Novel Systemic Therapies for Gastric and Colorectal Cancers

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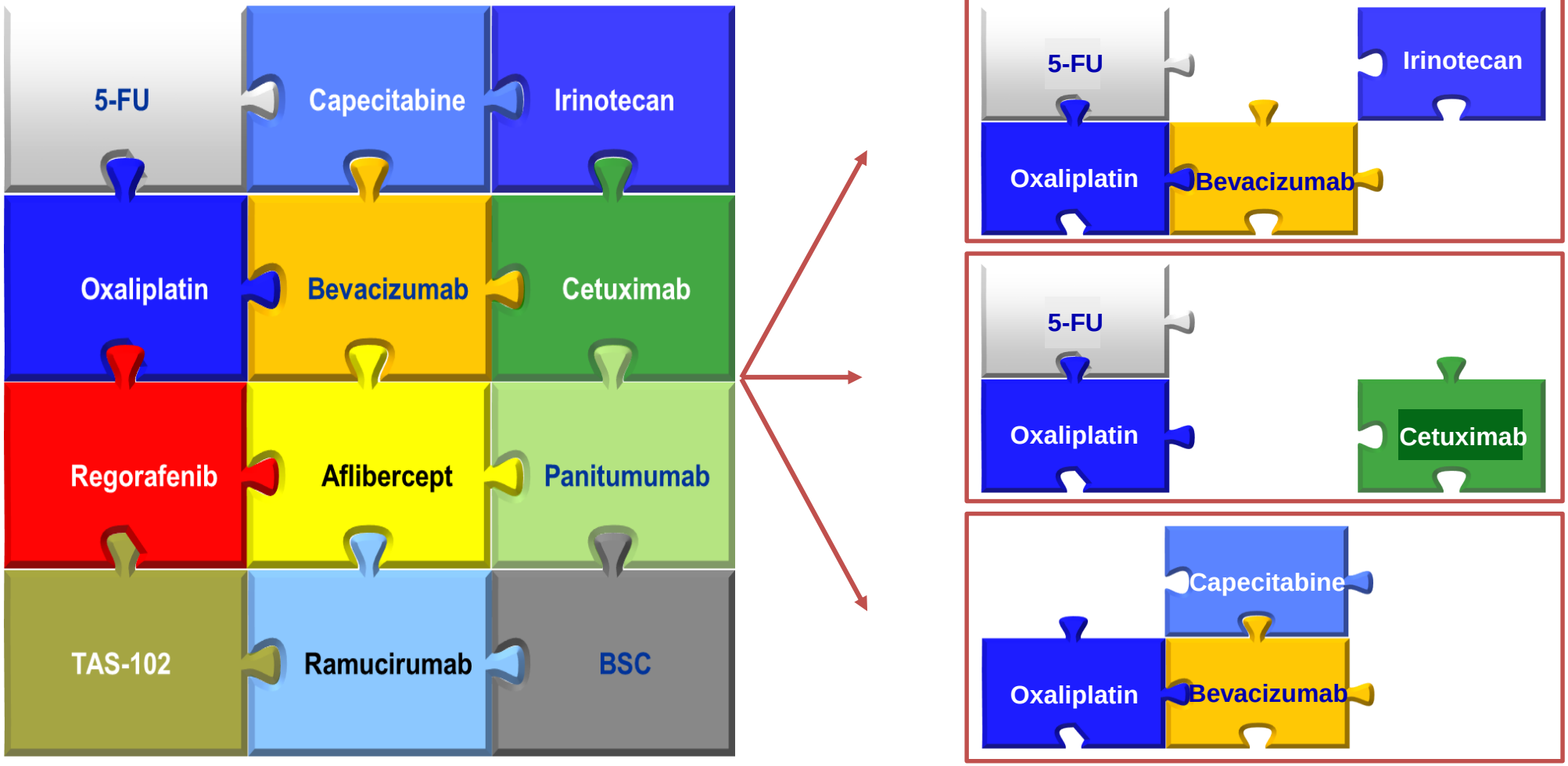
Gibbs Cancer Center
& Research Institute

Colon Cancer

How Do We Choose Therapy?



Molecular Pathology and Biomarkers

RAS testing

- ***RAS* is a predictive biomarker for therapeutic choices** involving EGFR antibody therapies in the metastatic disease setting .
- ***RAS* testing is mandatory prior to treatment** with EGFR-targeted monoclonal antibodies cetuximab and panitumumab .
- Primary or metastatic colorectal tumour tissue can be used for *RAS* testing.
- ***RAS* analysis** should include at least *KRAS* exons 2, 3 and 4 (codons 12, 13, 59, 61, 117 and 146) and *NRAS* exons 2, 3 and 4 (codons 12, 13, 59, 61 and 117).
- **Turnaround time for *RAS* testing** (expanded *RAS* analysis) should be ≤7 working days from the time of receipt of the specimen by the testing laboratory to the time of issuing of the final report, for >90% of specimens.

Molecular Pathology and Biomarkers

BRAF testing

- Tumour BRAF mutation status should be assessed alongside the assessment of tumour RAS mutational status for prognostic assessment (and/or potential selection for clinical trials)

MSI testing

- MSI testing in the metastatic disease setting can assist clinicians in genetic counselling
- MSI testing has strong predictive value for the use of immune check-point inhibitors in the treatment of patients with mCRC

Molecular Pathology and Biomarkers

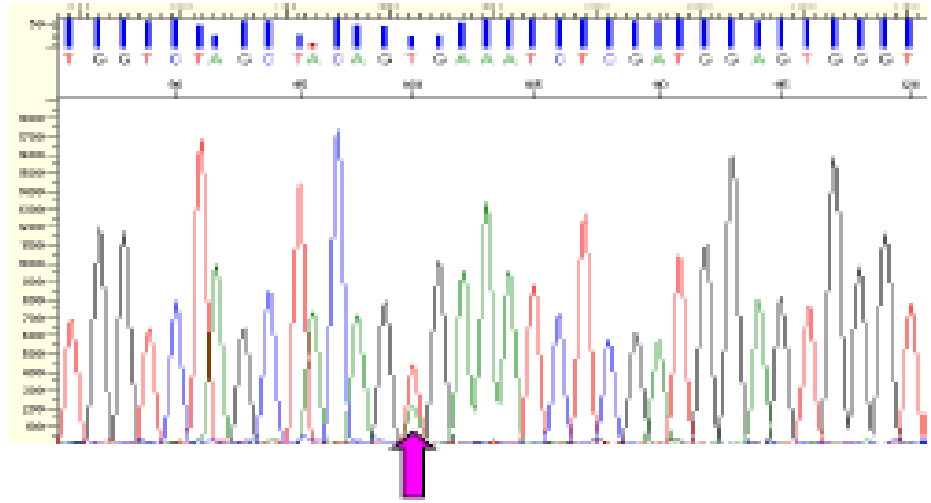
Emerging technologies

- Although CTC number correlates with prognosis in patients with mCRC, the clinical utility of CTC assessments is not yet clear and therefore cannot be recommended .
- The utility of liquid ctDNA biopsies to guide treatment decisions is currently under investigation in clinical trial.
  - Reproducible RAS testing
- Whole genome, whole exome and whole transcriptome analysis are generaly done in the research setting .

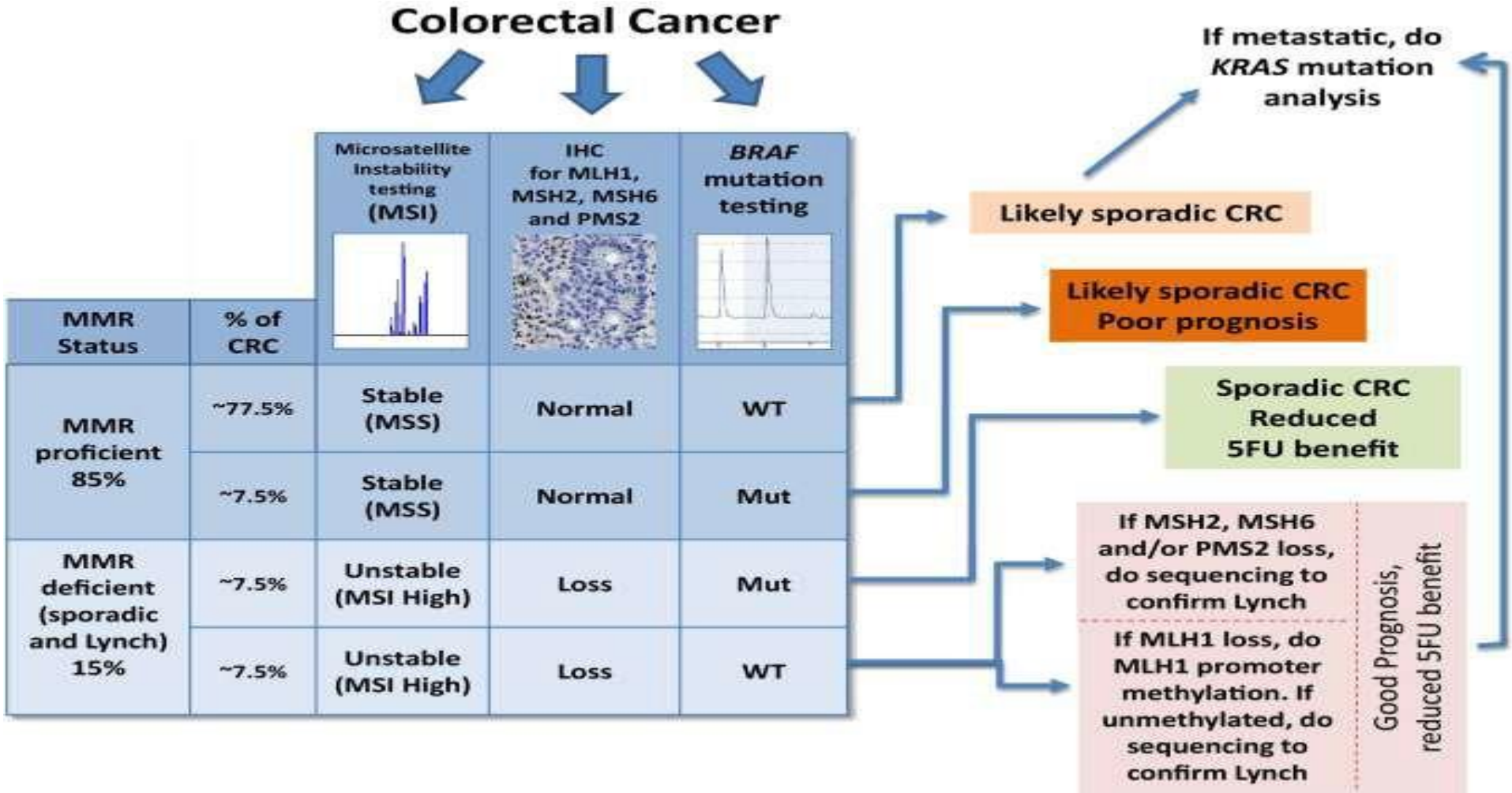
BRAF

BRAF gene mutations

Exon 15, codon 600 (mutation V600E)



Microsatellite instability



BRAF MUTATION IN MSI PATIENTS

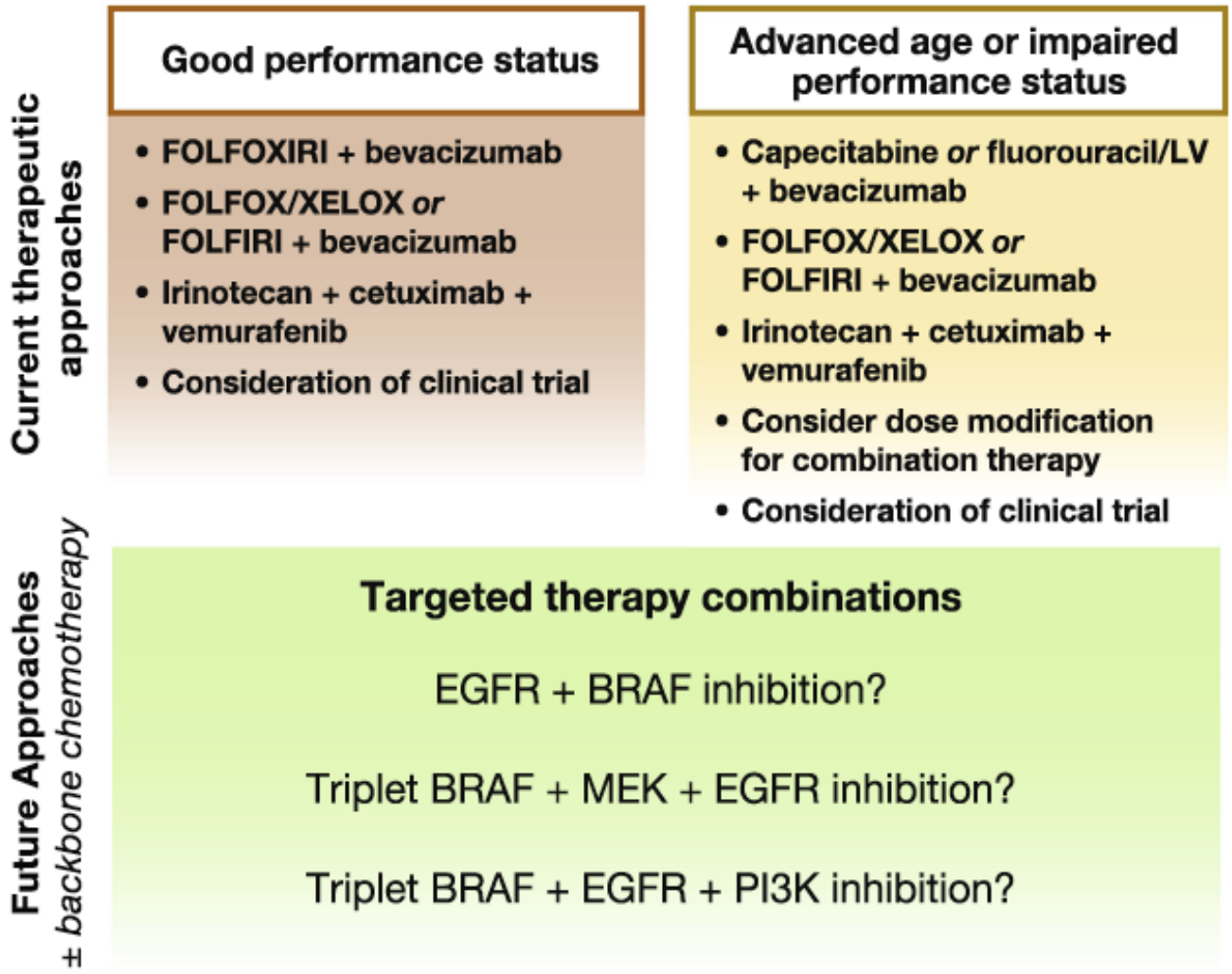
Checkmate 142 study

	Objective response	Disease control for ≥12 weeks
Mutation status		
BRAF mutant (n=12)	3 (25%)	9 (75%)
KRAS mutant (n=26)	7 (27%)	16 (62%)
Both *BRAF* and *KRAS* wild type (n=29)	12 (41%)	23 (79%)

- No effect of *BRAF* mutation tumour growth control with nivolumab
- But completely different population of patients….

Overman NJ et al. Lancet Oncol 2017; Published online

Treatment Options in *BRAF*-Mutant mCRC

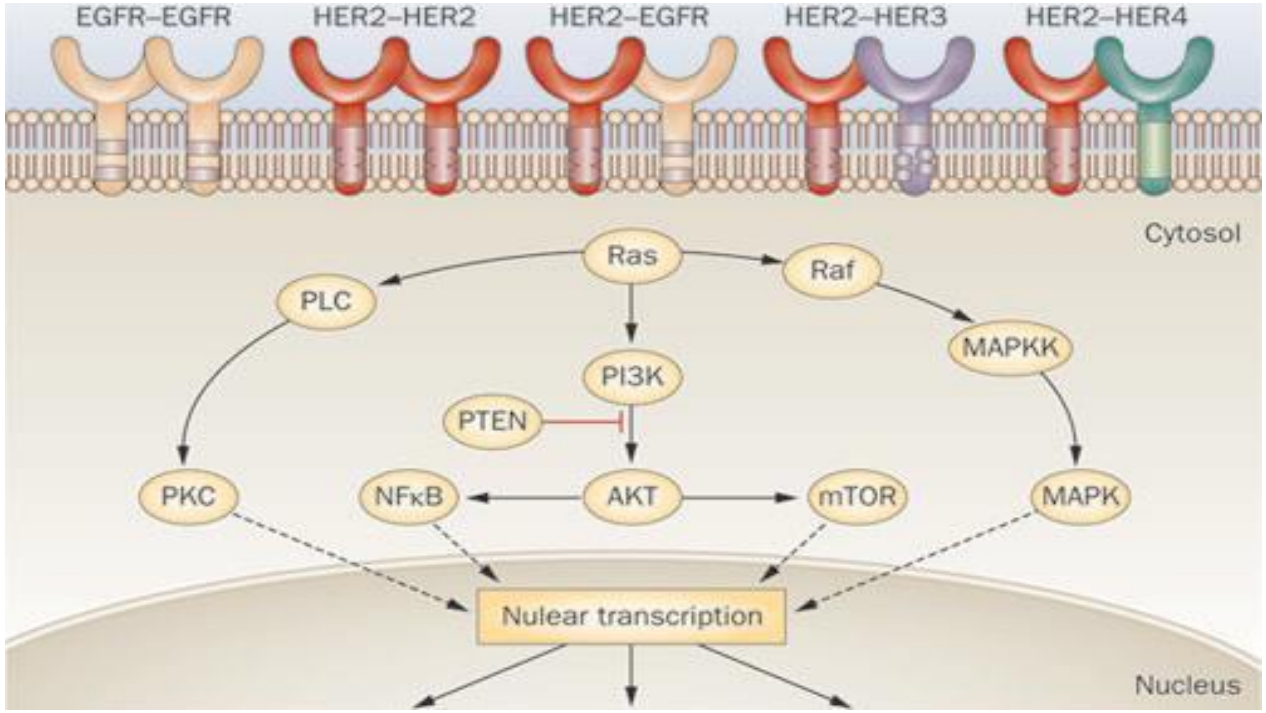


Strickler JH, et al. Cancer Treatment Rev. 2017;60:109-119.

BRAF V600E Mutation: Treatment Outcomes

Regimen	RR, %	mPFS, mo
Single/Doublet BRAF/MEK		
Vemurafenib[1]	5	2.1
Dabrafenib[2]	11	NR
Encorafenib[3]	6	4
Dabrafenib + Trametinib[4]	12	3.5
Doublet with EGFR		
Vemurafenib + Panitumumab[5]	13	3.2
Vemurafenib + Cetuximab[6]	20	3.2
Encorafenib + Cetuximab[7]	19	3.7
Dabrafenib + Panitumumab[8]	10	3.4
Triplet with EGFR		
Vemurafenib + Cetuximab + Irinotecan[9]	35	7.7
Dabrafenib +Trametinib + Panitumumab[8]	26	4.1
Encorafenib + Cetuximab + Alpelisib[7]	18	4.2

HER2 Aberrations in CRC:



-Her2 is receptor of the HER family Tyrosine-kinase receptors

-When dimerize activates MAPK and PI3K pathways

Overexpression, amplifications and mutations upregulate HER2 signaling

-Amplification: 5,4% of CRC
-Mutation: 2,8% of CRC

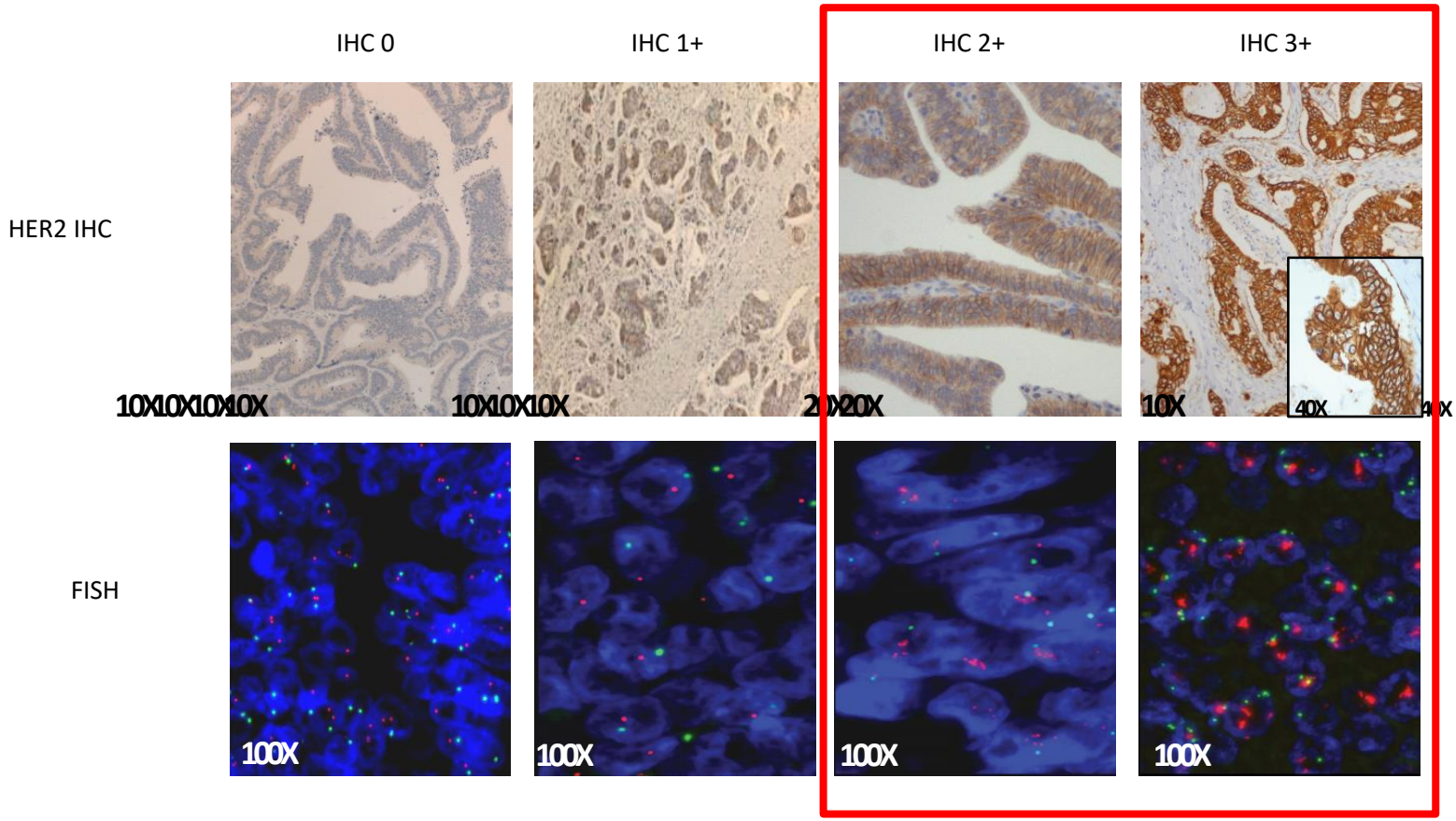
Yonesaka Sci Trans Med 2011
Bertotti Can Disc 2012
Kavuri Can Disc 2015

Heracles Results

- 23 eligible and evaluable:
- 2F/21M, median age 63 (r = 40-86), ECOG PS ≤ 1, median prior regimens 5 (r = 3-8).
- Primary endpoint was met with 8/23 Response [ORR = 35% (95% CL 20-55)]; 7/8
- ORs were observed in HER2 IHC3+ pts.
- Responses lasted: 8+, 12+, 14+, 24, 24.5+ 32, 54+ and 55+ weeks. Median time to progression was 5.5 months (95% CL 3.7-9.8).

Sartore-Bianchi.: Lancet Onc2016

HERACLES Diagnostic Criteria



Positive tumor cells ≥ 50%

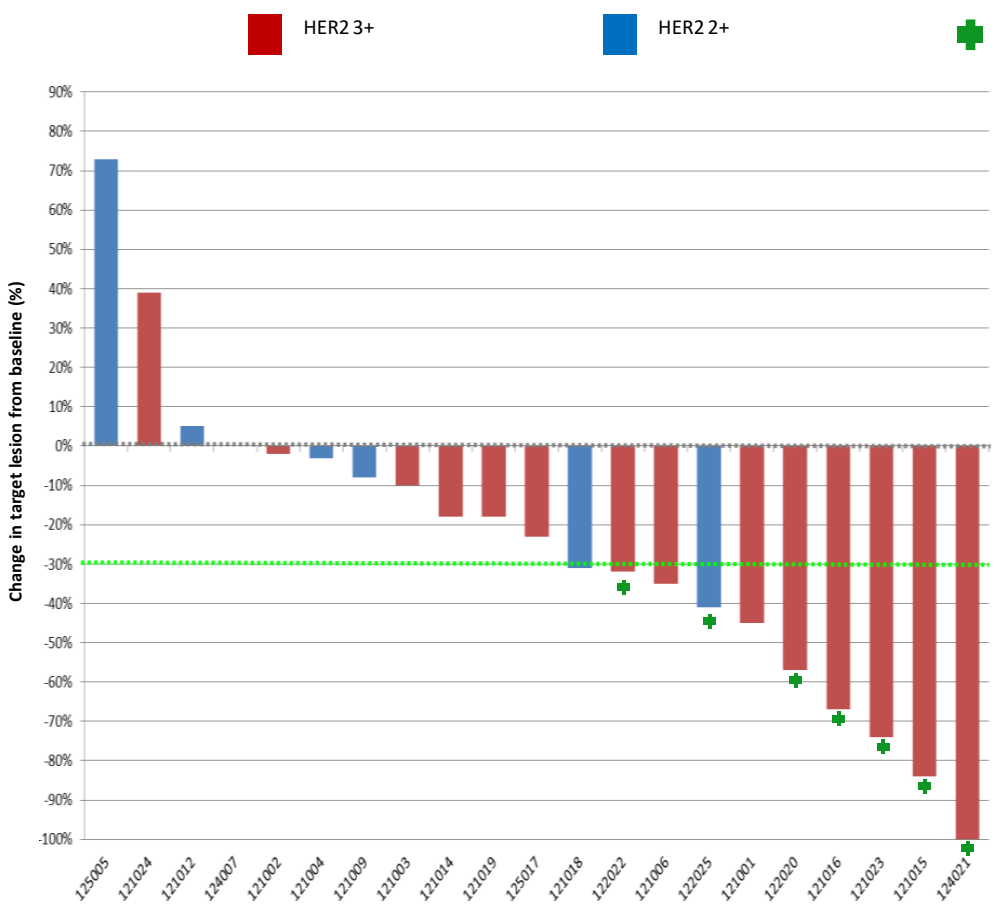
Valtorta E. et al, Modern Pathol 2015, in press

5,4% OF PTS

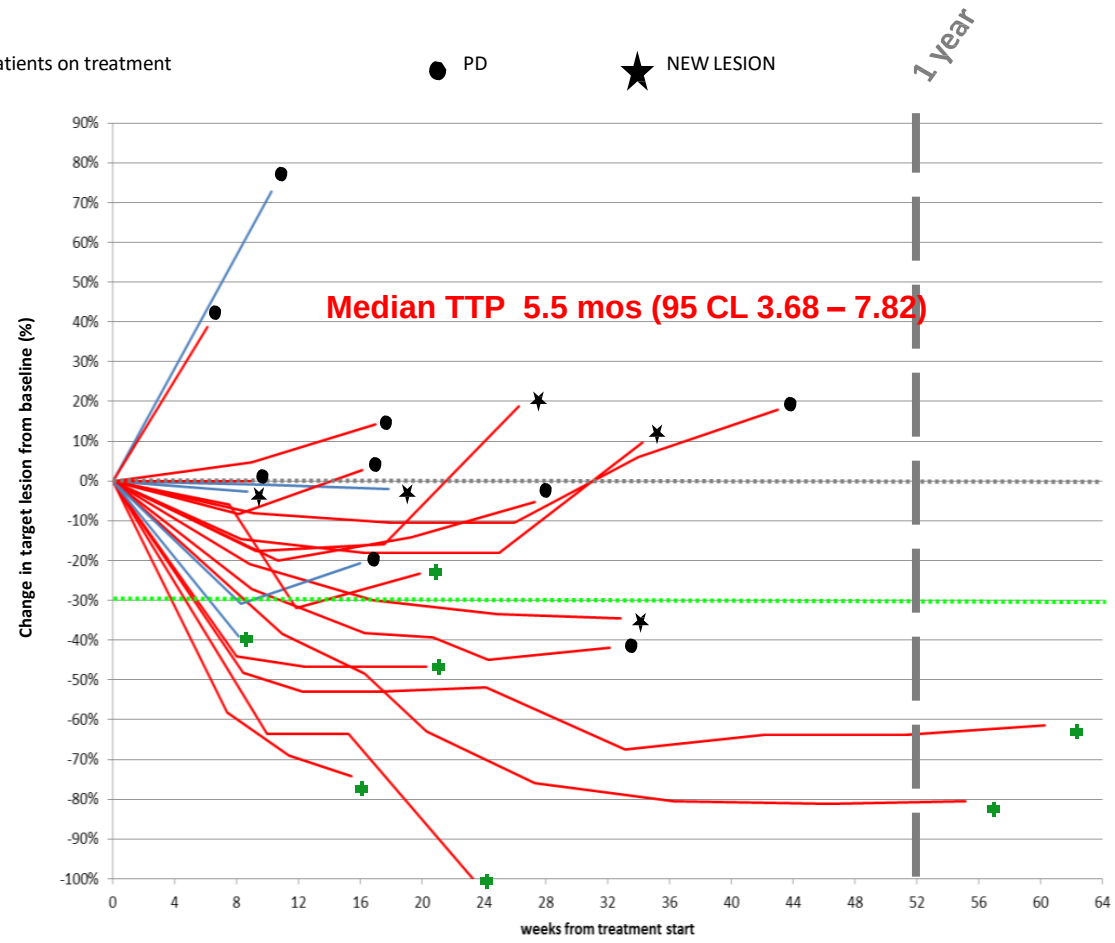
Eligible for HERACLES Trial

Responses by HER2 IHC Score

Waterfall plot



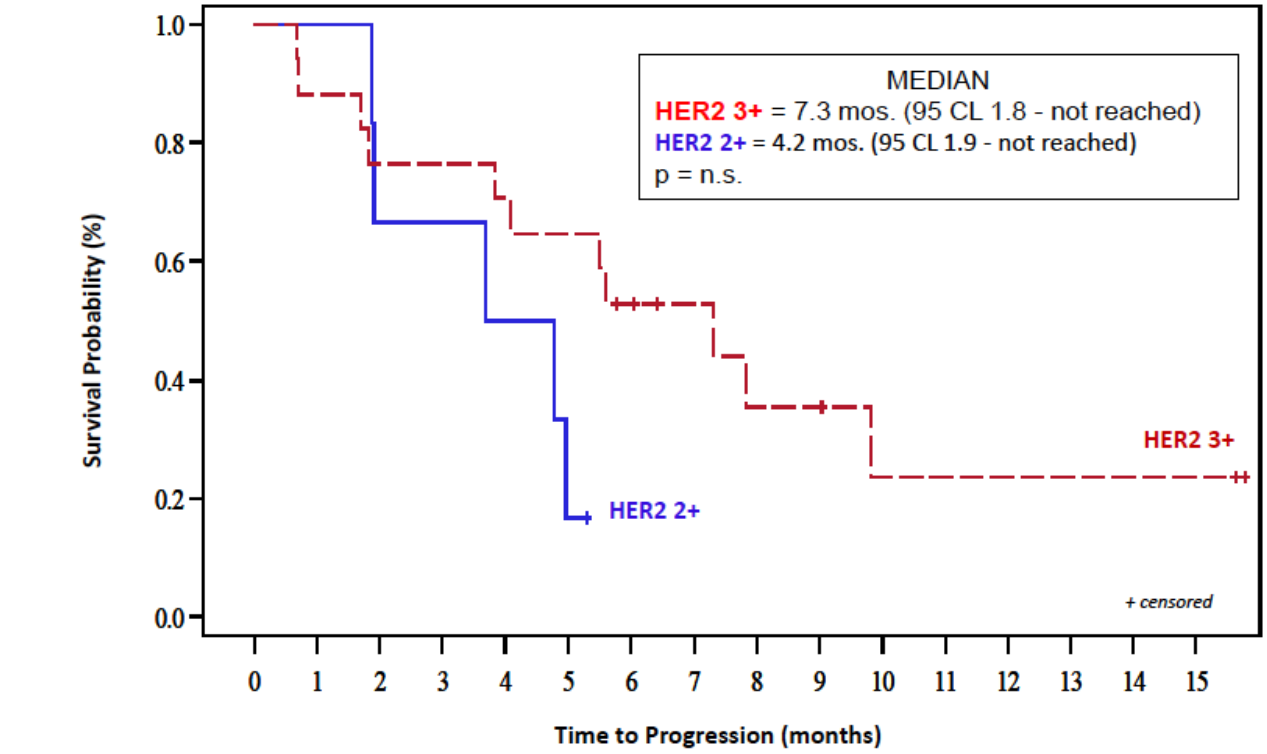
Spaghetti plot



*3 patients are not shown: 122026 (IHC 2+), not assessed yet; 121011 (IHC 3+) and 121013 (IHC 3+) early clinical PD.

Sartore-Bianchi.: Lancet Onc2016

Time To Progression



At risk:	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
HER2 2+	6	6	4	4	3	1	0									
HER2 3+	17	15	13	13	12	11	8	6	4	4	2	2	2	2	2	2

Sartore-Bianchi.: Lancet Onc2016

MOUNTAINEER: Tucatinib + Trastuzumab in *HER2*-Amplified mCRC

- Open-label, single-arm phase II study

Patients with previously treated, *RAS*-WT, *HER2*-Amp, metastatic or unresectable CRC (planned N = 25)

→

Tucatinib 300 mg PO Q2D +
Trastuzumab 8 mg/kg IV d1 cycle 1,
6 mg/kg IV d1 subsequent cycles

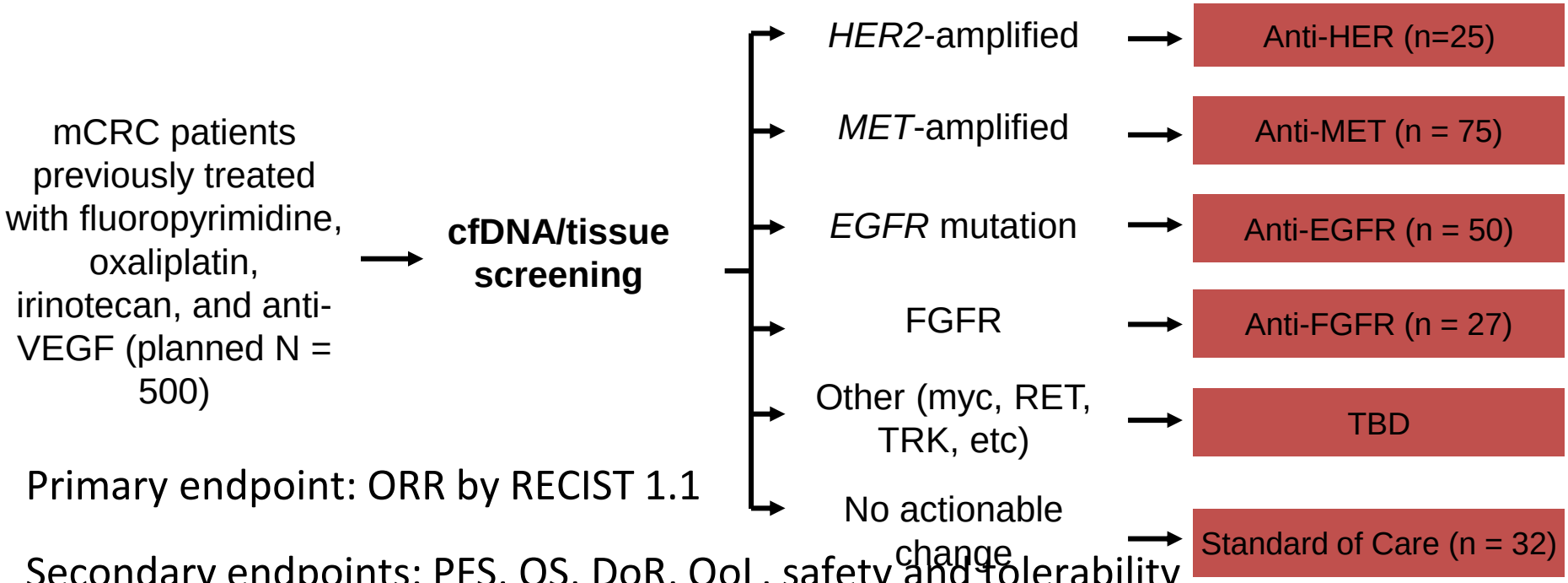
21-day cycles

- Primary endpoint: ORR by RECIST 1.1
- Secondary endpoints: PFS, OS, best clinical response, DoR, QoL, safety and tolerability

Strickler JH, et al. ASCO 2017. Abstract TPS3624. ClinicalTrials.gov. NCT03043313.

COLOMATE: COlorectal and Liquid BiOpsy Molecularly Assigned ThErapy

- Flexible-design trial with treatment arm selected based on genomic profiling by FFPE tumor testing or blood screening; arms open and close with best available science

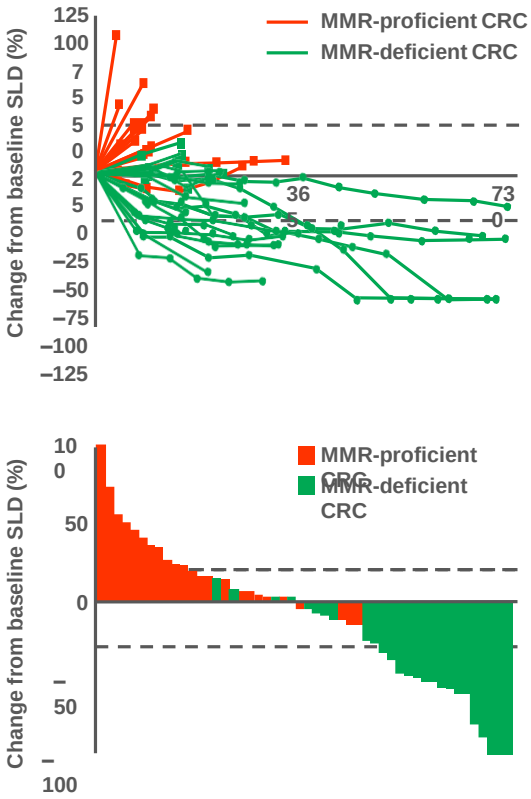


- Primary endpoint: ORR by RECIST 1.1
- Secondary endpoints: PFS, OS, DoR, QoL, safety and tolerability

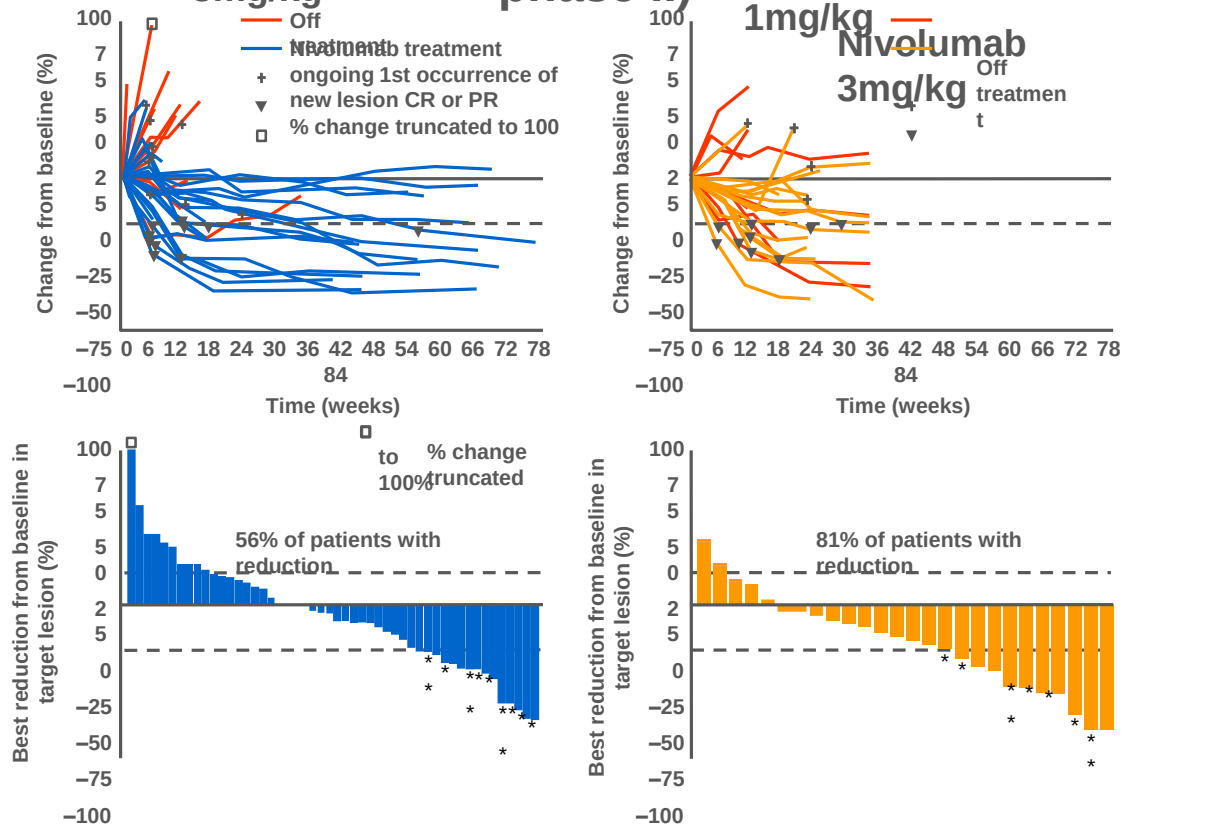
CHECKPOINT INHIBITORS

MSI-high tumours 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

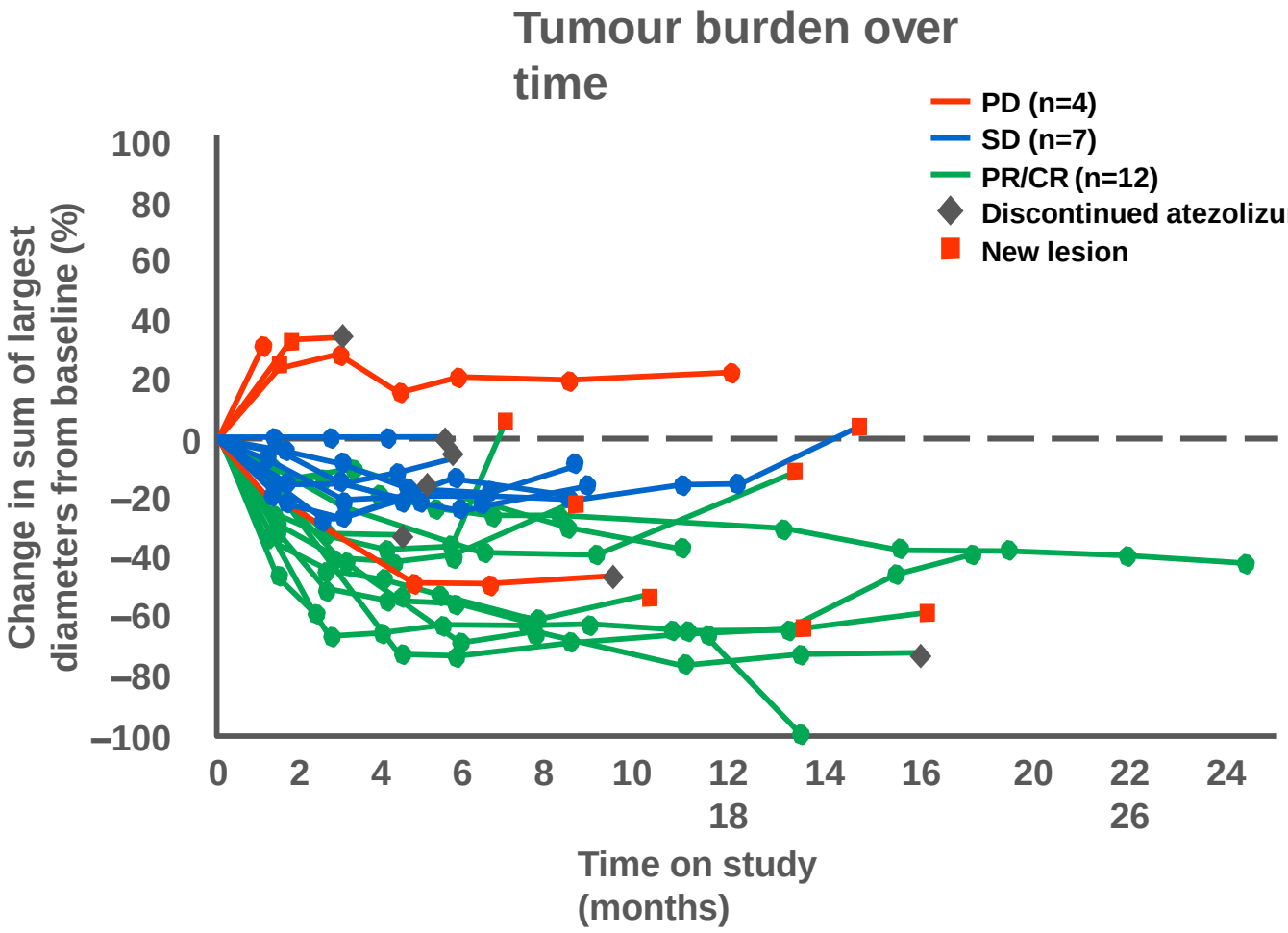
1. Le et al. ASCO 2016; 2.Overman et al. ASCO 2016

Nivolumab +/- Ipilimumab (Checkmate 142)

	MSI-H Nivo 3mg/kg	MSI-H Nivo 3 + Ipi 1	MSS Nivo 1 + Ipi 3	MSS Nivo 3 + Ipi 1
≥12w follow-up	N=47	N=27	N=10	N=10
ORR, N (%)	12 (25.5)	9 (33.3)	1 (10)	0
CR	0	0		
PR	12 (25.5)	9 (33.3)		
SD	14 (29.8)	14 (51.9)		
PD	17 (36.2)	3 (11.1)		
UNK	4 (8.5)	0		
All pts	N=70	N=30	N=10	N=10
mPFS (m)	5.3 (1.5-NE)	NE (3.4-NE)	2.28 (0.6-4.4)	1.31 (0.9-1.7)
mOS (m)	17.1 (8.6-NE)	NE (NE-NE)	11.5 (0.6-NE)	3.7 (1.2-5.6)

Overman MJ et al. Proc ASCO 2016

Atezolizumab plus Bevacizumab and/or FOLFOX in mCRC: phase Ib



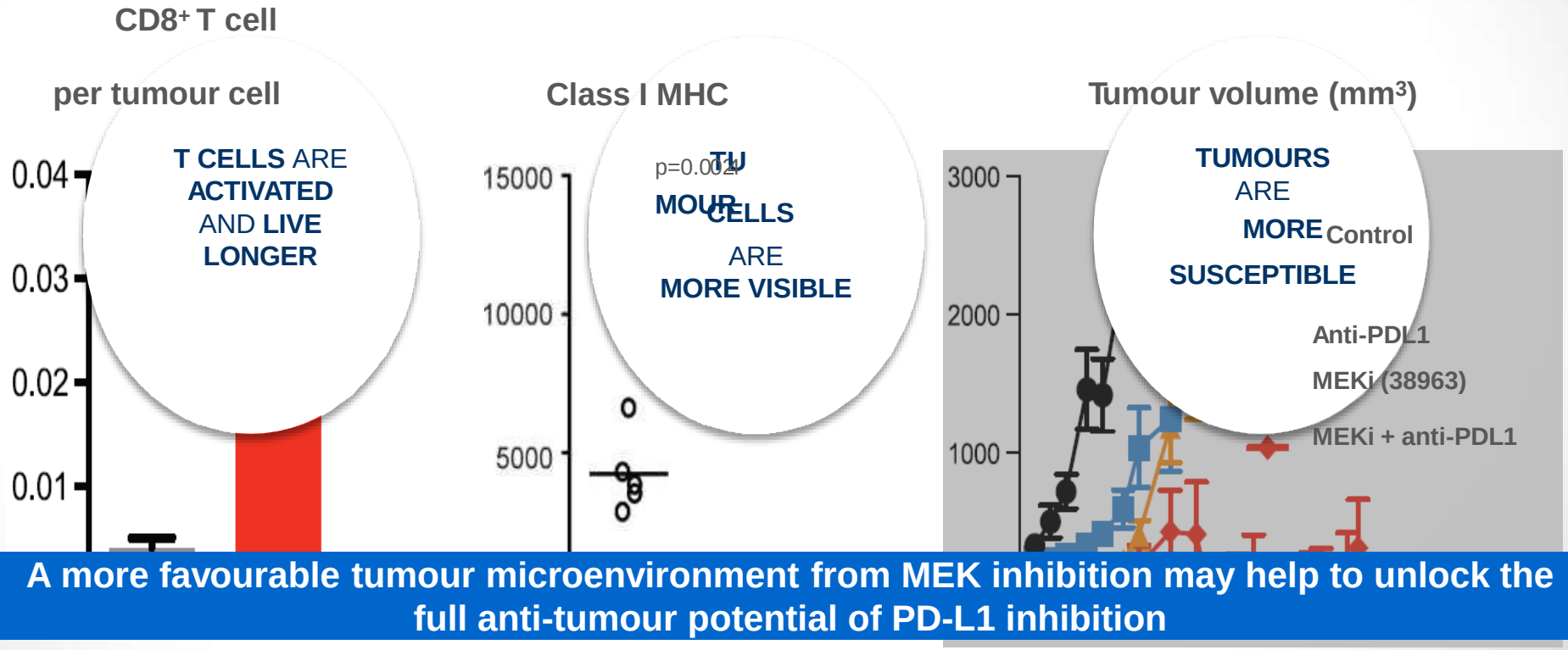
Patient number	ORR	mPFS	DOR
23	52%	14.1 months	11.4 months

- 3/9 patients treated beyond 15 months continue to be on treatment
- No unexpected toxicities were observed

Wallin et al. AACR 2016

MEK inhibition has a direct effect on T cells and the tumour microenvironment

- MEK inhibition alone can result in **intratumoural T cell accumulation** and **MHC Class I upregulation**
- MEK inhibition and anti-PDL1 are synergistic in xenograft models



A more favourable tumour microenvironment from MEK inhibition may help to unlock the full anti-tumour potential of PD-L1 inhibition

Ebert et al. Immunity 2016

Cobimetinib▼ + Atezolizumab in MSS mCRC (phase Ib)

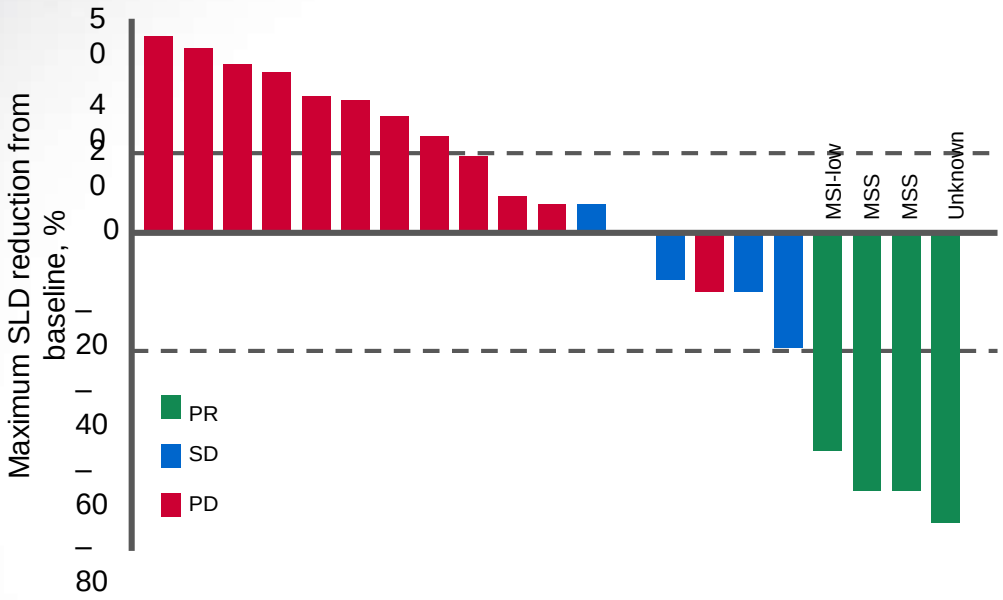
- Open-label, multicentre study including microsatellite stable (MSS) CRC tumours
- **Eligibility:** ECOG PS 0–1, measurable disease per RECIST v1.1
- **Primary endpoint:** dose limiting toxicity
- **Secondary endpoints:** DoR, AEs, C_{max}/C_{min} of atezolizumab and cobimetinib, ORR according to RECIST, PFS, OS

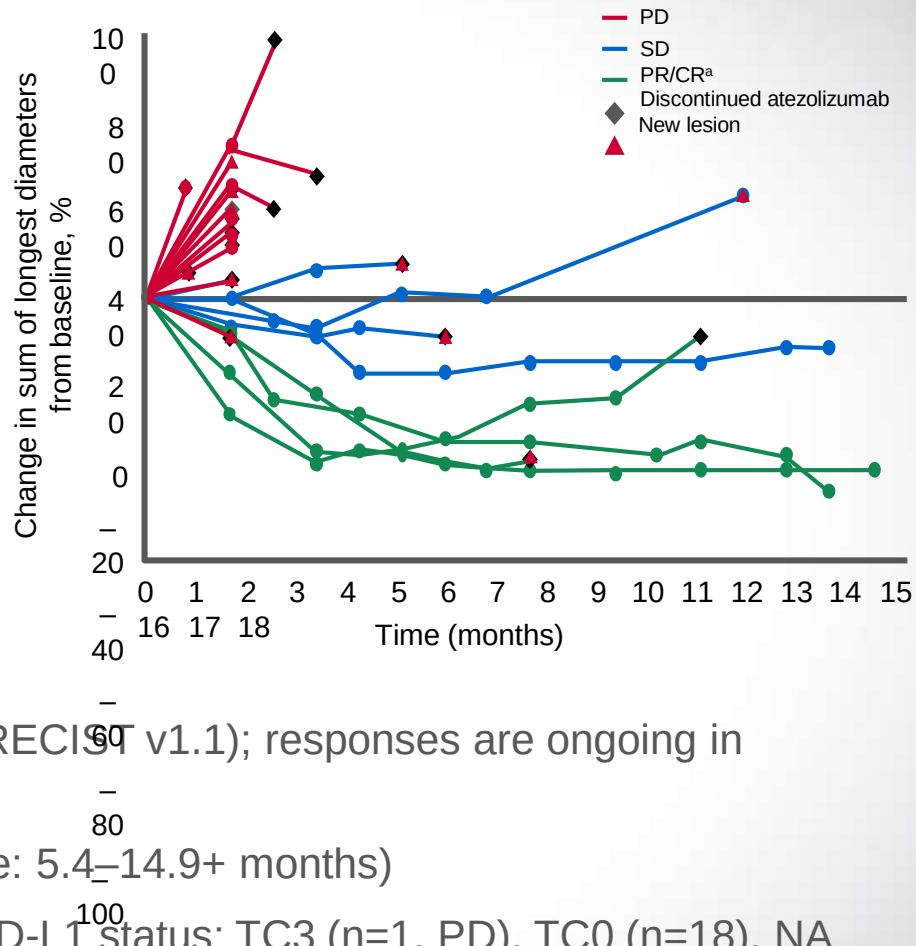
* This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. These should be reported to the Regulatory authorities in your country according to your national requirements.

*One KRAS WT and two KRAS MT patients clinicaltrials.gov identifier NCT01988896

Bendell et al. ASCO 2016 Desai et al. ESMO 2016

Cobimetinib + Atezolizumab efficacy: change in tumour burden



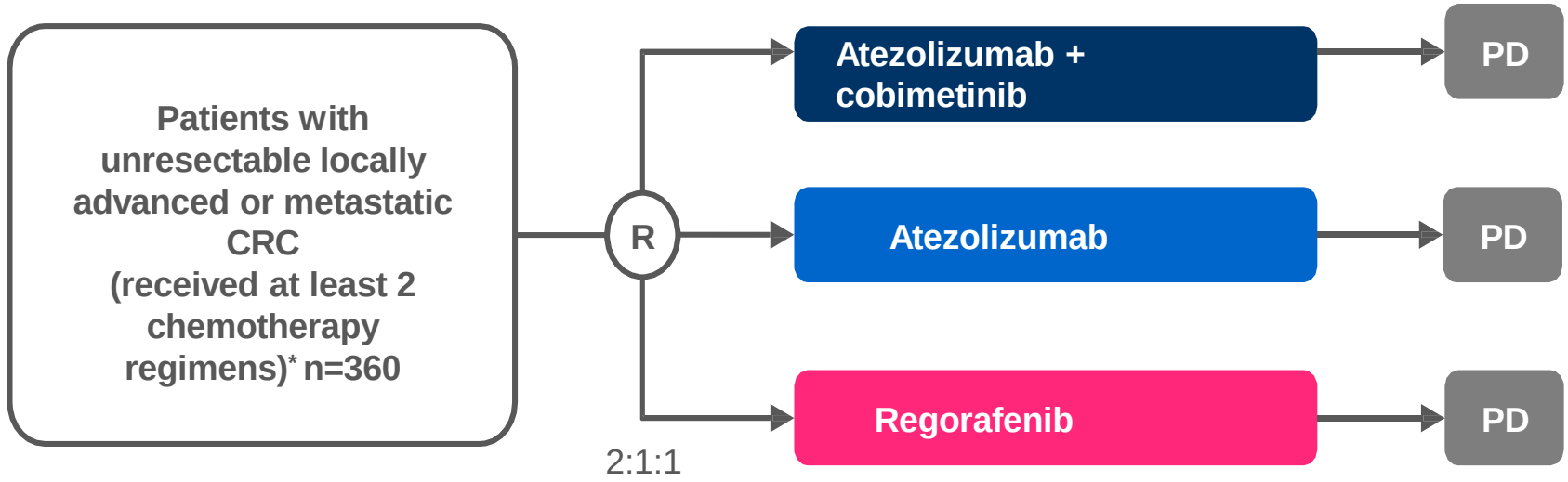


- Four patients had partial responses (confirmed per RECIST v1.1); responses are ongoing in two of these patients
- Median duration of response was not reached (range: 5.4–14.9+ months)
- Tumour volume reduction was not associated with PD-L1 status: TC3 (n=1, PD), TC0 (n=18), NA (n=4)

[a]Confirmed per RECIST v1.1

Bendell et al. ASCO 2016 Desai et al. ESMO 2016

Phase III trial of Cobimetinib and Atezolizumab in chemotherapy-refractory mCRC (COTEZO – IMBlaze 370)



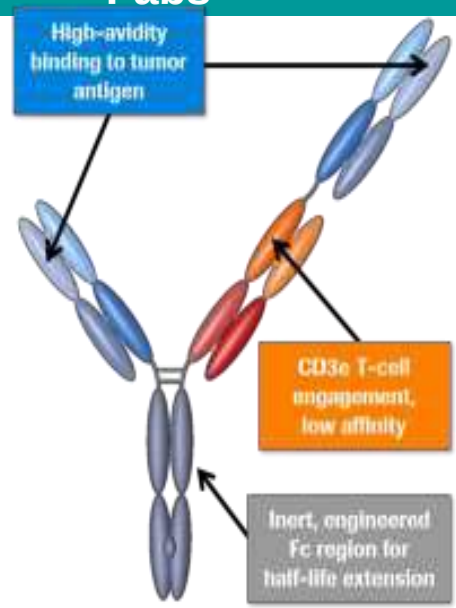
- Primary endpoint = OS

*Experienced disease progression or was intolerant to at least two systemic chemotherapy regimens including fluoropyrimidines, irinotecan, or oxaliplatin

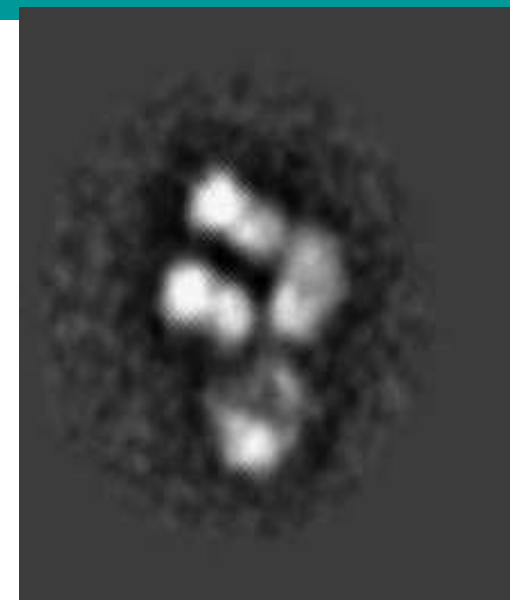
NCT02788279

CEA-TCB is the first T-cell bispecific antibody with a novel 2-to-1 format, optimized for efficacy and safety

2-to-1 Format[1] Fabs[1]



Flexible range of motion in



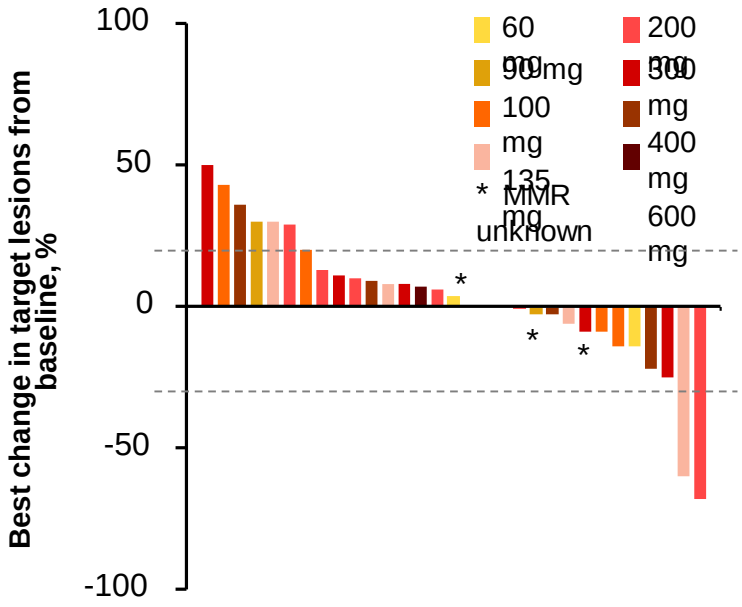
- Binds simultaneously with 1 arm to CD3 on T cells and with 2 arms to CEA on tumor cells
- Flexible 2-to-1 format enables high-avidity binding and selective killing of high CEA-expressing tumor cells
- Longer half-life compared with other TCB formats
- Silent Fc results in reduced risk of FcγR-related cytokine release/IRRs
- Killing of tumor cells independent of pre-existing immunity
- T-cell proliferation at site of activation

Fab, fragment antigen-binding region; IRR, infusion-related reaction. 1. Bacac et al, Clin Cancer Res 2016

Tabernero et al, Proc ASCO 2017

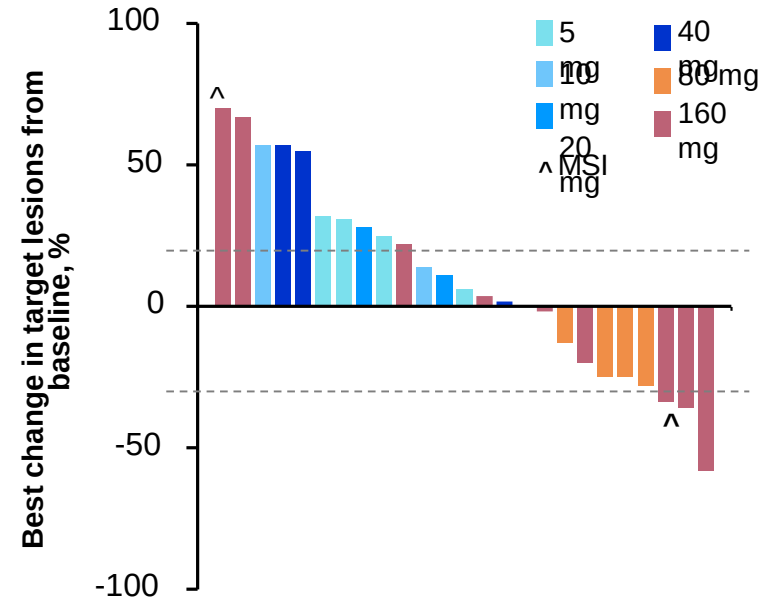
CEA-TCB at doses of ≥ 60 mg[a] demonstrated clinical activity in mCRC

Study 1: CEA-TCB monotherapy
n = 31, 60-600 mg



No clear correlation between CEA-TCB dose and response

Study 2: CEA-TCB + atezolizumab
n = 25, 5-160 mg



Correlation between CEA-TCB dose and response

Data reported by investigators, cutoff: March 3, 2017.
[a] Radiological signs of tumor inflammation seen at ≥ 60 mg (safety data cutoff is ≥ 40 mg).

Argilés G, et al. ESMO GI 2017.

Conclusions

- Survival of patients with mCRC continues to improve thanks to incremental additional effects of subsequent treatment lines
- Patients should receive all active agents to derive full benefits
- Molecular driven subgroups is leading to individualization of treatment
- Immunotherapy activity in MSI-High tumors is stablished
- Targeted Therapy and immunotherapy combo appears to improved efficacy.
- Biomarkers to predict benefit from IO are desperately needed.
- Solid tumor CAR-T is coming soon

Gastric/GEJ Adenocarcinoma

Localized Disease

FLOT-4 Study

Randomized, multicenter, Phase II/III Study

- **Gastric or EGJ cancer typ I-III**
- **Medically and anatomically operable**
- **cT2-4/cN-any/cM0 or cT-any/cN+/cM0**

STRATIFIKATION

R

n=716

FLOT x4 - RESECTION - FLOT x4

FLOT: Docetaxel 50mg/m2, d1; 5-FU 2600 mg/m², d1; Leucovorin 200 mg/m², d1; Oxaliplatin 85 mg/m², d1, q2w

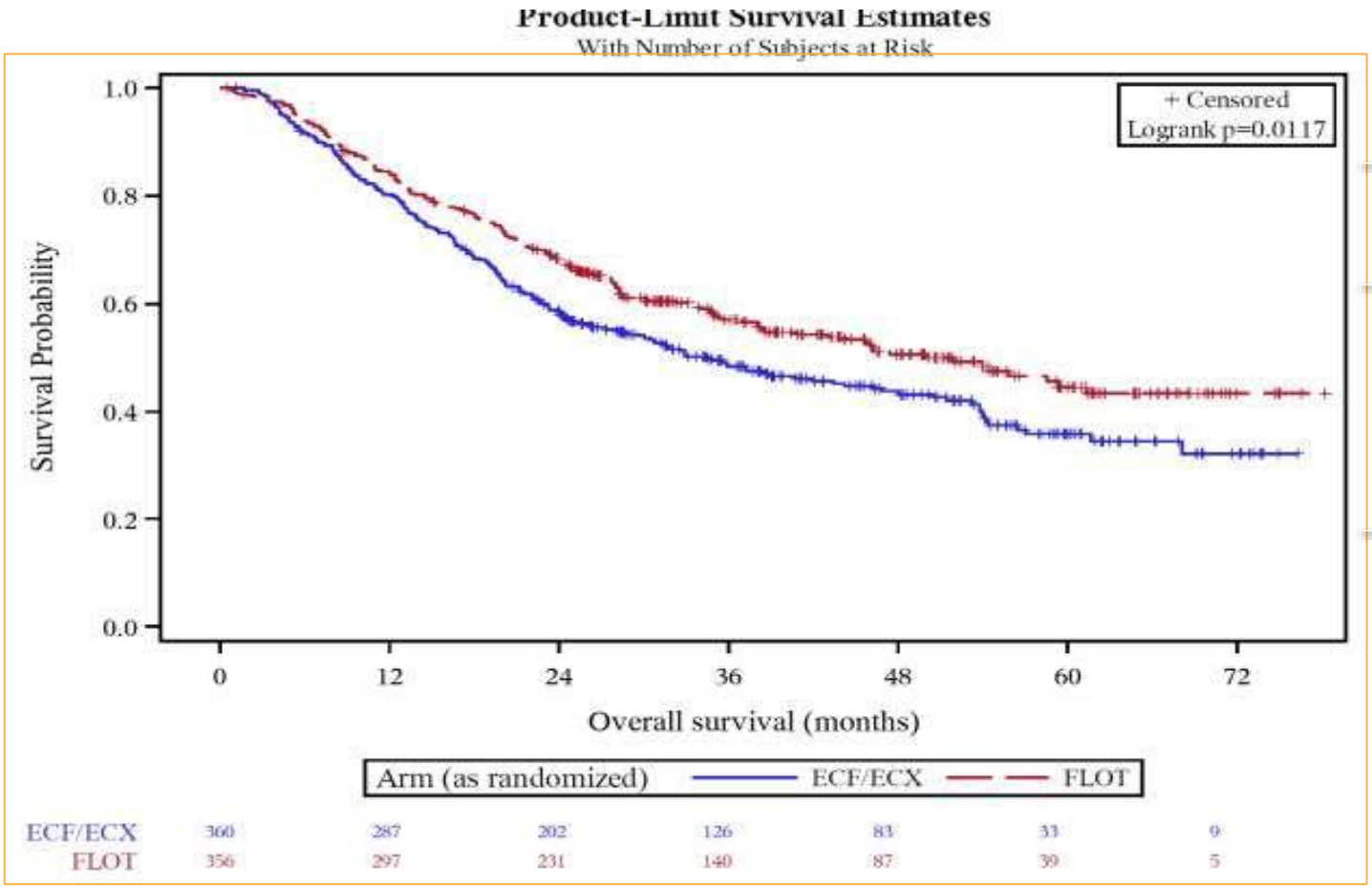
ECF/ECX x3 - RESECTION - ECF/ECX x3

ECF/ECX: Epirubicin 50 mg/m2, d1; Cisplatin 60 mg/m², d1; 5-FU 200 mg/m² (or Capecitabin 1250 mg/m² p.o. geteilt in 2 doses d1-d21), q2w

Stratification: **ECOG** (0 or 1 vs. 2), **localization** (GEJ Type I vs. Type II/III vs. Gastric), **age** (< 60 vs. 60-69 vs. ≥70 years) and **nodal status** (cN+ vs. cN-).

23% had Siewert type I 33% had Siewert type II/III

Survival ECF/ECX versus FLOT



	ECF/ECX	FLOT
mOS	35 months [27-46]	50 months [38-na]

HR 0.77 [0,63 – 0,94]
p=0.012 (log rank)

OS rate*	ECF/ECX	FLOT
2y.	59%	68%
3y.	48%	57%
5y.	36%	45%

*projected OS-rates

Median follow-up time: 43 months

Al-Batran et al. *J Clin Oncol 2017;* 35(suppl): #4004

Perioperative chemotherapy Esop/Gastric Ca

Trial	CT	No. pts control	No. pts Study Arm	5-year survival control	5-year survival CT	HR (CI at 95%)
Cunningham		253				
	ECF		250	23%	36 %	0.60-0.93
N Eng J Med 2006		No CT				
						p=0.009
Ychou	CDDP	111				
			113	24%	38%	0.50-0.95
J Clin Oncol 2011	5-FU	No CT				
						p=0.021
Allum	CDDP	402	400	17,6%	25.5%	0.72-0.98
J Clin Oncol 2009	FU	No CT				
						P=0.03
Al-Batran		360	356			
	FLOT			36%	45%	0.63-0.94
ASCO 2017		ECF	FLOT			
						P=0.012

1. Cunningham D, et al, N Engl J Med 2006;355:11–20.
2. Ychou M, et al. J Clin Oncol 2011;29:1715-1726.
3. Allum W, et al. J Clin Oncol 2009; 27:5062-5067. Only esophageal cancer
4. Al-Batran SA, et al 2017; 35(suppl): #4004

Metastatic Disease

Treatment options Metastatic Gastric Adenocarcinoma

1st line tx	2nd line tx	3rd line tx	Supportive care
5FU+ platinum (+/- taxane)	Ramucirumab+/- paclitaxell Paclitaxel irinotecan	Pembrolizumab/ Nivolumab PDL1+	
If HER2+, Add trastuzumab			
Pembrolizumab in MSI-high or dMMR →			

MSI in more than CRC

Cancer Type	General population risk	Lynch syndrome (MLH1 and MSH2 heterozygotes)	
		Risk	Mean age of onset
Colon	5.5%	52-82%	44-61 years
Endometrium	2.7%	25-60%	48-62 years
Stomach	< 1%	6-13%	56 years
Ovary	1.6%	4-12%	42.5 years
Hepatobiliary tract	< 1%	1.4-4%%	Not reported
Urinary tract	< 1%	1-4%	~55 years
Small bowel	< 1%	3-6%	49 years
Brain/central nervous system	< 1%	1-3%	~50 years
Sebaceous neoplasms	< 1%	1-9%	Not reported

Pembrolizumab Approved for MSI-H or Mismatch Repair Deficient Tumors

Table 25: Response by Tumor Type

	N	Objective response rate n (%)	95% CI	DOR range (months)
CRC	90	32 (36%)	(26%, 46%)	(1.6+, 22.7+)
Non-CRC	59	27 (46%)	(33%, 59%)	(1.9+, 22.1+)
Endometrial cancer	14	5 (36%)	(13%, 65%)	(4.2+, 17.3+)
Biliary cancer	11	3 (27%)	(6%, 61%)	(11.6+, 19.6+)
Gastric or GE junction cancer	9	5 (56%)	(21%, 86%)	(5.8+, 22.1+)
Pancreatic cancer	6	5 (83%)	(36%, 100%)	(2.6+, 9.2+)
Small intestinal cancer	8	3 (38%)	(9%, 76%)	(1.9+, 9.1+)
Breast cancer	2	PR, PR		(7.6, 15.9)
Prostate cancer	2	PR, SD		9.8+
Bladder cancer	1	NE		
Esophageal cancer	1	PR		18.2+
Sarcoma	1	PD		
Thyroid cancer	1	NE		
Retroperitoneal adenocarcinoma	1	PR		7.5+
Small cell lung cancer	1	CR		8.9+
Renal cell cancer	1	PD		

CR = complete response
PR = partial response
SD = stable disease
PD = progressive disease
NE = not evaluable

Package insert

Presented By Dung Le at 2017 ASCO Annual Meeting

Bristol-Myers Squibb

Press Release

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Japan Ministry of Health, Labor and Welfare Approves Opdivo (nivolumab) for the Treatment of Patients with Unresectable Advanced or Recurrent Gastric Cancer Which Has Progressed After Chemotherapy

Opdivo is the first and only Immuno-Oncology treatment to demonstrate survival benefit in patients who underwent two or more prior treatments

Opdivo is the first Immuno-Oncology agent anywhere in the world to receive approval for unresectable advanced or recurrent gastric cancer based on a Phase 3 study

CATEGORY: CORPORATE/FINANCIAL NEWS

FRIDAY, SEPTEMBER 22, 2017 5:00 AM EDT

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE:BMY) today announced that the Japanese Ministry of Health, Labor and Welfare (MHLW) has approved *Opdivo* (nivolumab) for the treatment of unresectable advanced or recurrent gastric cancer which has

#MEDIA: $BMY treatment now approved in Japan to treat #GastricCancer:

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Approved Drugs

Hematology/Oncology (Cancer) Approvals & Safety Notifications

Drug Information Soundcast in Clinical Oncology (D.I.S.C.O.)

Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)

FDA grants accelerated approval to pembrolizumab for advanced gastric cancer

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On September 22, 2017, the Food and Drug Administration granted accelerated approval to pembrolizumab (KEYTRUDA, Merck & Co., Inc.) for patients with recurrent locally advanced or metastatic, gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 as determined by an FDA-approved test. Patients must have had disease progression on or after two or more prior systemic therapies, including fluoropyrimidine- and platinum-containing chemotherapy and, if appropriate, HER2/neu-targeted therapy.

Approval is based on the results of KEYNOTE 059 (NCT02335411), an open-label, multicenter, non-comparative, multi-cohort trial that enrolled 259 patients with gastric or gastroesophageal junction adenocarcinoma. Among the 259 patients, 55% (n=143) had tumors expressing PD-L1 and either microsatellite stable (MSS), or undetermined microsatellite instability (MSI) or mismatch repair (MMR) status.

PD-L1 expression was evaluated by the PD-L1 IHC 22C3 pharmDx Kit (Dako) and PD-L1 positivity was based on a combined positive score (CPS) ≥ 1. CPS is determined by the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by total number of tumor cells evaluated, multiplied by 100.

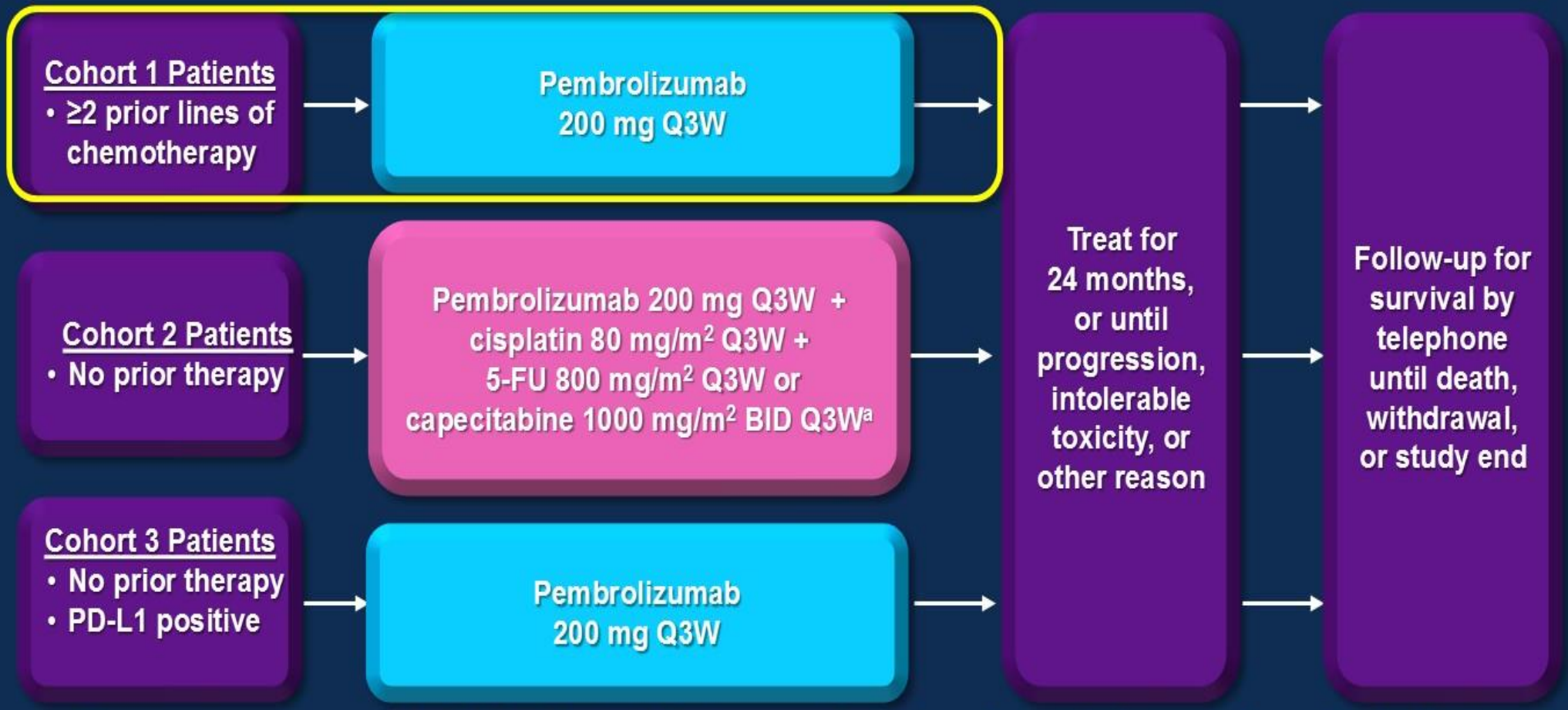
For the 143 patients with tumors expressing PD-L1 and who were either MSS or had unknown MSI or dMMR status, the objective response rate was 13.3% (95% CI: 8.2, 20.0); 1.4% had complete responses and 11.9% had partial responses. Among the 19 responding patients, the response duration ranged from 2.8+ to 19.4+ months, with 11 patients (58%) having response durations of 6 months or longer and 5 patients (26%) having response durations of 12 months or longer.

Among the 259 patients enrolled in KEYNOTE 059, 7 (3%) had tumors that were determined to be MSI-high. Responses were observed in 4 of these 7 patients (ORR 57%), with one complete response. The response duration ranged from 5.3+ to 14.1+ months.

Adverse reactions occurring in patients with gastric cancer were similar to those presently described in product labelling. The most common adverse reactions are fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, and constipation. Pembrolizumab is associated with immune-mediated side effects, including pneumonitis, colitis, hepatitis, endocrinopathies, and nephritis.

In September 2017, based largely upon the results of the KEYNOTE-059 study, pembrolizumab approval was extended to include patients with PD-L1-overexpressing gastric and EGJ adenocarcinomas who had received two or more lines of chemotherapy, and, if appropriate, HER2-targeted therapy. In Japan, a second PD-1 inhibitor, nivolumab, has been approved for any unresectable advanced or recurrent gastric cancer that has progressed after conventional chemotherapy.

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

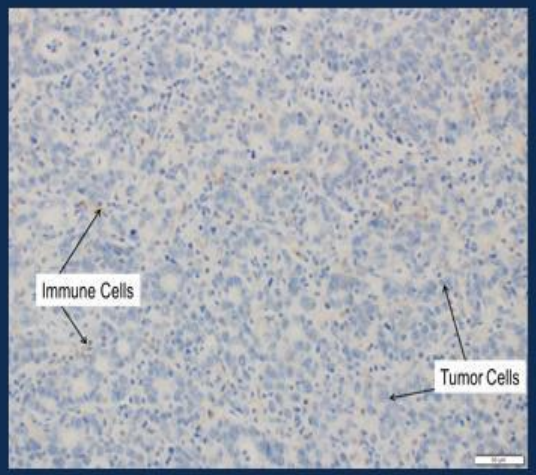
PD-L1 Expression IHC[a]

- PD-L1 expression is determined by combined positive score (CPS)

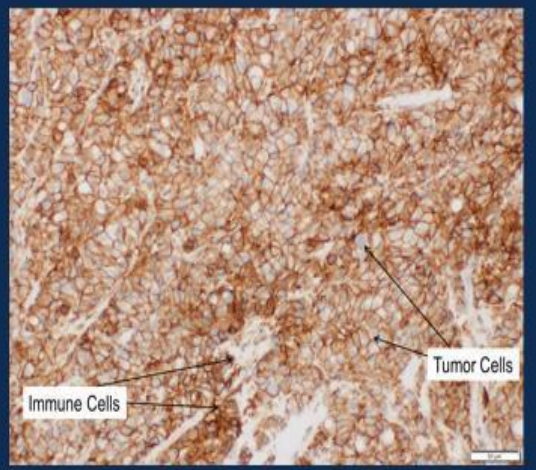
$$\text{CPS} = \frac{\text{No. of PD-L1 staining cells (tumor cells, lymphocytes, macrophages)}}{\text{Total No. of viable tumor cells}} \times 100$$

- **A specimen is considered to have positive PD-L1 expression if CPS ≥1%**

PD-L1 negative



PD-L1 positive



[a]22C3 pharmDx IHC, Agilent Technologies, Carpinteria, CA

Cohort 1: Response

FUCHS C: J Clin Oncol 35, 2017 (suppl; abstr 4003).

	All Patients N = 259		PD-L1 Positive N 148		PD-L1 Negative N 109	
Responses	%	95% CI	%	95% CI	%	95o/o CI
ORR	12	8-17	16	11-23	6	3-13
DCR	27	22-33	34	26-42	19	12-28
OR:						
CR	3	1-6	3	1-8	3	1-8
PR	9	6-13	13	8-19	4	1-9
SD	16	12-21	18	12-25	15	9-23
PD	56	49-62	53	44-61	60	50-69

- Median (range) follow-up in cohort 1: 5.6 (0.5-24.7) months
- 134 patients received pembrolizumab as third-line therapy; ORR was 16%, and DCR was 31%
- 125 patients received pembrolizumab as fourth plus -line therapy; ORR was 7%, and DCR was 23%

"P[)L1 positiYevras defined as combined positiYe soore (CPS) '1:1 {preYio11Sly re;ported ais and equiYa.lent to CPS '1:1%). where CPS = ratio of P[).l1 - positiYe oells {tumor oel s, lymphocytes. and macrophages) to the total mrmber of tumor cells x 100.

"Only confirmed re ponses v>ere ooluded.

<CR+ PR + SD '12 months. DataicutoH: April 2t ,2017.

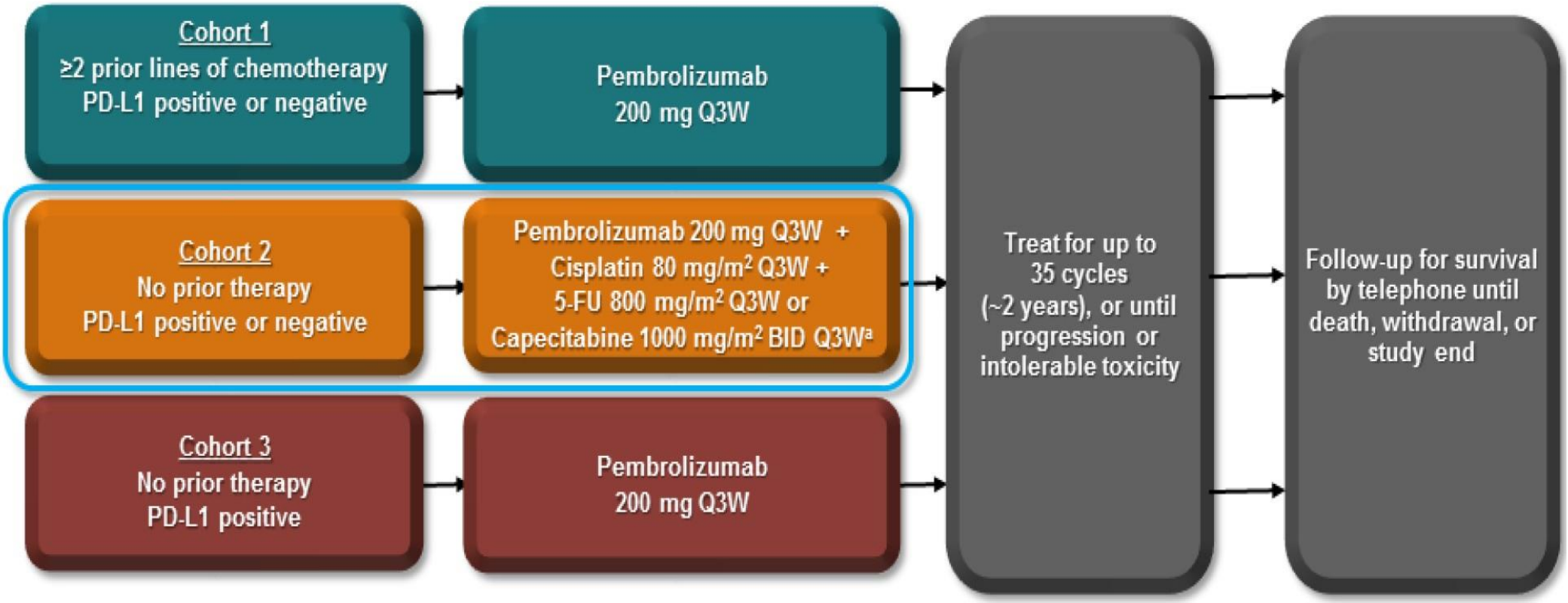
Cohort 1: Immune-Mediated Adverse Events

Event (%)	All Grades in >2 Patients	Grade Jb
Any	50 (19)	13 (5)
Hypothyroidism	24 (9)	1(<1)
Hyperthyroidism	9 (4)	0
Colitis	4 (2)	3 (1)
Infusion-related reactions	4 (2)	0
Pneumonitis	4 (2)	2 (1)
Thyroiditis	3 (1)	1(<1)

There were no grade 4/5 immune-mediated or infusion reactions

Wainberg, ESMO, Sept 2017

KEYNOTE-059 Study Design



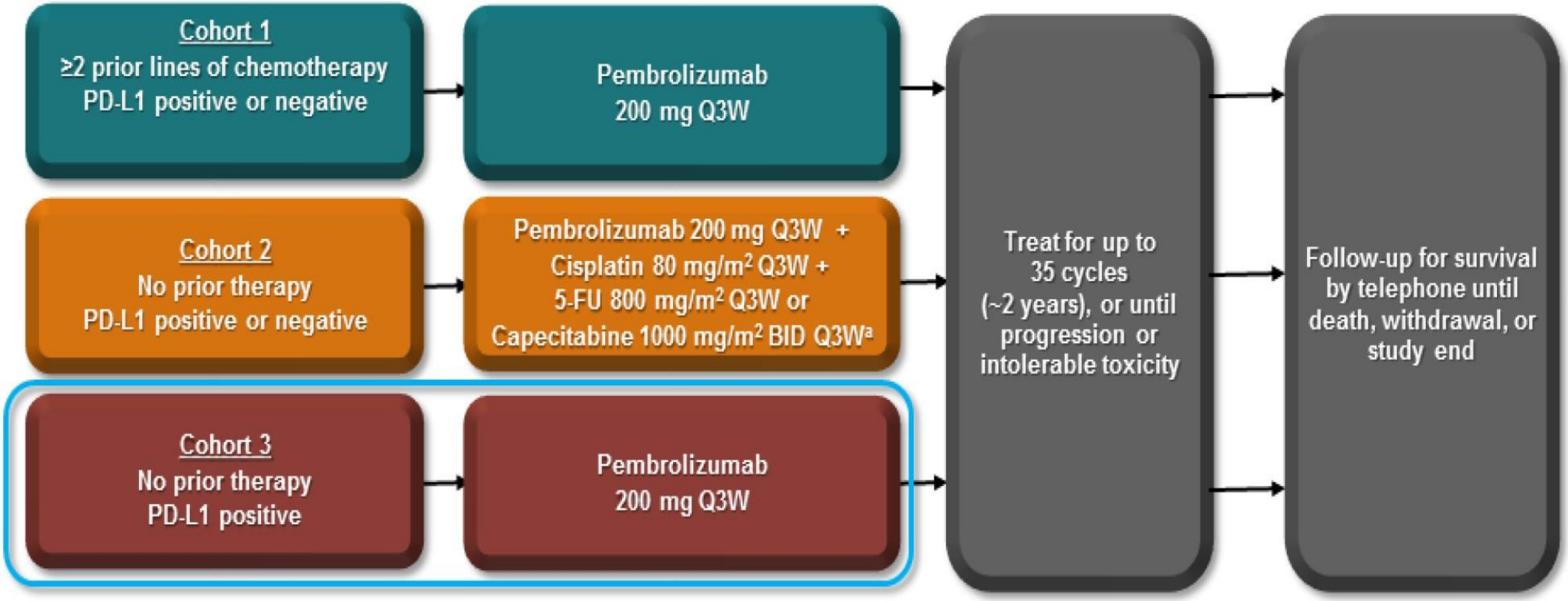
Cohort 2: Response

	All Patients N = 25		PD-L1 Positivea n = 16		PD-L1 Negative n = 8	
Responseb	%	95% CI	%	95% CI	%	95% CI
ORR	60	39-79	69	41-89	38	9-76
DCR C	80	59-93	75	48-93	75	35-97
BOR						
CR	4	0-20	0	0-22	13	0-53
PR	56	35-76	69	41-89	25	3-65
SD	32	15-54	19	4-46	50	16-84
PD	4	0-20	6	0-30	0	0-37

- Median (range) follow-up in cohort 2: 13.8 (1.8-24.1) months

• PD-L1 positive was defined as combined positive score (CPS) 1 (previously reported as and equivalent to CPS 1%), where CPS = number of PD-L1- positive cells (tumor cells, lymphocytes, and macrophages) divided by the total number of tumor cells " 100.
bOnly confirmed responses were included.
=CR + PR + SD :ZS
months. Data
cutoff: April 21, 2017.

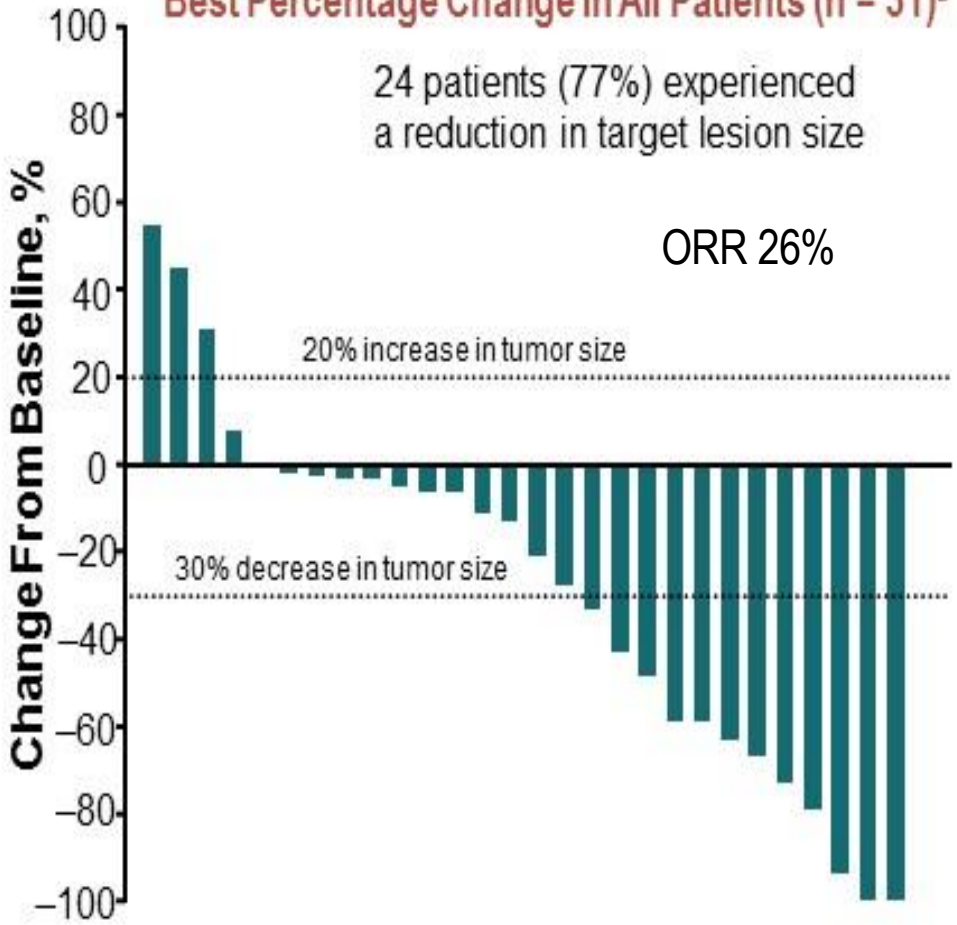
KEYNOTE-059 Study Design



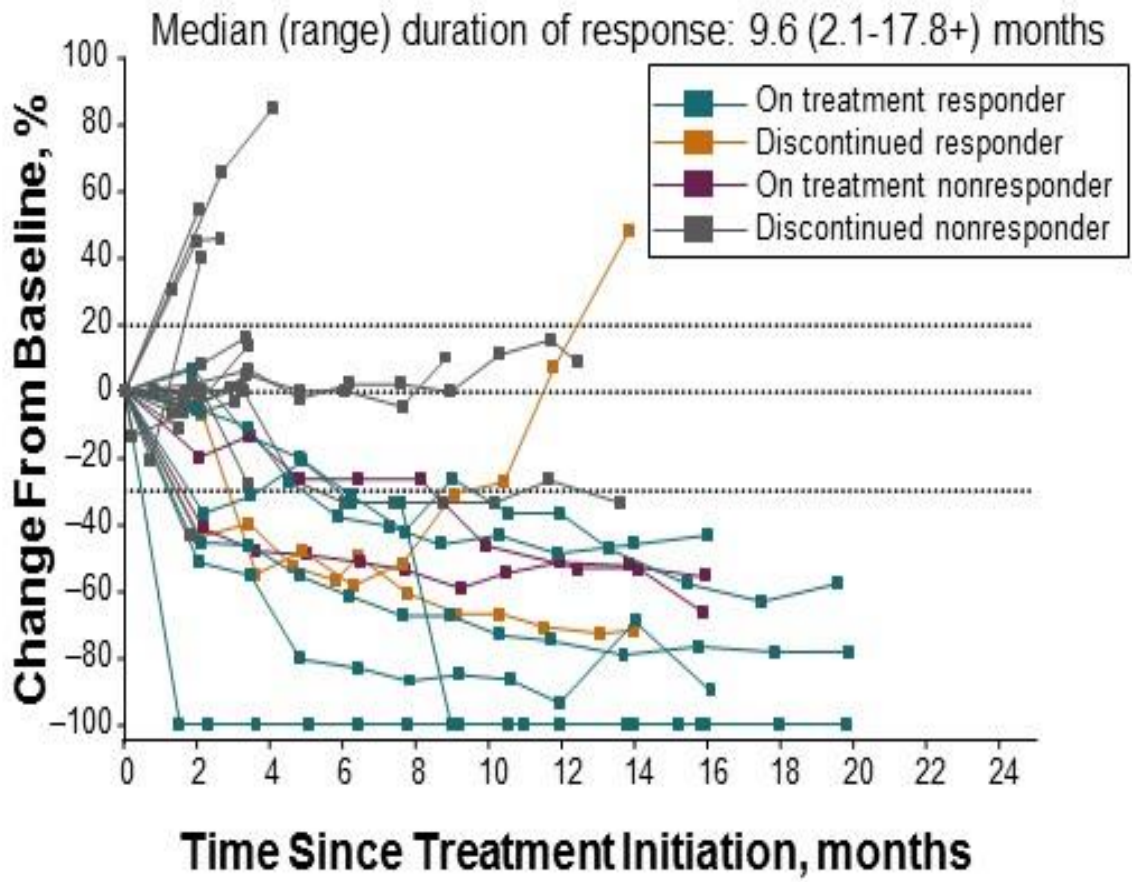
Cohort 3: Best Percentage Change and Longitudinal Change in Target Lesion Size

Wainberg, ESMO, Sept 2017

Best Percentage Change in All Patients (n = 31)[a]

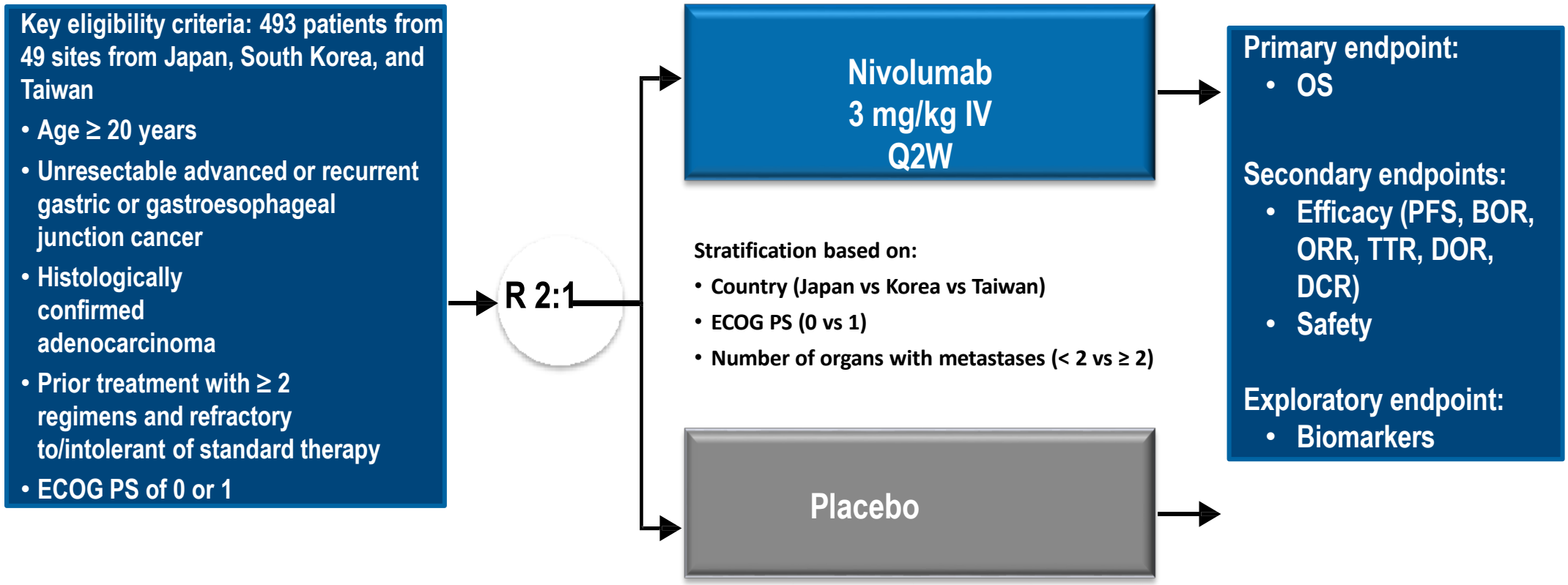


Longitudinal Change in All Patients (n = 30)[b]



[a]Only patients with measurable disease per RECIST v1.1 by central review at baseline who had ≥1 postbaseline assessment were included (n = 31) and assessments were nonevaluable/not available in 3 patients.
[b]Longitudinal change in the sum of the longest target lesion diameters from baseline in patients with CR or PR (n = 30).
+No progressive disease at last disease assessment.
Data cutoff: April 21, 2017.

ATTRACTION-2: Phase 3 trial



- 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

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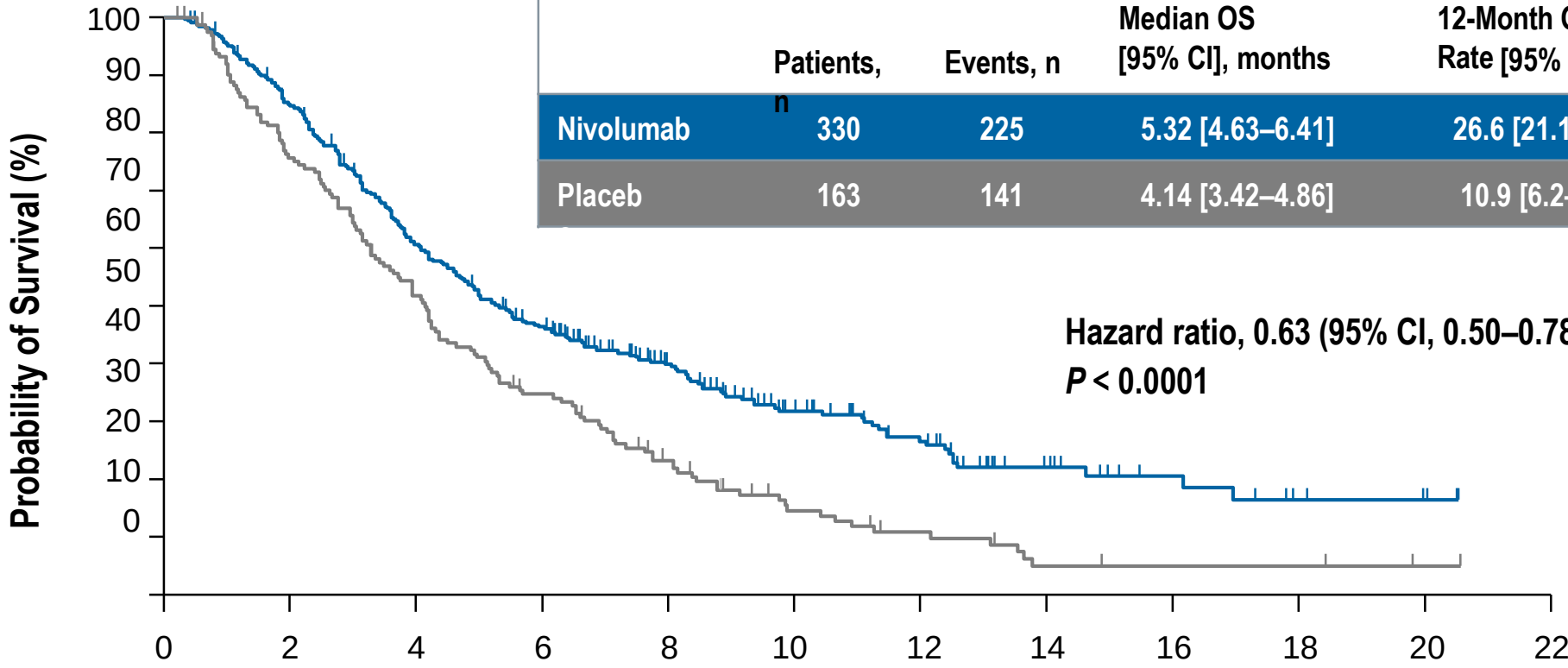
Young K et al. Lancet: 390, 2461, December 2017

Overall Survival

	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]
Placeb	163	141	4.14 [3.42–4.86]	10.9 [6.2–17.0]



At risk:												
Nivolumab	330	275	193	142	95	57	39	19	10	5	3	0
Placebo	163	121	82	53	32	16	10	4	3	3	1	0

Young K et al. Lancet: 390, 2461, December 2017

Conclusions Metastatic Gastric cancer

- Platinum based chemotherapy
- Trastuzumab improves survival in HER2 positive cancers (+++)
- Second line chemotherapy prolongs survival in good PS patients
- Ramucirumab improves survival compared BSC.
  - In combination with paclitaxel improves outcomes over paclitaxel
- Immunotherapy with checkpoint inhibitors is active.
  - Pembrolizumab approved in the USA as second/third lines in PDL-1 positive patients.
  - Pembrolizumab is approved for MSI high patients.

Thanks for the attention!!!