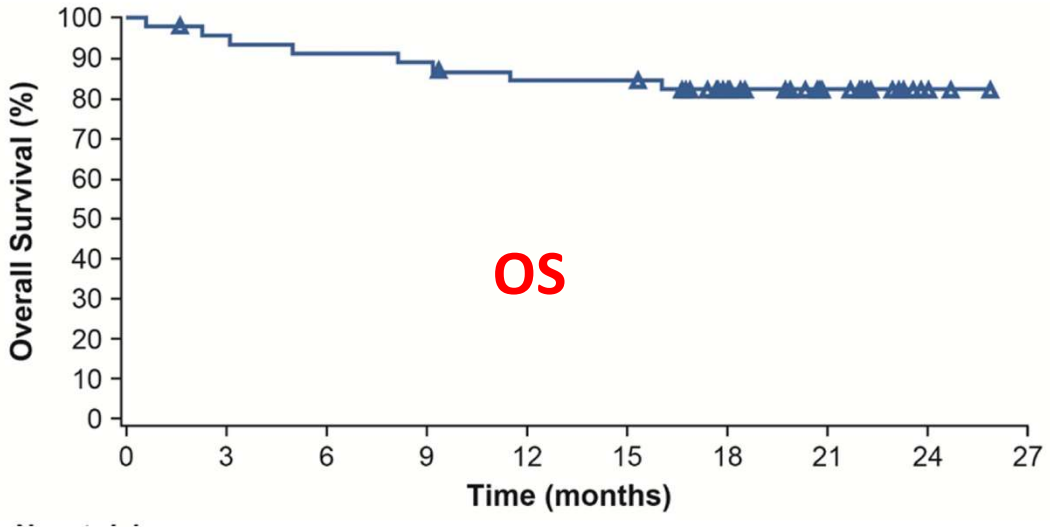
Lenz et al., ASCO GI 2020

Progression-Free and Overall Survival



PFS

We do not see this with chemotherapy!

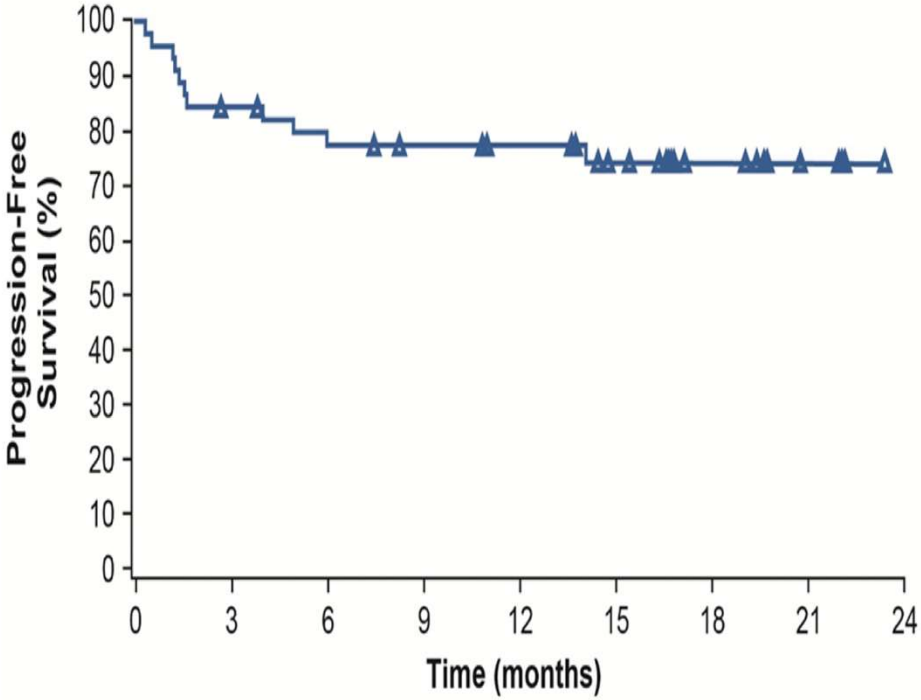


OS

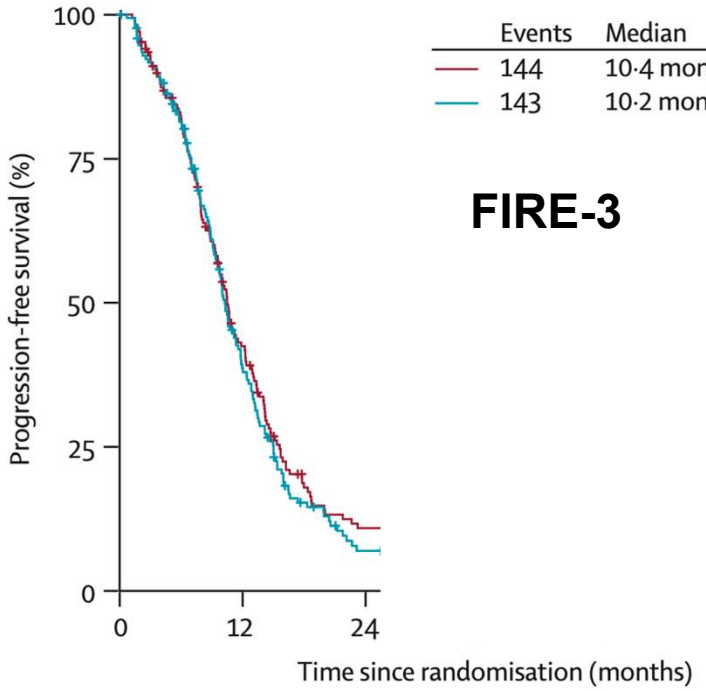
Median follow-up: 20 months

Lenz et al., ASCO GI 2020

Progression-Free Survival



Lenz et al., ASCO GI 2020

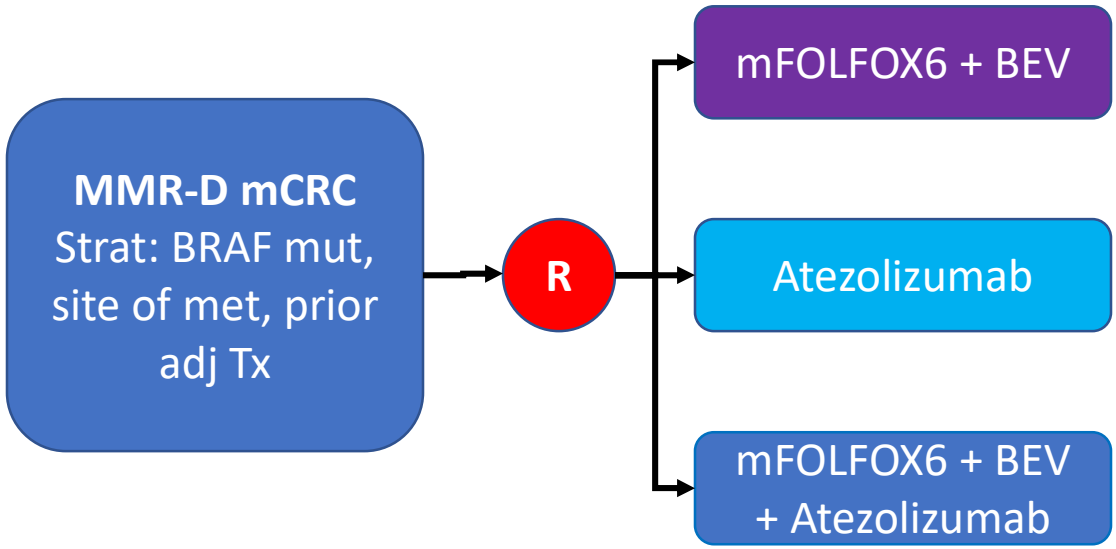


	Events	Median	95% CI
—	144	10·4 months	9·5–12·2
—	143	10·2 months	9·3–11·5

FIRE-3

Heinemann et al., Lancet Oncol 2014

Evaluation of First-Line IO in MSI-H mCRC is Ongoing



COMMIT Trial
NRG-GI004/
SWOG 1610

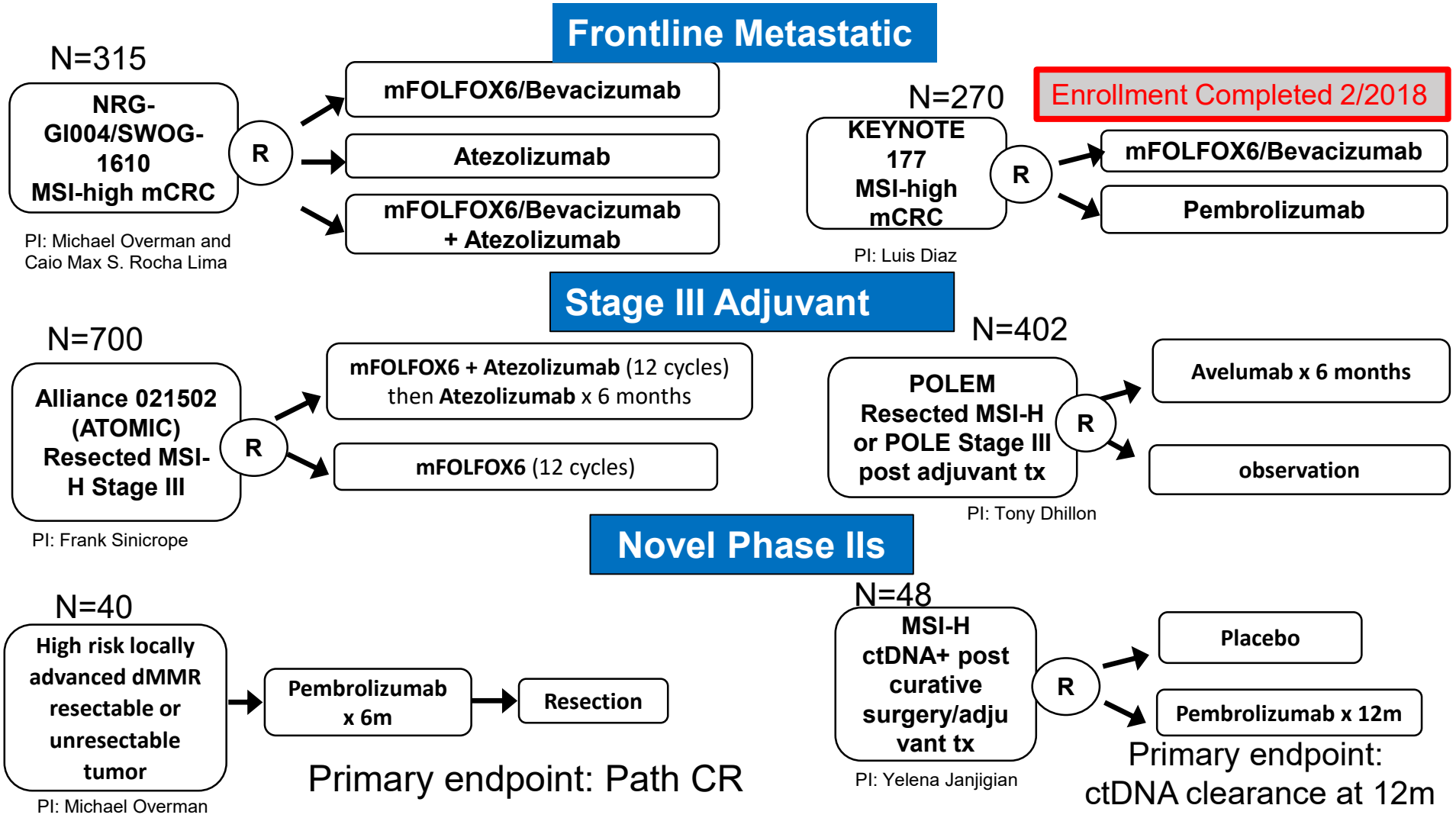
N=51/347
(since 11/17)

Primary EP: PFS

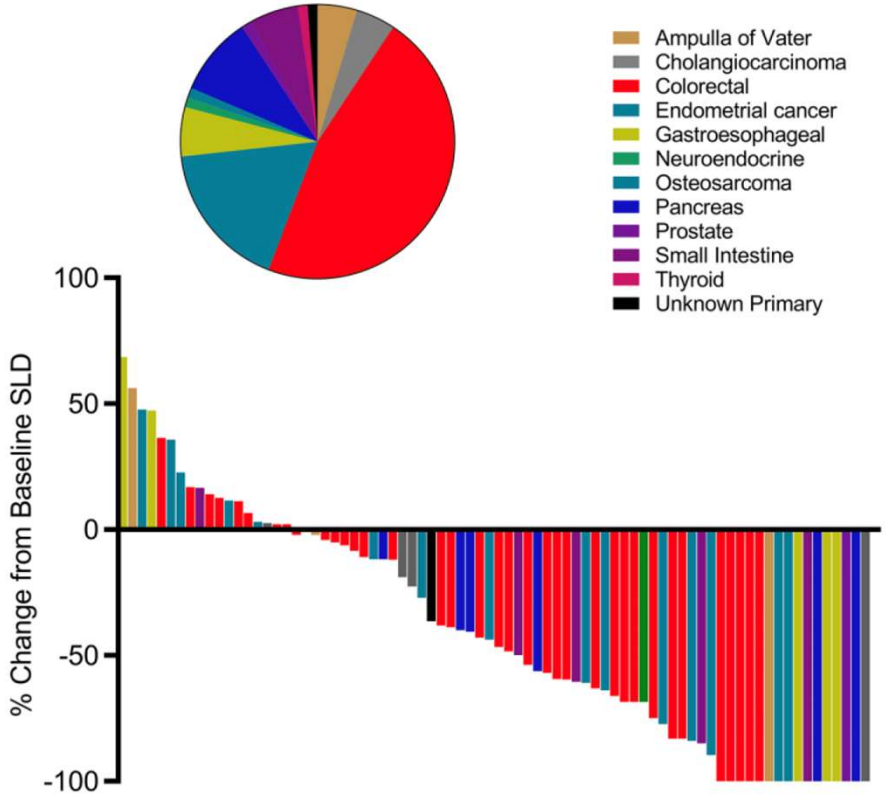
To be redesigned,
Atezo alone arm dropped

KEYNOTE-177 has finished accrual
Results TBD

PIs: James Lee, Mike Overman


Frontline Metastatic
N=315
NRG-GI004/SWOG-1610
MSI-high mCRC
R
mFOLFOX6/Bevacizumab
Atezolizumab
mFOLFOX6/Bevacizumab + Atezolizumab
PI: Michael Overman and Caio Max S. Rocha Lima
N=270
Enrollment Completed 2/2018
KEYNOTE 177
MSI-high mCRC
R
mFOLFOX6/Bevacizumab
Pembrolizumab
PI: Luis Diaz
Stage III Adjuvant
N=700
Alliance 021502 (ATOMIC)
Resected MSI-H Stage III
R
mFOLFOX6 + Atezolizumab (12 cycles) then Atezolizumab x 6 months
mFOLFOX6 (12 cycles)
PI: Frank Sinicrope
N=402
POLEM
Resected MSI-H or POLE Stage III post adjuvant tx
R
Avelumab x 6 months
observation
PI: Tony Dhillon
Novel Phase IIs
N=40
High risk locally advanced dMMR resectable or unresectable tumor
Pembrolizumab x 6m
Resection
Primary endpoint: Path CR
PI: Michael Overman
N=48
MSI-H ctDNA+ post curative surgery/adjuvant tx
R
Placebo
Pembrolizumab x 12m
Primary endpoint: ctDNA clearance at 12m
PI: Yelena Janjigian

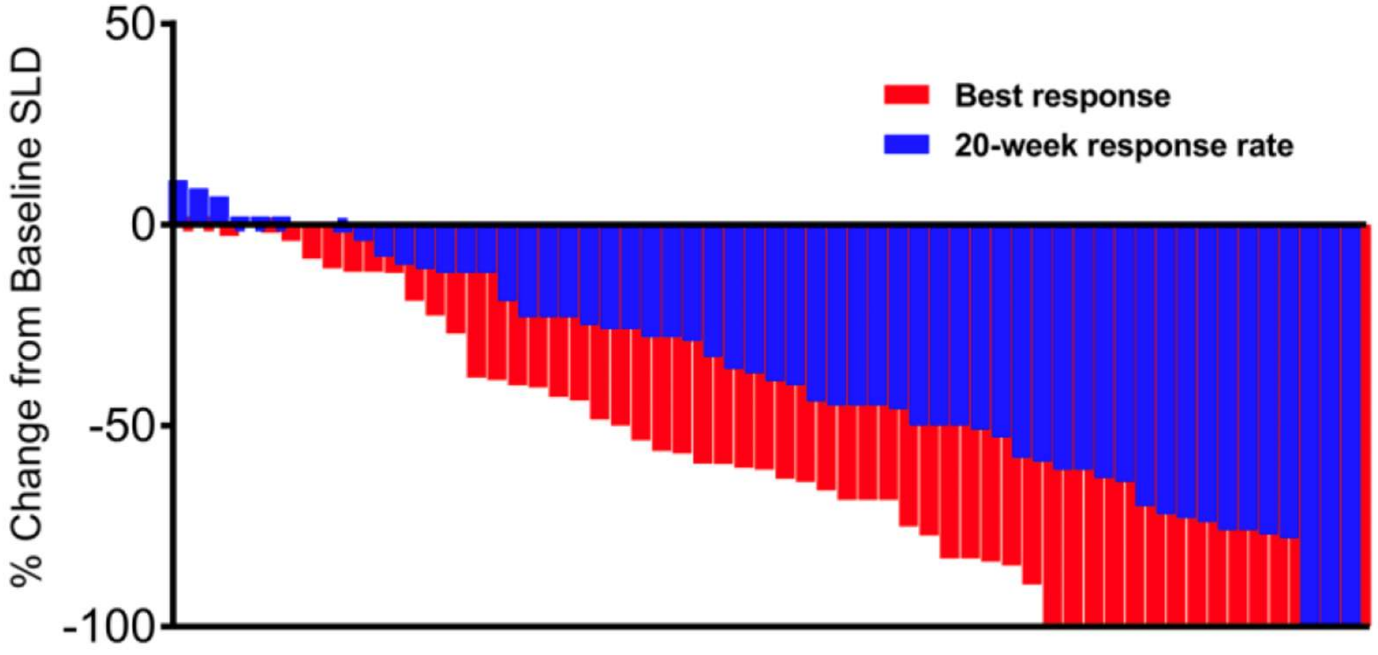
Response of MMR-D/ MSI-H Cancers to Pembrolizumab Monotherapy



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%

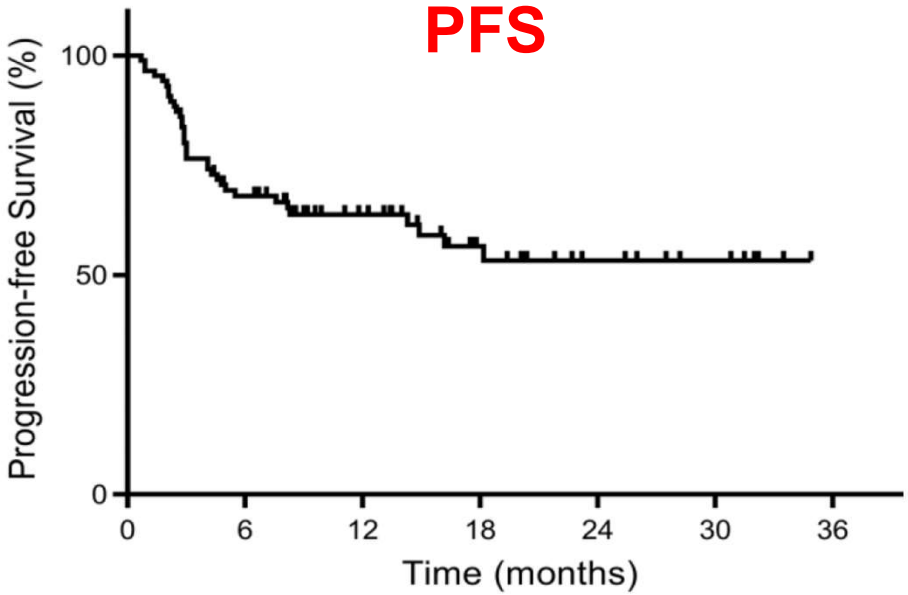
Le et al., Science 2017

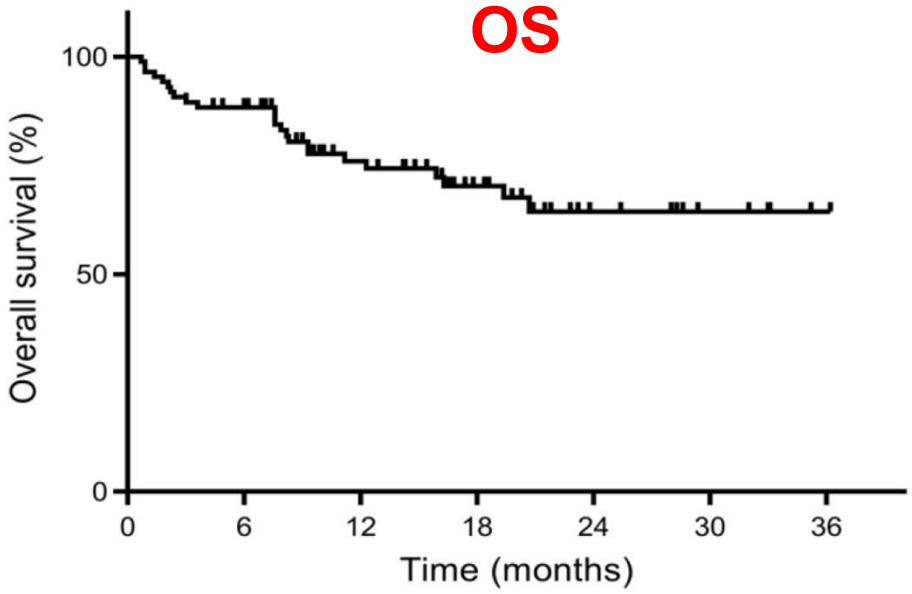
Response of MMR-D/ MSI-H Cancers to Pembrolizumab Monotherapy



Le et al., Science 2017

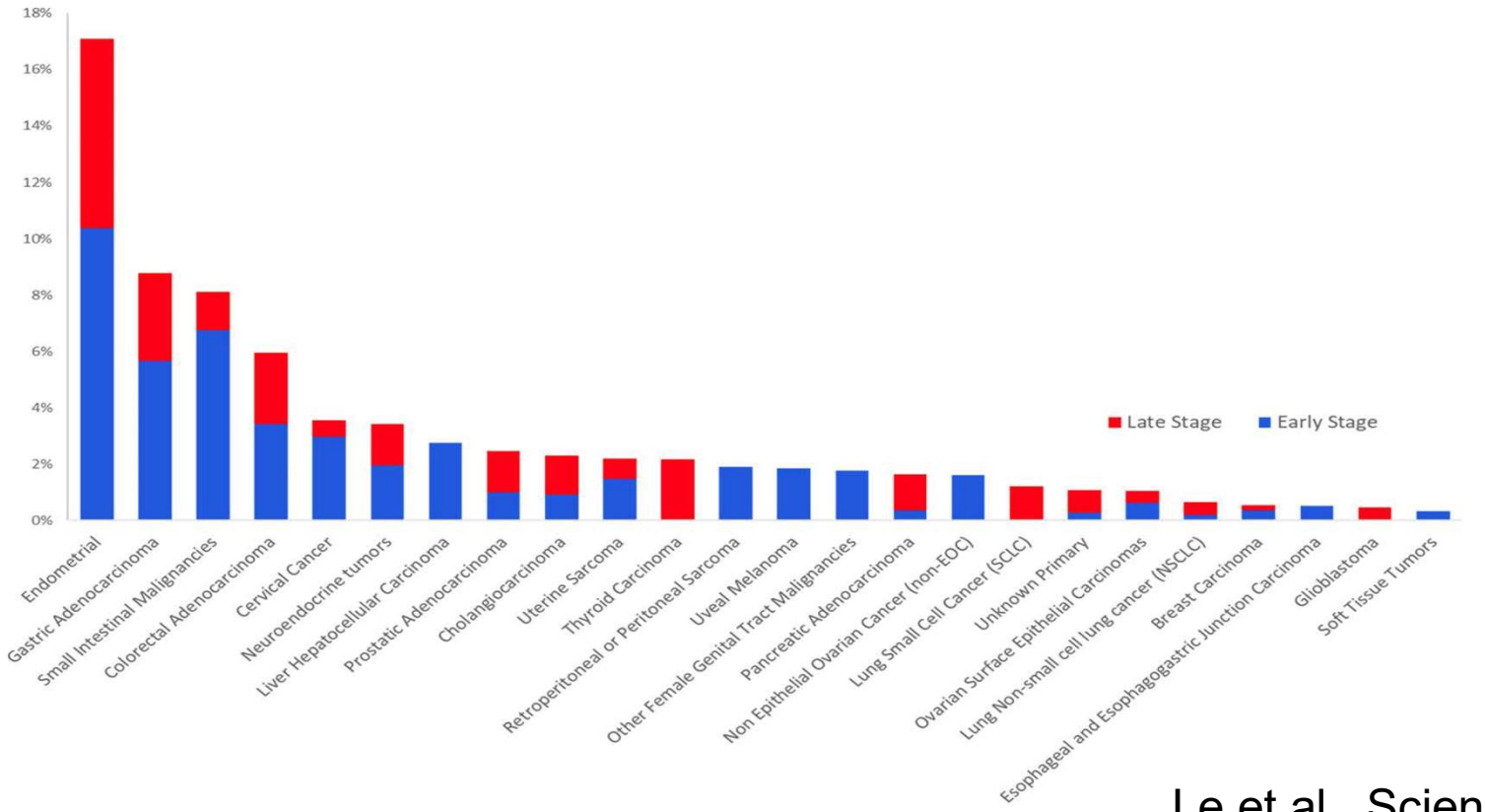
PFS and OS of MMR-D/ MSI-H Cancers on Pembrolizumab Monotherapy





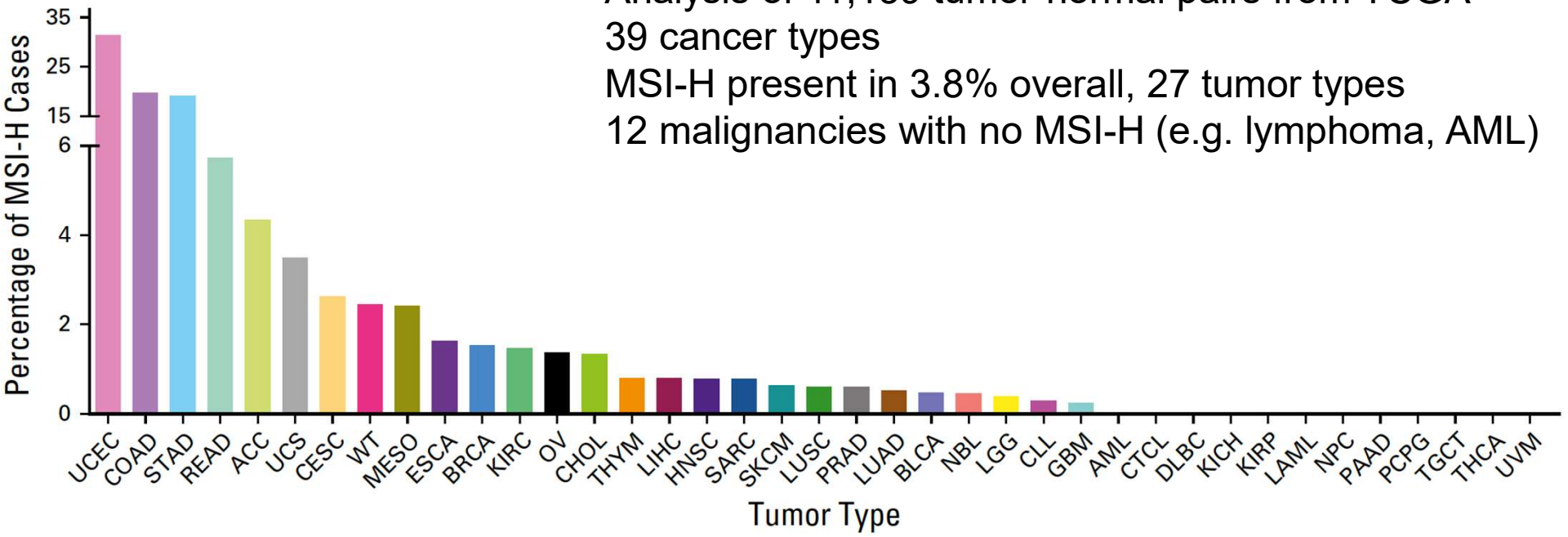
Le et al., Science 2017

How Common is MSI-H/ MMR-D in Cancer?



Le et al., Science 2017

How Common is MSI-H/ MMR-D in Cancer?



Analysis of 11,139 tumor-normal pairs from TCGA
39 cancer types
MSI-H present in 3.8% overall, 27 tumor types
12 malignancies with no MSI-H (e.g. lymphoma, AML)

Bonneville et al., Precis Oncol 2017

FDA Approvals for MSI-H / MMR-D Cancers

- **May 23, 2017: Pembrolizumab is indicated for the treatment of adult and pediatric patients with unresectable or metastatic solid tumors that have been identified as having a biomarker referred to as microsatellite instability-high (MSI-H) or mismatch repair deficient (MMR-D). This indication covers patients with solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options and patients with colorectal cancer that has progressed following treatment with certain chemotherapy drugs.**

Who, when and how should be tested for MSI/ MMR?

- No clear guidelines which test (IHC, PCR, NGS) should be used to identify patients
- Should all patients with solid cancers be tested, in view of the fact that frequency of MSI-H/ MMR-D varies between cancers?
- When in the treatment sequence should the tests be performed?
- Will the results have implications for treatment even in the adjuvant setting?
- Could Tumor Mutation Burden (TMB) be an even better marker?

Joint effort between Japan and US underway to provide guidelines

CO.26 Durvalumab/Tremilimumab in MSS CRC

Figure 6. Overall survival for pts with TMB ≥ 28

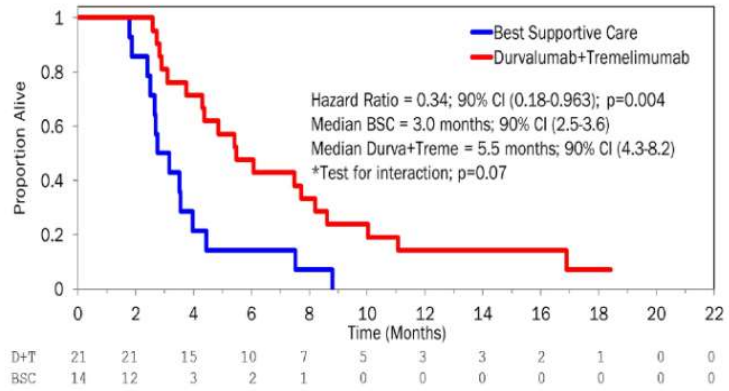
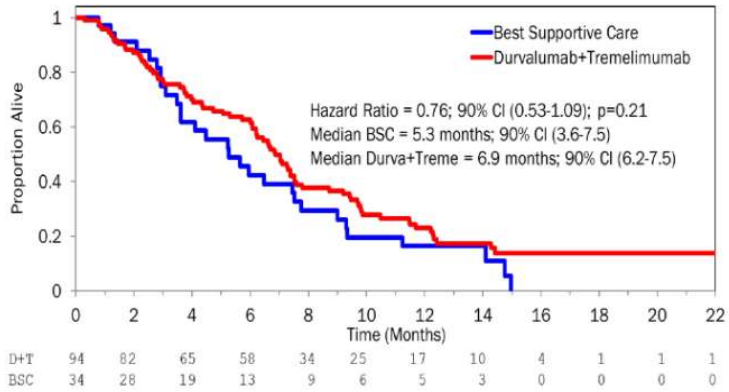
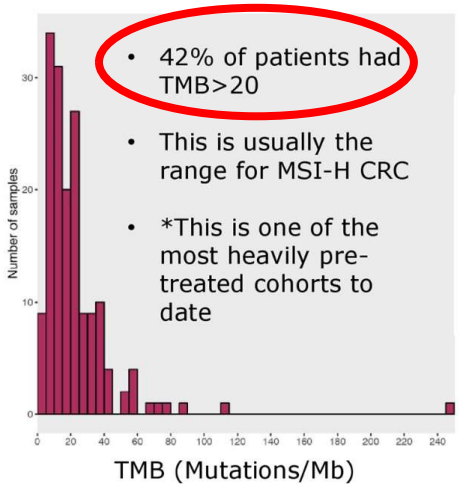


Figure 7. Overall survival for pts with TMB < 28

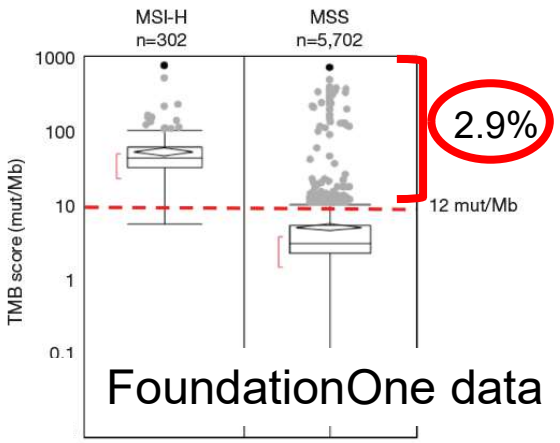


GuardantOMNI cfDNA panel: 500genes, 2.1MB



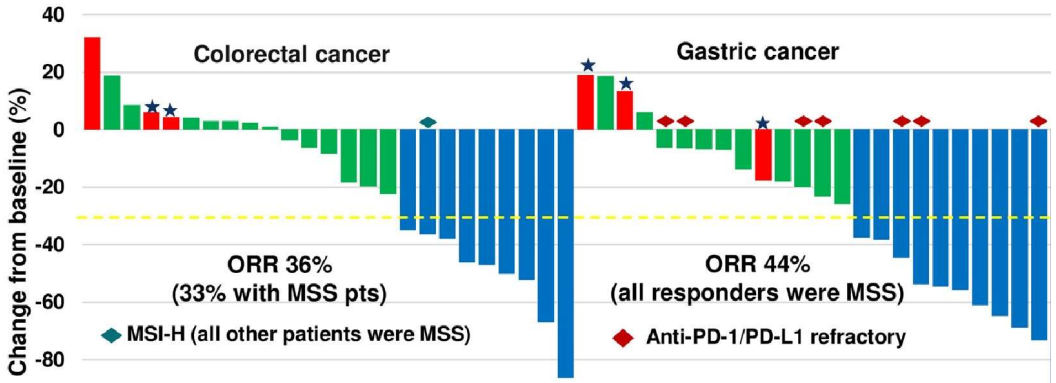
- 42% of patients had TMB>20
- This is usually the range for MSI-H CRC
- *This is one of the most heavily pre-treated cohorts to date

- Excluding 2 patients with MSI-H
- TMB in MSS patients:
  - Mean: 20.4 ± 16.3 mts/Mb
  - Range: 0.96 – 114.0

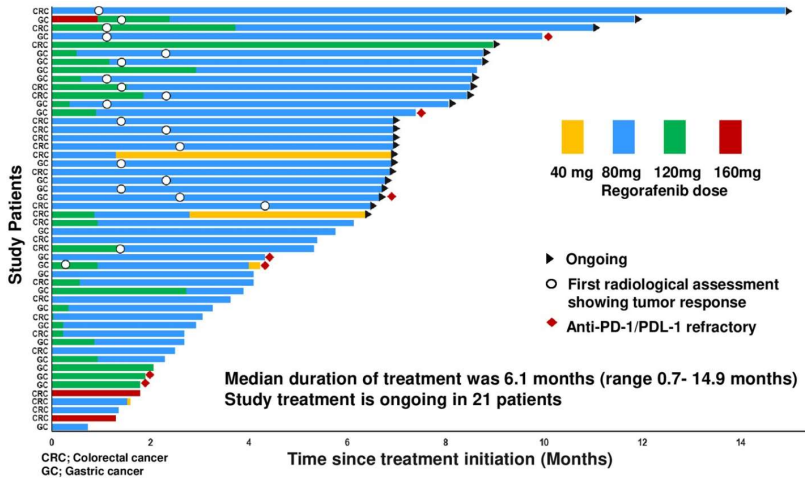


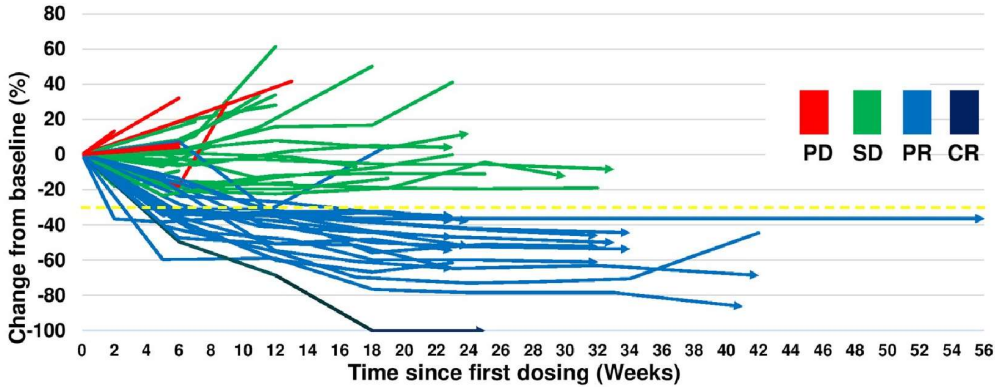
Fabrizio J of Gastro Onc 2018; Chen ASCO 2019

Regorafenib and Nivolumab



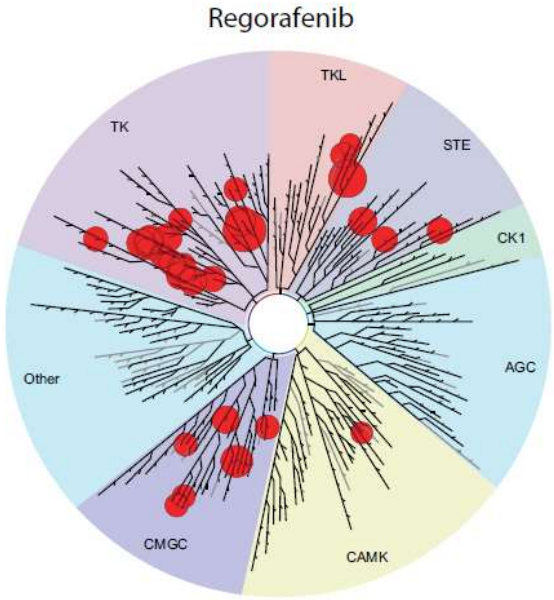
Regorafenib 80mg/d 21on/7off
Nivolumab 3mg/kd q2wks





Fukuoka et al. a2522 ASCO 2019

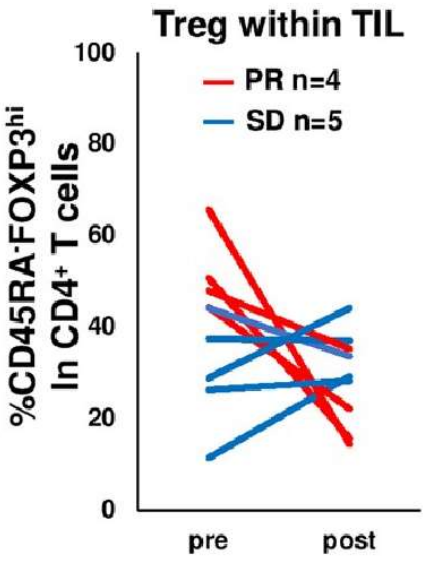
Regorafenib Kinase Spectrum



All Kd values <100 nml/l K_d (nmol/l)

Compound/gene symbol	Regorafenib	M-2	M-5
ABL1-np	32/16	23	20
BRAF	42/52	24	17
CDK11	67/43	33	86
CDK8	100/73	43	140
CDKL2	48/58	76	1100
CSF1R	43/10	21	13
DDR1	0.9/0.8	0.5	0.4
DDR2	9.2/9.7	5.3	2.5
EPHA6	48/23	210	640
EPHA8	140/130	61	73
ERK8	25/17	16	26
FLT1	28/27	23	17
FLT3	9.6/4.8	6.7	2.6
FLT4	41/15	46	40
FRK	69/42	42	24
HIPK4	6.9/4.5	15	26
JNK2	1,400/1,900	67/44	670
KIT	35/6.9	9.8	5.8
LOK	15/10	9.3	11
MAP4K4	450/400	42	89
MEK5	40	10	10
MKNK2	90/64	20	11
MUSK	68/67	140	140
p38-alpha	58/48	17	48
p38-beta	44/28	8.7	25
PDGFRA	21/19	7.3	11
PDGFRB	19/8.3	11	11
RAF1	87/59	130	66
RET	7.7/5.2	7.6	5.8
SLK	120/98	64	100
TAK1	170/260	79	120
TAOK3	200/290	94/77	450
TIE-1	30/27	48	73
TNIK	1,100/970	41	120
TNNI3K	170/110	160	77
TRKC	180/280	15	56
VEGFR2	57/28	29	31
YSK4	38/94	55	70
ZAK	2.8/2	6.7	7

Reduction in Tregs in Responders



Zopf et al. Cancer Medicine 2015;
Fukuoka et al. a2522 ASCO 2019

MSS CRC IO Combination Trials – HIGH Priority

NCT04030260
P2 nivolumab + regorafenib (multi-TKI) + RT +/- irinotecan
3L+ MSS CRC
(IST, China)

NCT03797326
LEAP-005 P2 pembrolizumab + lenvatinib (multi TKI), 3L, non-MSI-H/pMMR
(MSD/Eisai, basket)

NCT03414983
CM-9X8 P2/3 nivolumab + SoC + bevacizumab (VEGF), 1L, MSI-H/dMMR, MSS
(BMS/Ono)

ChiCTR1900027398
P2 camrelizumab + regorafenib (multi-TKI)
MSS CRC
(IST/Jiangsu HengRui)

NCT03170960
P1/2 cabozantinib (multi TKI) + atezolizumab, 2L+ (Exelixis, large basket)

NCT03657641
P1/2 regorafenib (multi-TKI) + pembrolizumab, 3L/4L
(IST)

NCT02484404
P1/2 durvalumab + cediranib (VEGF), 2L+, MSI stable/low
(NCI)

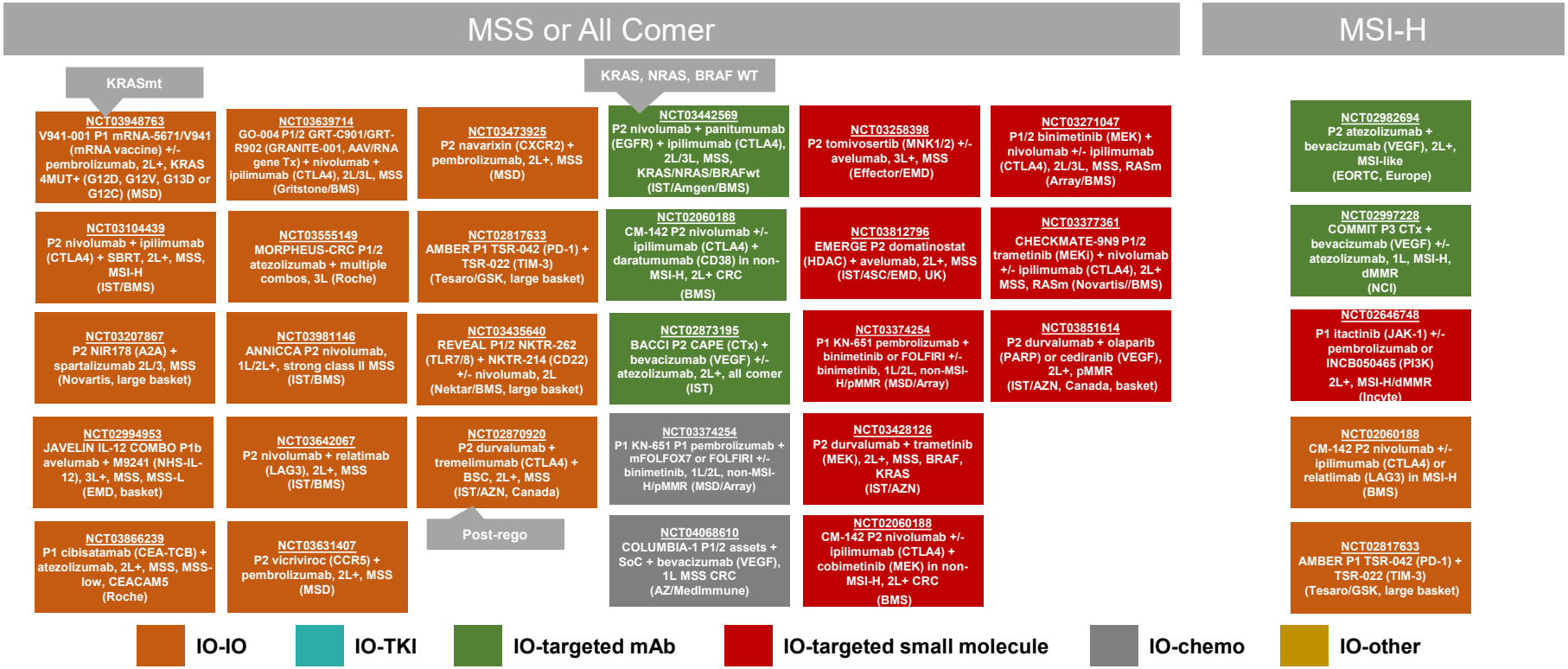
NCT03539822
CAMILLA P1 cabozantinib (multi-TKI) + durvalumab, 3L+
(IST/AZN/Exelixis, basket)

IO-IO | IO-TKI | IO-targeted mAb | IO-targeted small molecule | IO-chemo | IO-other

High Priority: Ph3/pivotal, data readout – promising, label expansion, timeline to approval <3 years, industry sponsored randomized, IO+TKI or SOC, LoT 2L+

1. Clinicaltrials.gov accessed December 20, 2019. 2. Chinese Clinical Trial Registry. Accessed December 20, 2019.

CRC IO Combination Trials – MEDIUM Priority



Medium Priority: Ph2 or large expansion cohort, data readout anticipated, label expansion/novel product, timeline to approval <5 years, industry sponsored single arm, IO+approved agents (non-TKI/SOC), LoT 1L+

Clinicaltrials.gov accessed December 20, 2019.

MSS CRC IO Combination Trials – LOW Priority

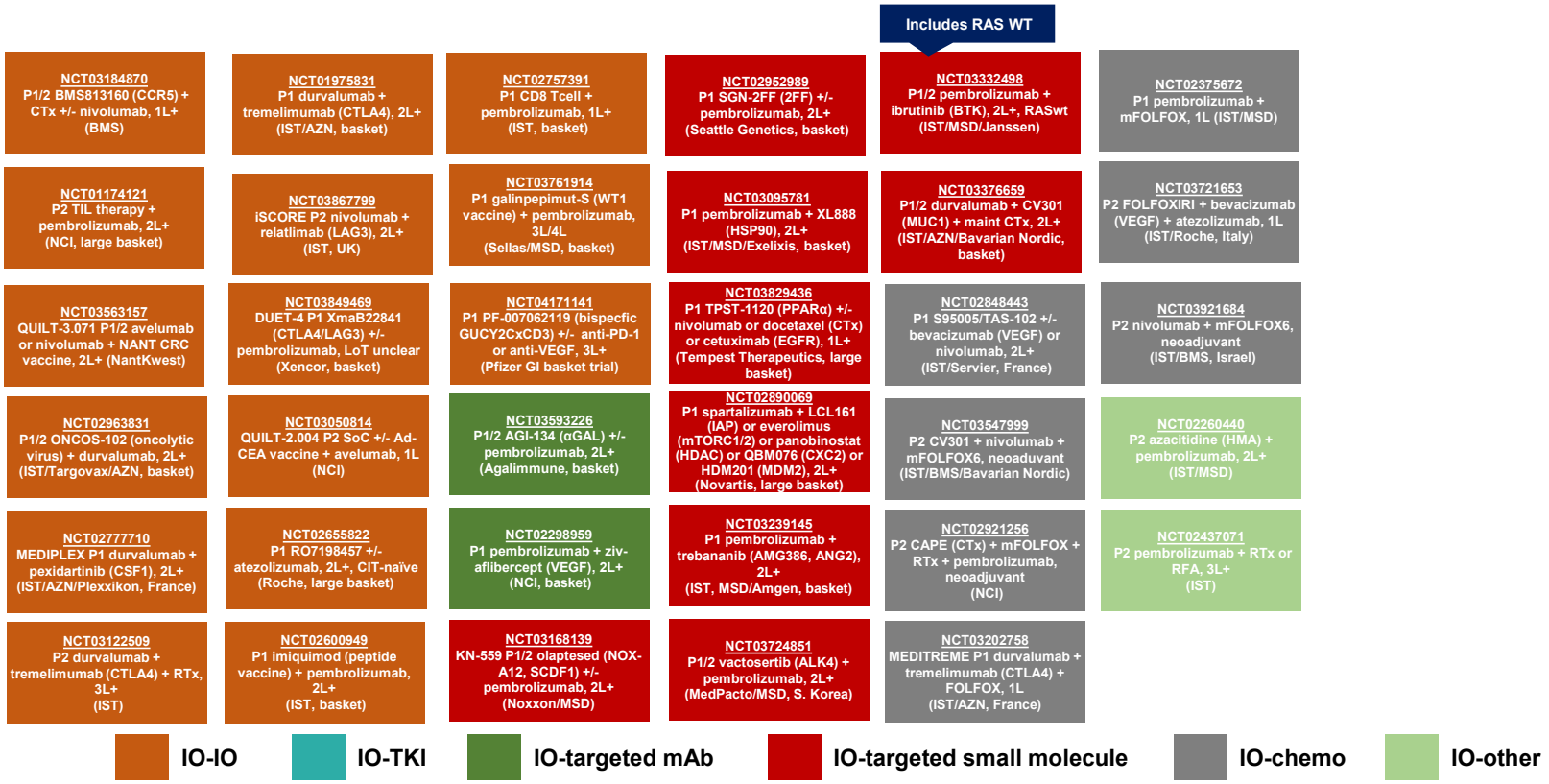
NCT03388190 METIMMOX P2 FLOX + nivolumab, 1L, MSS (IST, Norway)	NCT03026140 NICHE P2 nivolumab + ipilimumab +/- celecoxib (COX2) in MSS, neoadjuvant (IST/BMS, Netherlands)	NCT04014530 ATAPEMBRO P1/2 ataluren (nonsense mutation regulator) + pembrolizumab, 2L+ pMMR/dMMR CRC (IST/MSD/PTC Therapeutics)	NCT04119830 P2 pembrolizumab + rintatolimod, 3L+ MSS/pMMR (IST/NCI)	NCT03658772 ARRYS-001/KN-878 P1 grapiprant (EP4) + pembrolizumab, 3L+, MSS (Arrys/MSD)	NCT02947165 P1b NIS793 (TGFβ) + spartalizumab, 2L+, MSS (Novartis, large basket)	NCT02888743 P2 durvalumab + tremelimumab (CTLA4) + HD or LD RTx, MSS (NCI, basket)	NCT03396926 P2 pembrolizumab + bevacizumab (VEGF) + CAPE, 2L+, MSS, pMMR (IST/MSD)
NCT03626922 P1 of pembrolizumab + pemetrexed (CTx) + oxaliplatin (CTx), 2L+, MSS (IST/MSD/Lilly)	NCT02972034 P1 MK-8353 (MAPK3) + pembrolizumab, 2L-6L, MSS (MSD)	NCT03832621 MAYA P2 nivolumab + ipilimumab (CTLA4) + temozolomide (CTx), 2L+, MSS, MGMT-silenced (IST, Italy)	NCT03274804 PICASSO P1 pembrolizumab + maraviroc (CCR5), 2L+, MSS (IST, Germany)	NCT02834052 P1/2 pembrolizumab + poly-ICLC (TLR3), 3L+, pMMR (IST/Oncovir/MSD)	NCT03549000 P1 NZV930 (CD73) +/- spartalizumab or +/- NIR178 (A2A), 2L+, MSS (Novartis, large basket)	NCT02671435 P1/2 durvalumab + monalizumab (NKG2A), 1L/2L, MSS (AZN, large basket)	NCT02811497 METADUR P1/2 azacitidine (HMA) + durvalumab, 2L+, MSS (IST, Canada, basket)
NCT03102047 P2 durvalumab post-CRTx, neoadjuvant, MSS (IST)	NCT03871959 CATRIPCA P1 pembrolizumab + DEBIO1143 (IAP), 2L+, non-MSI-H (IST/MSD/Debiopharm, basket)	NCT03647839 MODULATE P2 nivolumab + BNC105 (tubulin polymerization) or + napabucasin (STAT3), 2L+, MSS (IST, Australia)	NCT02981524 P2 Cy/GVAX (GM-CSF) + pembrolizumab, 3L+, pMMR (IST)	NCT03693846 P2 nivolumab + ipilimumab (CTLA4), 2L+, MSS (IST)	NCT03891953 P1 DKY709 (IKAROS ZF2) +/- spartalizumab, 2L+, MSS, PDx-naïve (Novartis, large basket)	NCT04046445 KISIMA-01 P1/2 BI 754091 + ATP128 (vaccine), 2L+, MSS (Amal Therapeutics/ Boehringer)	NCT04166383 P2 nivolumab + VB-111 (anti-angiogenic adenovirus), 3L+ MSS/KRASwt (NCI)
NCT03854799 AVANA P2 avelumab + CAPE (CTx) + RTx, adjuvant, pMMR (IST, Italy)	NCT03711058 P1/2 copanlisib (PI3K) + nivolumab, 3L+, MSS, pMMR (IST/Bayer/BMS)	NCT02512172 P1 pembrolizumab + romidepsin (HDAC) +/- 5-azacytidine (HMA), 2L+, MSS (IST/MSD/Celgene)	NCT03313778 KN-603 P1 mRNA-4157 (mRNA vaccine) + pembrolizumab, 2L+, MSS, MSI-H/dMMR (ModernaTx/MSD, basket)	NCT03373188 P1 pepinemab + nivolumab or iplimumab MSS CRC Cohort (IST/Vaccinex)	NCT03152565 AVEVAC P1/2 avelumab + auto' dendritic cell vaccine, 3L+, MSS (IST, Spain)	NCT03608046 AVETUXIRI P2 avelumab + cetuximab (EGFR) + IRI, 2L+, MSS and BRAF V600Ewt (IST, France)	NCT03576963 P1/2 nivolumab + guadecitabine (DNMT), 2L+, MSS (IST/BMS/Astex)
NCT02586987 P1 durvalumab + selumetinib (MEK) + tremelimumab (CTLA4), 2L+, MSS, MSS-L/unknown (AZN, basket)	NCT03993626 CAROSELL P1/2 CXD101 (HDAC) + nivolumab, 2L+, MSS (Celleron)	NCT04067986 P1/2 camrelizumab + apatinib, 3L+, MSS or pMMR (IST, China)	NCT03265080 ADXS-NEO-002 P1 ADXS-NEO (neoantigen vaccine) +/- pembrolizumab, 2L-5L, non-MSI-H (Advaxis, basket)	NCT02636036 SPICE P1 enadenotucirev (oncolytic virus) + nivolumab, 2L+, MSS, MSS-L (PsiOxius/BMS, basket)	NCT03007407 P2 durvalumab + tremelimumab (CTLA4), 2L+, MSS (IST)	NCT02876224 P1 cobimetinib (MEK) + atezolizumab + bevacizumab (VEGF), 2L+, non-MSI-H (Roche)	NCT03800602 P2 nivolumab + metformin (biguanide), 2L+, MSS (IST/BMS)
NCT03428126 P1 durvalumab + selumetinib (MEK) +/- MSI-L/Unknown (AZN, basket)	NCT03791398 BRUOG 379 P1/2 ONC-201 (dopamine D2/TRAIL) + nivolumab, 3L, MSS (IST/Oncoceutics/BMS)	NCT03865082 ILLUMINATE-206 P2 Nivolumab +Tilsotolimod (TLR9 agonist) + ipilimumab 3L+ IO naïve MSS (Idera/BMS)	NCT02903914 P1/2 INCB001158 (arginase) +/- pembrolizumab, LoT unclear, MSS/MSI-H (Incyte, large basket)	NCT02900664 P1 spartalizumab + CJM112 (IL-17A) or EGF816 (EGFR) or canakinumab (IL-1β) or trametinib (MEK), 2L+, dMMR excluded (Novartis, large basket)	NCT03206073 P1/2 Pexa-Vec (oncolytic virus) + durvalumab, 2L+, MSS, MSI-H, KRASwt (NCI)	NCT03775850 PI EDP1503 (microbial mAb) +/- pembrolizumab, 2L+ MS,S (Evelo/SCRI/MSD)	

IO-IO | IO-TKI | IO-targeted mAb | IO-targeted small molecule | IO-chemo | IO-other

Low Priority: Ph1 or basket trial, data readout unknown, ovel product, timeline to approval >5 years, IST, Other IO combinations, LoT 1L or localized

Clinicaltrials.gov accessed December 20, 2019.

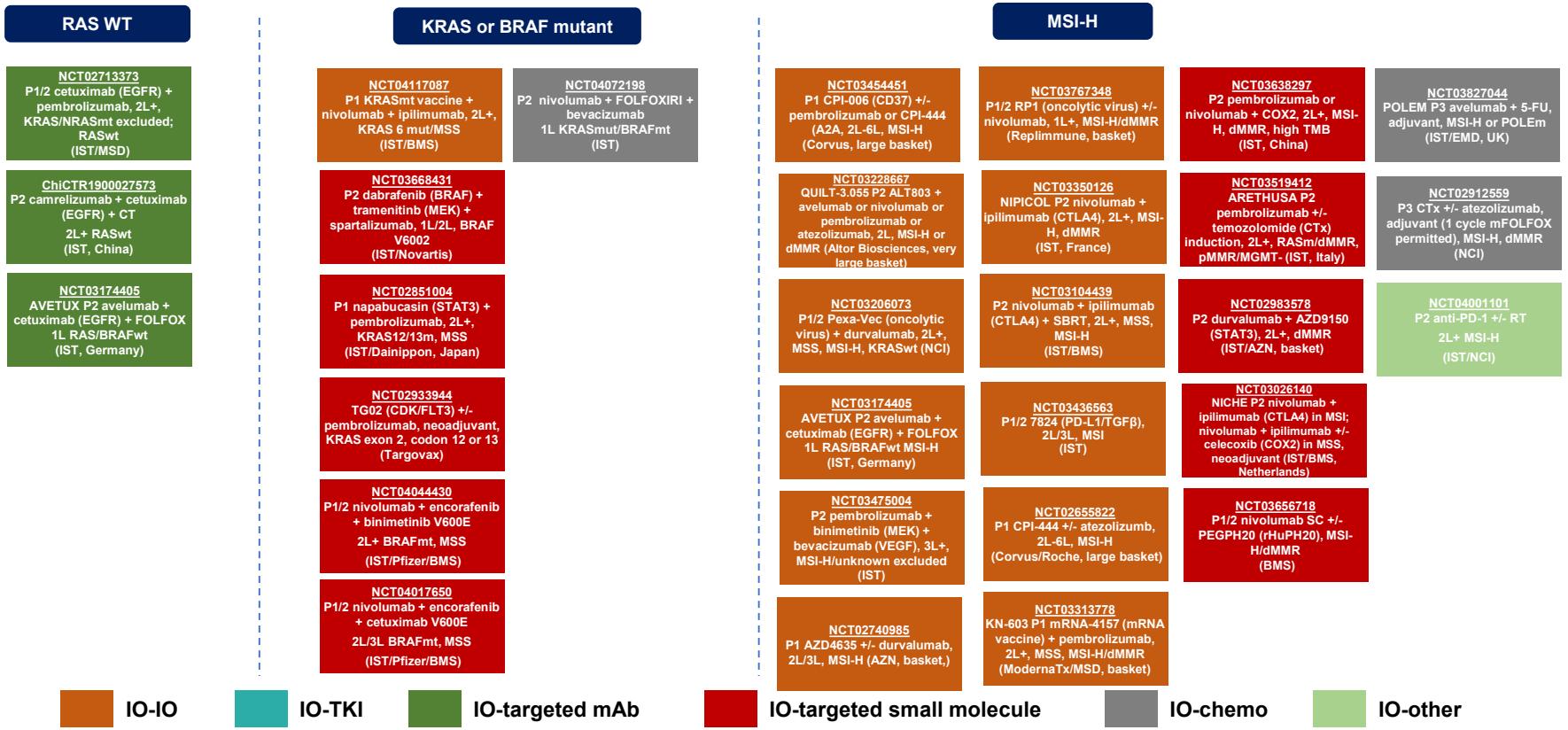
All Comer CRC IO Combination Trials – LOW Priority



Low Priority: Ph1 or basket trial, data readout unknown, ovel product, timeline to approval >5 years, IST, Other IO combinations, LoT 1L or localized

Clinicaltrials.gov accessed December 20, 2019.

CRC IO Combination Trials – LOW Priority



1. Clinicaltrials.gov accessed December 20, 2019.
2. Chinese Clinical Trial Registry. Accessed December 20, 2019.

Evidence-based Treatment Options in uHCC

FDA-approved

Line of Therapy	Treatment Option	Comments
1st line	**Sorafenib** **Lenvatinib**	• LEN superior to SOR in RR and PFS, not OS • NIVO vs SOR trial results at ESMO 2019?
2nd line	**Regorafenib** **Nivolumab** **Pembrolizumab** Cabozantinib Ramucirumab (for AFP>400)	• All agents tested after SOR failure • NIVO and PEMBRO approved based on single-arm studies (RR and DOR)
3rd line	Cabozantinib	• Only randomized trial with pt population in 3rd line

KEYNOTE-224[1] and CheckMate 040[2]: Open-Label Phase II Trials

Response rates

CheckMate 040 (nivolumab)	Sorafenib-experienced 3 mg/kg, N = 154
Objective response	**22 (14%)**
Complete response	4 (3%)
Partial response	18 (12%)
Stable disease	65 (42%)
Progressive disease	59 (38%)

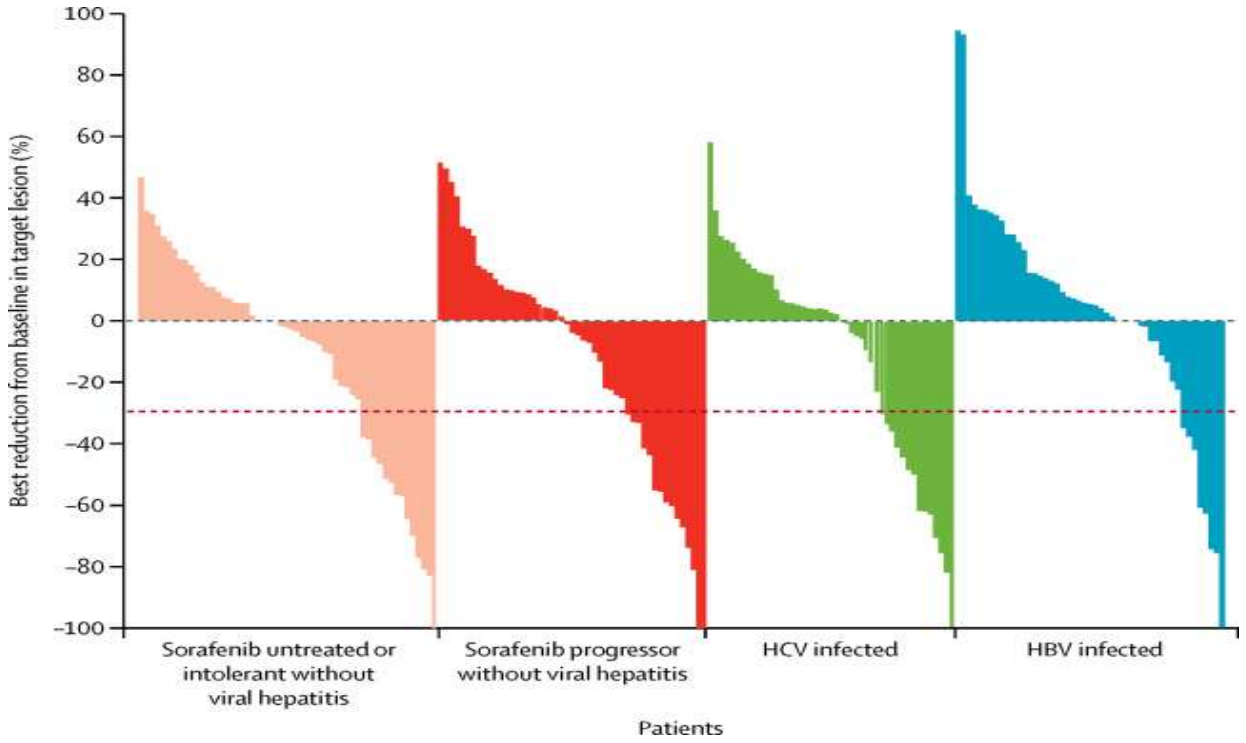
KEYNOTE 224 (pembrolizumab)	All treated participants (n = 104)
Objective response	**18 (17%; 11-26)**
Complete response	1 (1%)
Partial response	17 (16%)
Stable disease	46 (44%)
Progressive disease	34 (33%)

Nivolumab AE profile[3]

AEs	Proportion
Pneumonitis	3.1%
Colitis	2.9%
Hepatitis	1.8%
Nephritis	1.2%
Hypothyroidism	9%
Hyperthyroidism	2.7%
Adrenal insufficiency	1%
Skin reaction	9%

1. Zhu AX, et al. *Lancet Oncol.* 2018;19(7):940-952; 2. El Khoueiry AB, et al. ASCO GI 2018. Abstract 475; 3. Opdivo (nivolumab) website. Immune-mediated adverse reactions data. 2018. http://www.opdivohcp.com/advanced-hcc/selected-safety-profile/immune-mediated-adverse-reactions-data. Accessed October 3, 2018.

CheckMate 040: Best Percentage Change in Tumor Size From Baseline



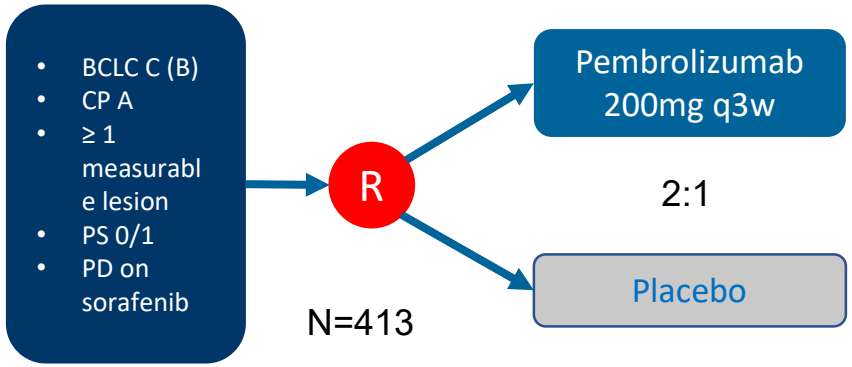
El-Khoueiry AB, et al. *Lancet*. 2017;389(10088):2492-2502.

CheckMate 040: Efficacy

	Uninfected untreated/intolerant (n=56)	Uninfected progressor (n=57)	HCV infected (n=50)	HBV infected (n=51)	All patients (n=214)
Objective responses	**13 (23%)**	**12 (21%)**	**10 (20%)**	**7 (14%)**	**42 (20%)**
Complete responses	0	2 (4%)	0	1 (2%)	3 (1%)
Partial responses	13 (23%)	10 (18%)	10 (20%)	6 (12%)	39 (18%)
Stable diseases	29 (52%)	23 (40%)	23 (46%)	21 (41%)	96 (45%)
Response duration (mos)	**8·4**	**NR**	**9·9**	**NR**	**9·9**
DCR	42 (75%)	35 (61%)	33 (66%)	28 (55%)	138 (64%)
6-month OS	89%	75%	85%	84%	83%
9-month OS	82%	63%	81%	70%	74%
Median OS	NR	13·2	NR	NR	NR
Median PFS	5·4	4·0	4·0	4·0	4·0

El-Khoueiry AB, et al. *Lancet*. 2017;389(10088):2492-2502.

KEYNOTE-240: Negative (?) Results for Pembrolizumab vs BSC in 2nd-Line Therapy



Double-blinded phase III
Co-primary EP: PFS + OS

PFS: HR 0.78, CI 0.61-0.99, P=0.0022

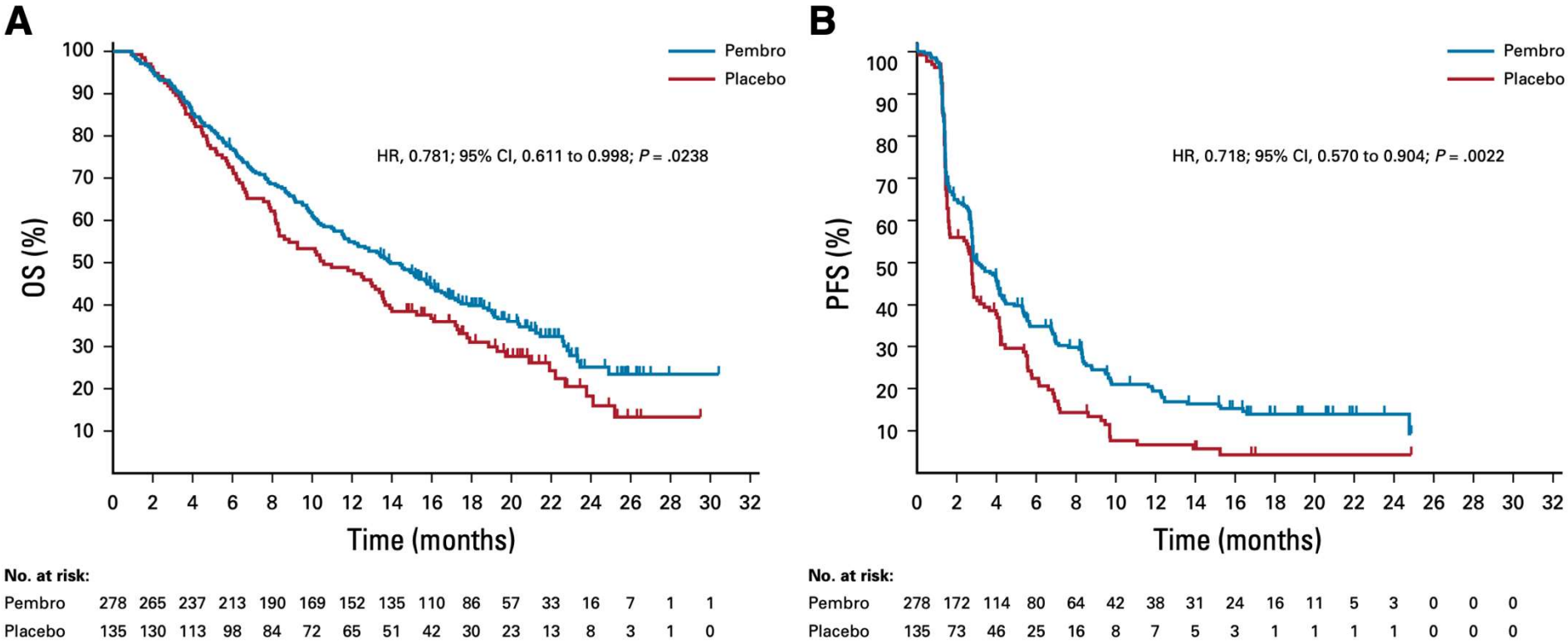
OS: HR 0.78, CI 0.611-0.998, P=0.024

Did not meet prespecified boundaries for significance

RR 18.3 vs 4.4%

Finn et al, JCO 2019

KEYNOTE-240: Negative (?) Results for Pembrolizumab vs BSC in 2nd-Line Therapy



Finn et al, JCO 2019

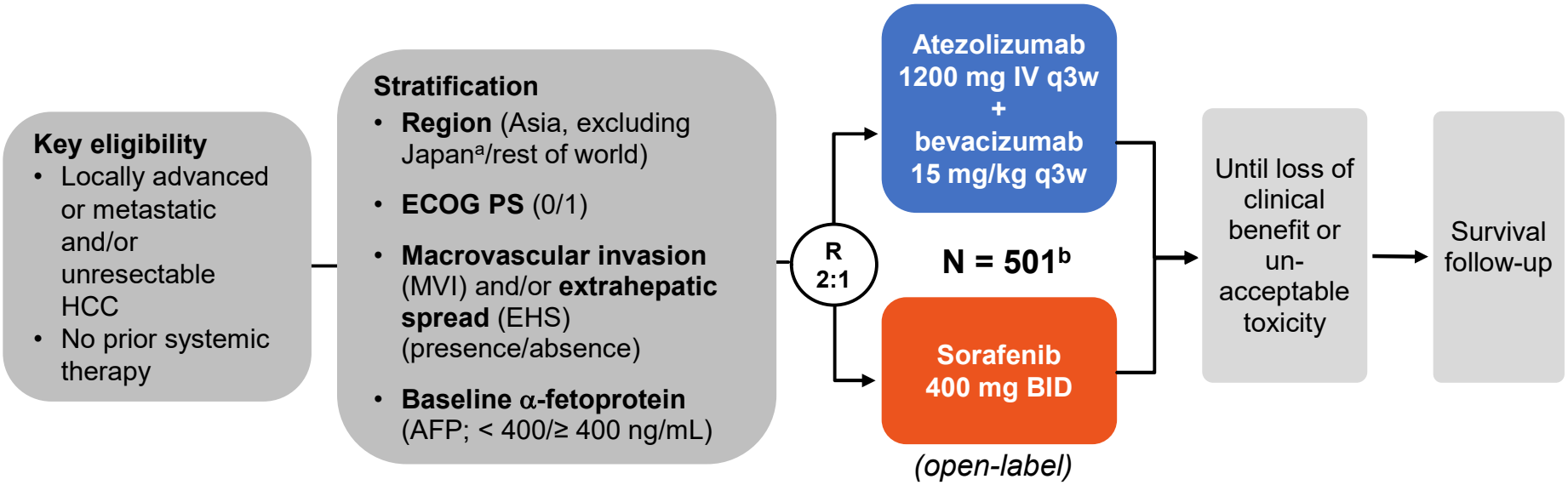
Atezolizumab + bevacizumab vs sorafenib in patients with unresectable hepatocellular carcinoma: Phase 3 results from IMbrave150

Ann-Lii Cheng,[1] Shukui Qin,[2] Masafumi Ikeda,[3] Peter R. Galle,[4] Michel Ducreux,[5] Andrew X. Zhu,[6] Tae-You Kim,[7] Masatoshi Kudo,[8] Valeriy Breder,[9] Philippe Merle,[10] Ahmed Kaseb,[11] Daneng Li,[12] Wendy Verret,[13] Derek-Zhen Xu,[14] Sairy Hernandez,[13] Juan Liu,[14] Chen Huang,[14] Sohail Mulla,[15] Ho Yeong Lim,[16] Richard S. Finn[17]

[1]National Taiwan University Cancer Center and National Taiwan University Hospital, Taipei, Taiwan; [2]People's Liberation Army Cancer Center, Jinling Hospital, Nanjing, People's Republic of China; [3]National Cancer Center Hospital East, Kashiwa, Japan; [4]University Medical Center Mainz, Mainz, Germany; [5]Gustave Roussy Cancer Center, Villejuif, France; [6]Harvard Medical School, Massachusetts General Hospital Cancer Center, Boston, MA, USA; [7]Seoul National University College of Medicine, Seoul, Korea; [8]Kindai University Faculty of Medicine, Osaka, Japan; [9]N.N. Blokhin Russian Cancer Research Center, Moscow, Russia; [10]Hospital La Croix-Rousse, Lyon, France; [11]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [12]City of Hope Comprehensive Cancer Center and Beckman Research Institute, Duarte, CA, USA; [13]Genentech, Inc., South San Francisco, CA, USA; [14]Roche Product Development, Shanghai, People's Republic of China; [15]Hoffmann-La Roche Limited, Mississauga, ON, Canada; [16]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [17]Jonsson Comprehensive Cancer Center, Geffen School of Medicine at UCLA, Los Angeles, CA, USA

ESMO ASIA 2019

IMbrave150 study design



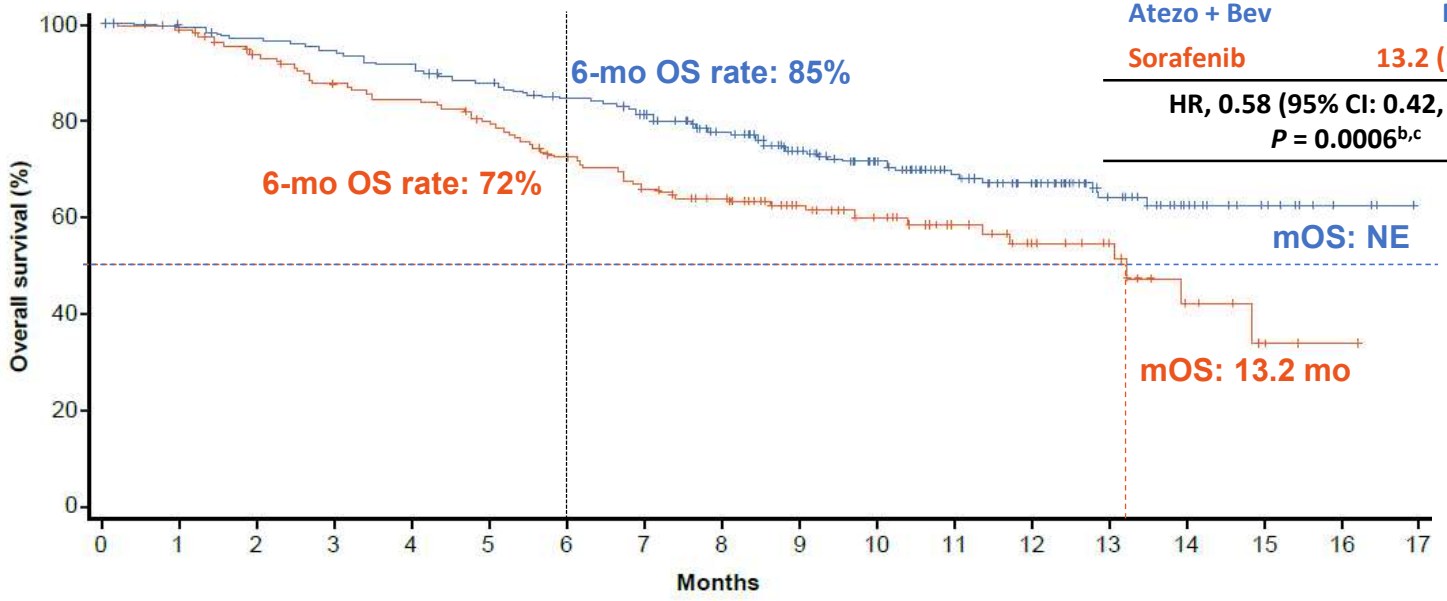
Co-primary endpoints
- OS
- IRF-assessed PFS per RECIST 1.1

Key secondary endpoints (in testing strategy)
- IRF-assessed ORR per RECIST 1.1
- IRF-assessed ORR per HCC mRECIST

[a] Japan is included in rest of world.
[b] An additional 57 Chinese patients in the China extension cohort were not included in the global population/analysis.

OS: Co-primary endpoint

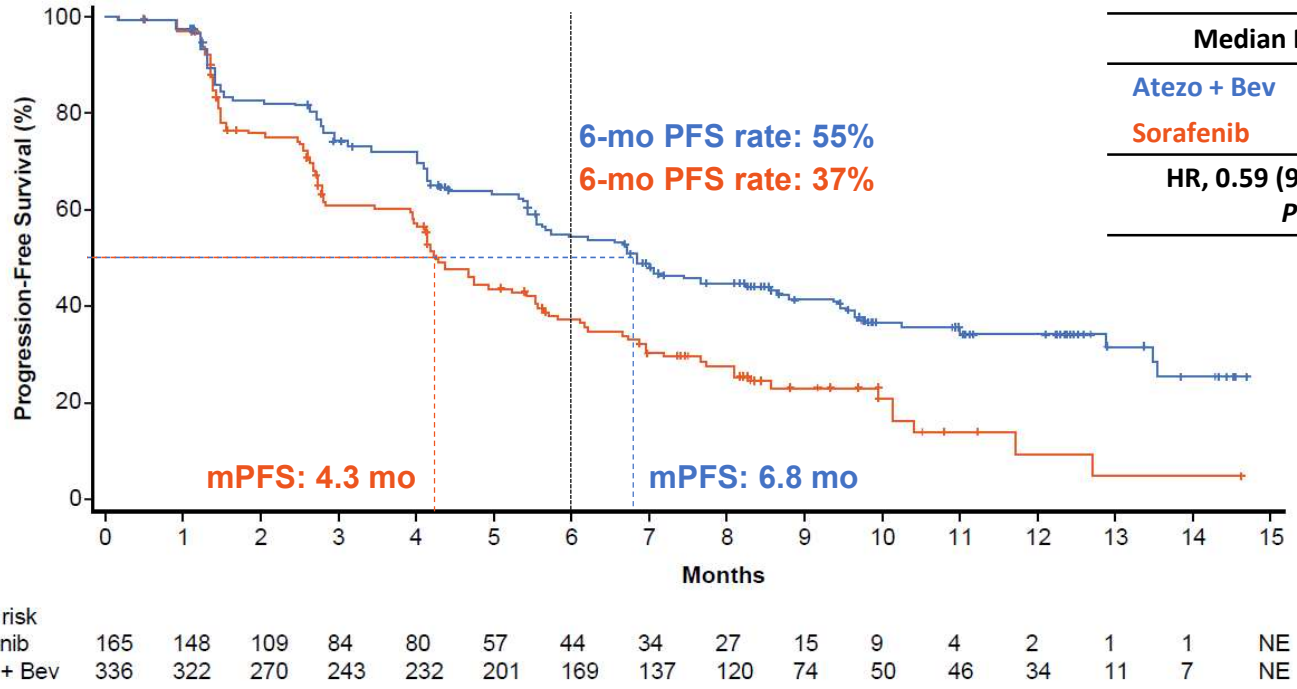
Median OS (95% CI), mo[a]	
Atezo + Bev	NE
Sorafenib	13.2 (10.4, NE)
HR, 0.58 (95% CI: 0.42, 0.79)[b]	
P = 0.0006[b,c]	



No. at risk																		
Sorafenib	165	157	143	132	127	118	105	94	86	60	45	33	24	16	7	3	1	NE
Atezo + Bev	336	329	320	312	302	288	275	255	222	165	118	87	64	40	20	11	3	NE

NE, not estimable. [a] 96 patients (29%) in the Atezo + Bev arm vs 65 (39%) in the sorafenib arm had an event. [b] HR and *P* value were from Cox model and log-rank test and were stratified by geographic region (Asia vs rest of world, including Japan), AFP level (< 400 vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS. [c] The 2-sided *P* value boundary based on 161 events is 0.0033. Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

Confirmed PFS[a]: Co-primary endpoint



No. at risk																
Sorafenib	165	148	109	84	80	57	44	34	27	15	9	4	2	1	1	NE
Atezo + Bev	336	322	270	243	232	201	169	137	120	74	50	46	34	11	7	NE

Median PFS (95% CI), mo[b]	
Atezo + Bev	6.8 (5.7, 8.3)
Sorafenib	4.3 (4.0, 5.6)
HR, 0.59 (95% CI: 0.47, 0.76)[c,d]	
P < 0.0001[d]	

[a] Assessed by IRF per RECIST 1.1. [b] 197 patients (59%) in the Atezo + Bev arm vs 109 (66%) in the sorafenib arm had an event. [c] HR and *P* value were from Cox model and log-rank test and were stratified by geographic region (Asia vs rest of world, including Japan), AFP level (< 400 vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS. [d] The 2-sided *P* value boundary is 0.002. Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

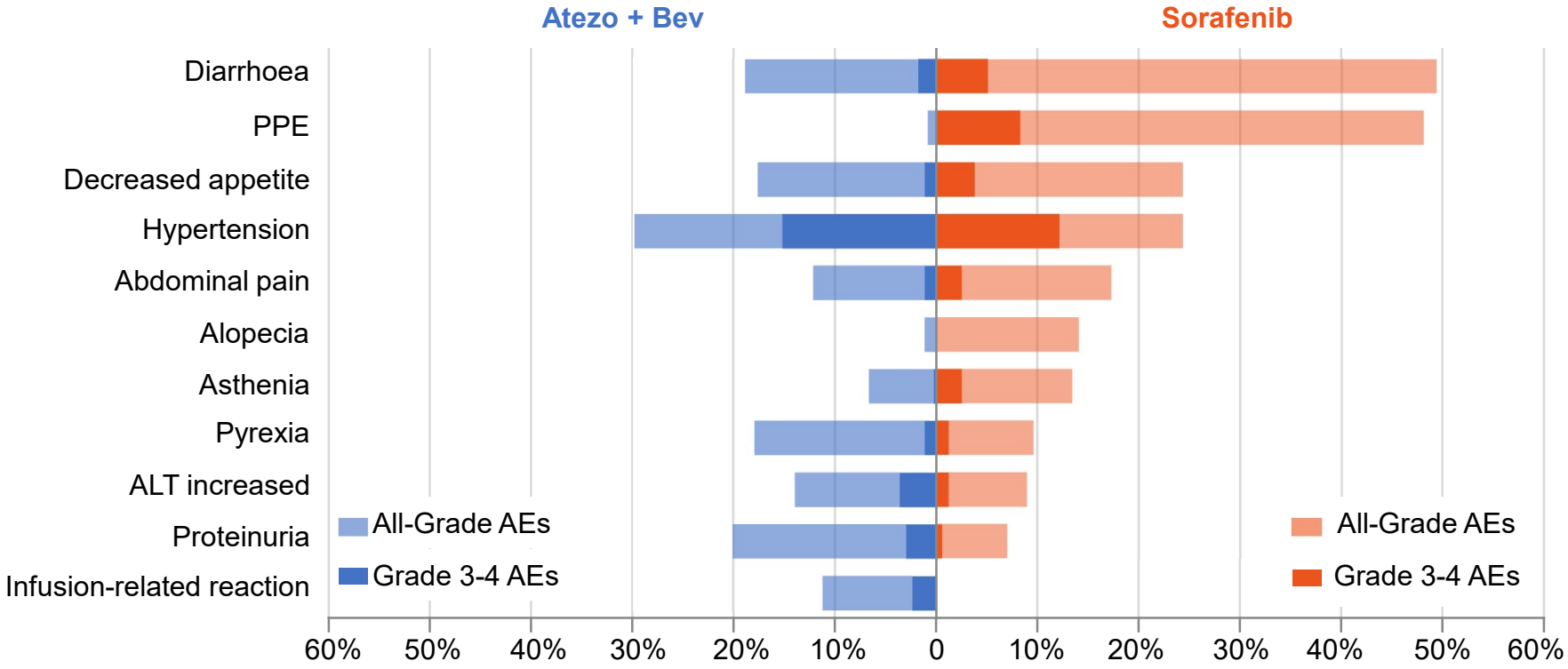
Response rate and duration of response

	IRF RECIST 1.1		IRF HCC mRECIST	
	Atezo + Bev (n = 326)	Sorafenib (n = 159)	Atezo + Bev (n = 325)[a]	Sorafenib (n = 158)
Confirmed ORR, n **(%)** (95% CI)	89 **(27)** (23, 33)	19 **(12)** (7, 18)	108 **(33)** (28, 39)	21 **(13)** (8, 20)
CR	18 (6)	0	33 (10)	3 (2)
PR	71 (22)	19 (12)	75 (23)	18 (11)
Stratified *P* value[b]	**< 0.0001**		**< 0.0001**	
SD, n (%)	151 (46)	69 (43)	127 (39)	66 (42)
PD, n (%)	64 (20)	39 (25)	66 (20)	40 (25)
DCR, n (%)	240 (74)	88 (55)	235 (72)	87 (55)
Ongoing response, n (%)[c]	77 (87)	13 (68)	84 (78)	13 (62)
Median DOR, months (95% CI)	NE	6.3 (4.7, NE)	NE	6.3 (4.9, NE)
Event-free rate at 6 months, n (%)	88	59	82	63

[a] IRF HCC mRECIST–evaluable population was based on patients who presented with measurable disease at baseline per HCC mRECIST criteria.
[b] Stratification factors included geographic region (Asia vs rest of world, including Japan), AFP level (< 400 vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS. [c] Denominator is patients with confirmed CR/PR. Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

Safety[a]

≥ 10% frequency of AEs in either arm and > 5% difference between arms

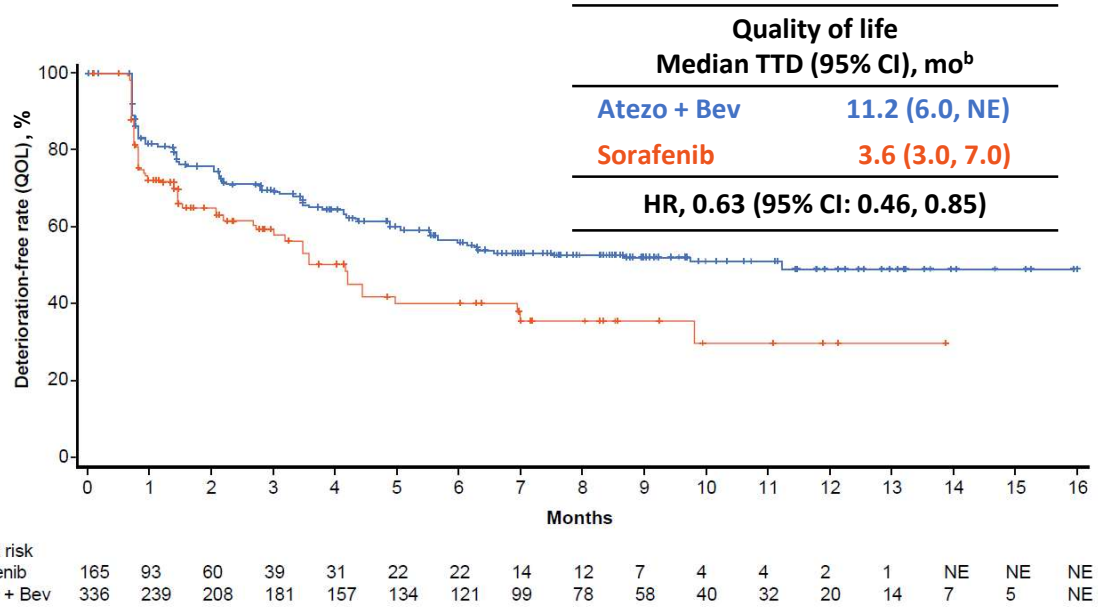


PPE, palmar-plantar erythrodysaesthesia.

[a] Safety-evaluable population.

Patient-reported outcomes[a]

- **Atezolizumab + bevacizumab delayed the time to deterioration of patient-reported quality of life compared with sorafenib**



EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire for Cancer; TTD, time to deterioration.
[a] Pre-specified secondary endpoint that was not formally tested; EORTC QLQ-C30 administered every 3 weeks on treatment and every 3 months after treatment discontinuation or progression. [b] Time to deterioration defined as first decrease from baseline of ≥ 10 points[1] in the patient-reported health-related global health status/quality of life (GHS/QoL) scale of the EORTC QLQ-C30 maintained for 2 consecutive assessments or 1 assessment followed by death from any cause within 3 weeks.
1. Osoba D, et al. *J Clin Oncol.* 1998.
Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

Evidence-based Treatment Options in uHCC

FDA-approved

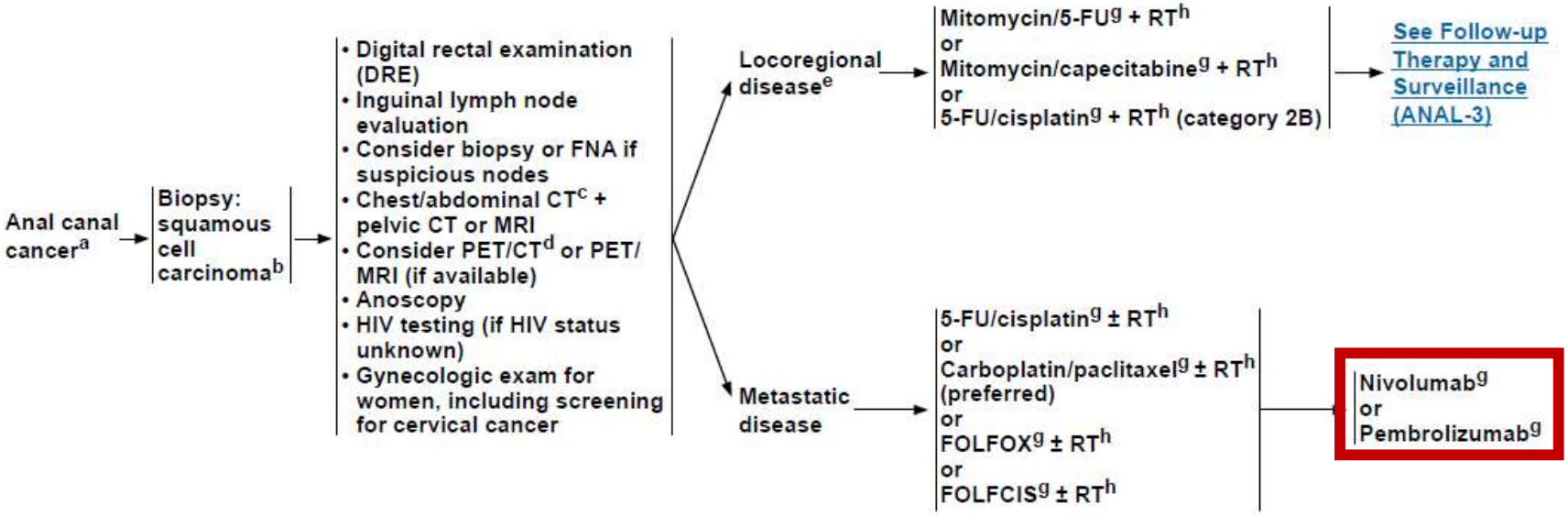
Line of Therapy	Treatment Option	Comments
-1 line`	**Atezo + BEV**	• Other emerging options: Lenvatinib + Pembro | MKI + anti-PD-1
1st line	**Sorafenib** **Lenvatinib**	• LEN superior to SOR in RR and PFS, not OS • NIVO vs SOR trial results at ESMO 2019?
2nd line	**Regorafenib** **Nivolumab** **Pembrolizumab** Cabozantinib Ramucirumab (for AFP>400)	• All agents tested after SOR failure • NIVO and PEMBRO approved based on single-arm studies (RR and DOR)
3rd line	Cabozantinib	• Only randomized trial with pt population in 3rd line

Ongoing Phase III clinical trials in HCC

Study	Line	#	Endpoint	Intervention
Cosmic-312	1st	640	PFS + OS	Sorafenib vs. Cabozantinib vs. Cabozantinib/Atezolizumab
Leap-002	1st	750	PFS + OS	Lenvatinib vs. Levantinib/Pembro
Himalaya	1st	1310	OS	Durvalumab/Tremelimumab vs. Durvalumab vs. Sorafenib
Checkmate 040	1st	610	ORR	Nivolumab vs. Sorafenib
SHR-1210-III-310	1st	510	PFS + OS	SHR-1210 (anti-PD1)/Apatinib s. Sorafenib
Keynote 394	2nd	450	OS	Pembrolizumab vs. Placebo

Immunotherapy for Anal Squamous Cell Carcinoma

- **No FDA approval**
- NCCN Guidelines:



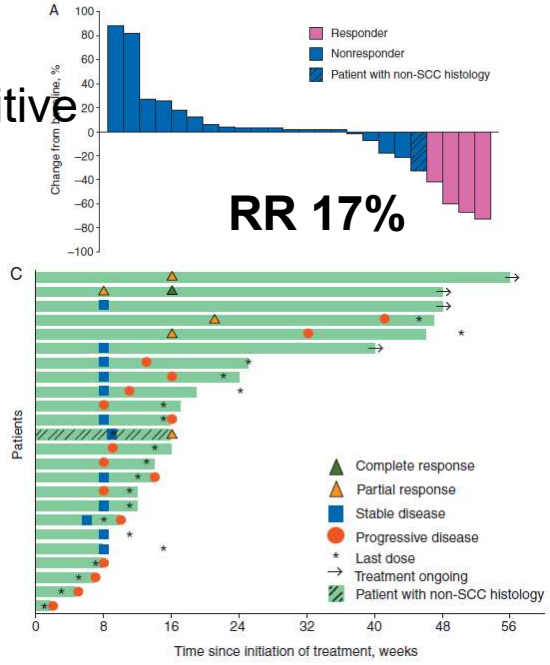
Immunotherapy for Anal Squamous Cell Carcinoma

Keynote-028

N=25 (screened 43 of which 32 [74%] ≥1% PD-L1+)

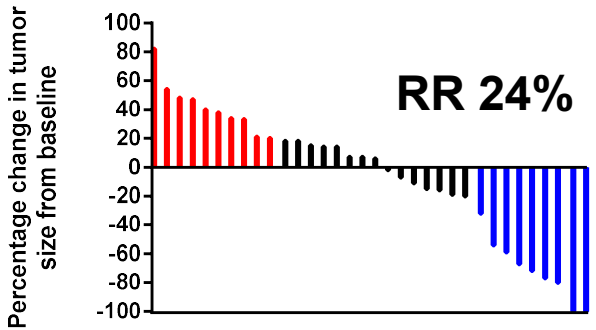
(PD-L1 based on “neoplastic cells and contiguous mononuclear cells”)

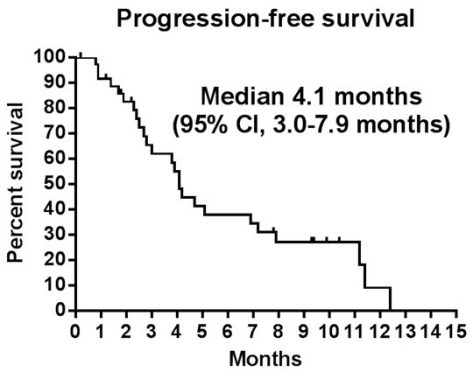
PD-L1 positive



NCI9673

N=37

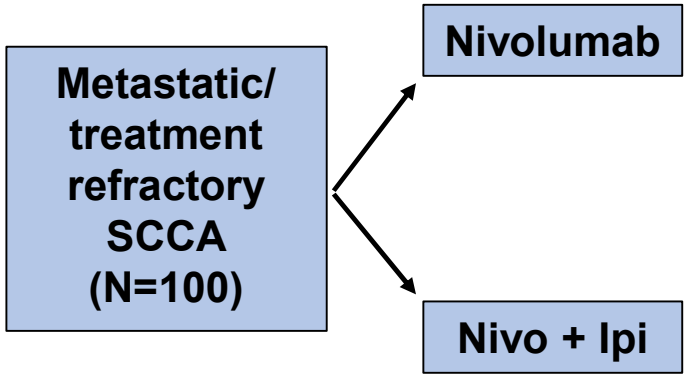




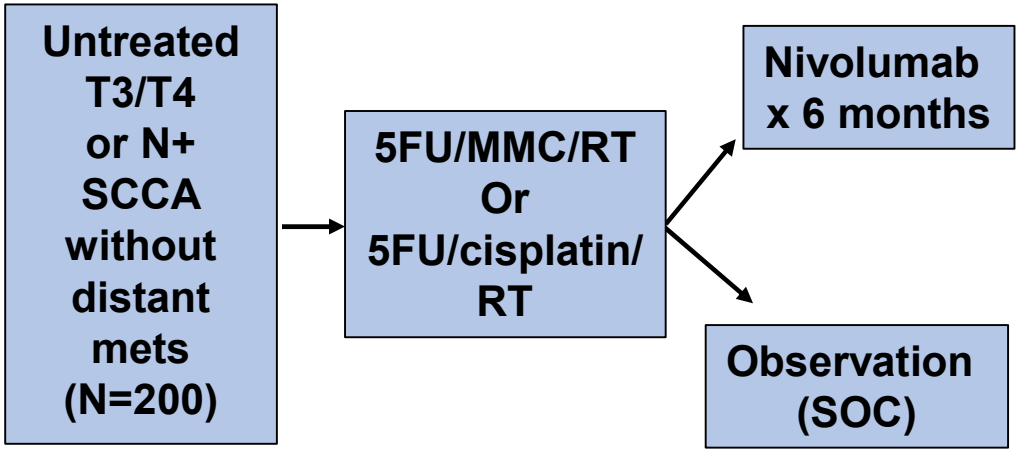
Morris VK et al Lancet Oncology 2017, Ott AoO 2017

Ongoing Phase III clinical trials in Anal Squamous Cell

NCI9673 trial (part B)



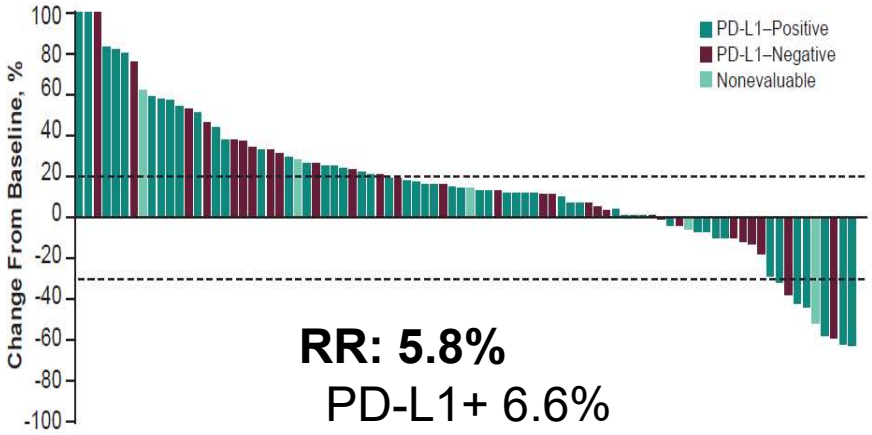
EA2165 Trial for non-metastatic, high-risk SCCA



Immunotherapy for Other GI Cancers

Biliary

Keynote 158, N=104 (58.7% PD-L1+)



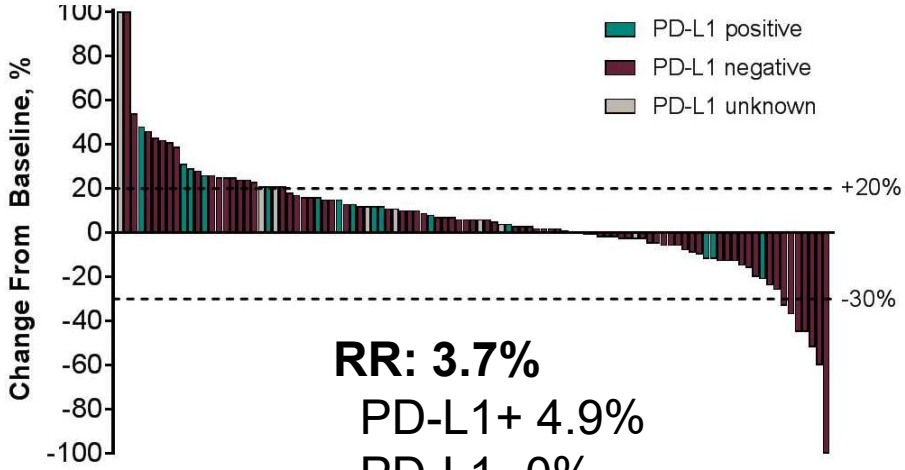
RR: 5.8%

PD-L1+ 6.6%

PD-L1- 2.9%

Neuroendocrine

Keynote 158, N=107 (16% PD-L1+)



RR: 3.7%

PD-L1+ 4.9%

PD-L1- 0%

- Well + Moderate NETs
- 38% pancreas, 22% small bowel

(MSI status unknown)

Ueno et al. ESMO 2018, Strosberg ASCO GI 2019

Conclusions

- **Across different tumor types, IO therapy has shown activity in GI malignancies**
- **Strong efficacy in MSI-H cancers independent of tumor type**
- **Beyond MSI status, good predictive factors are still lacking**
  - PD-L1 expression level (CPS) not a prerequisite for activity, but there is some correlation
  - Viral etiology of cancers (EBV, Hep B/C, HPV) not convincing
- **Combination therapy approaches emerging to augment IO response (IO + IO, IO + MKI, IO + chemo…)**
- **Largest potential impact: make MSS CRC respond to IO!**

Which of the following malignancies does NOT have an FDA-approved immunotherapy option?

A. Second-line squamous cell cancer of the esophagus, PD-L1 CPS score >10

B. Biliary cancer, MSI-H, after failure of standard therapy

C. HPV positive anal cancer, PD-L1 CPS >1

D. Second-line advanced hepatocellular cancer

E. Third-line therapy of PD-L1 positive gastric cancer

Explanation for Answer C

While there are some limited phase 2 data on the activity of immune checkpoint inhibitors in HPV positive squamous cell anal cancer, the response rates and durability of response have so far been surprisingly low and have not yet warranted FDA approval of IO agents. This is in contrast to HCC, gastric, and esophageal cancer where in spite of negative randomized trials, the response rate and especially the durability of response in a largely to-be-defined subset of patients has led to FDA approvals of pembrolizumab and/ or nivolumab. All MSI-H cancers, independent of histo-origin, including biliary cancers, can receive pembrolizumab after failure of standard therapy.