Immuntherapie in der Erstlinie beim met. Kolorektalkarzinom

MEDICAL UNIVERSITY OF VIENNA

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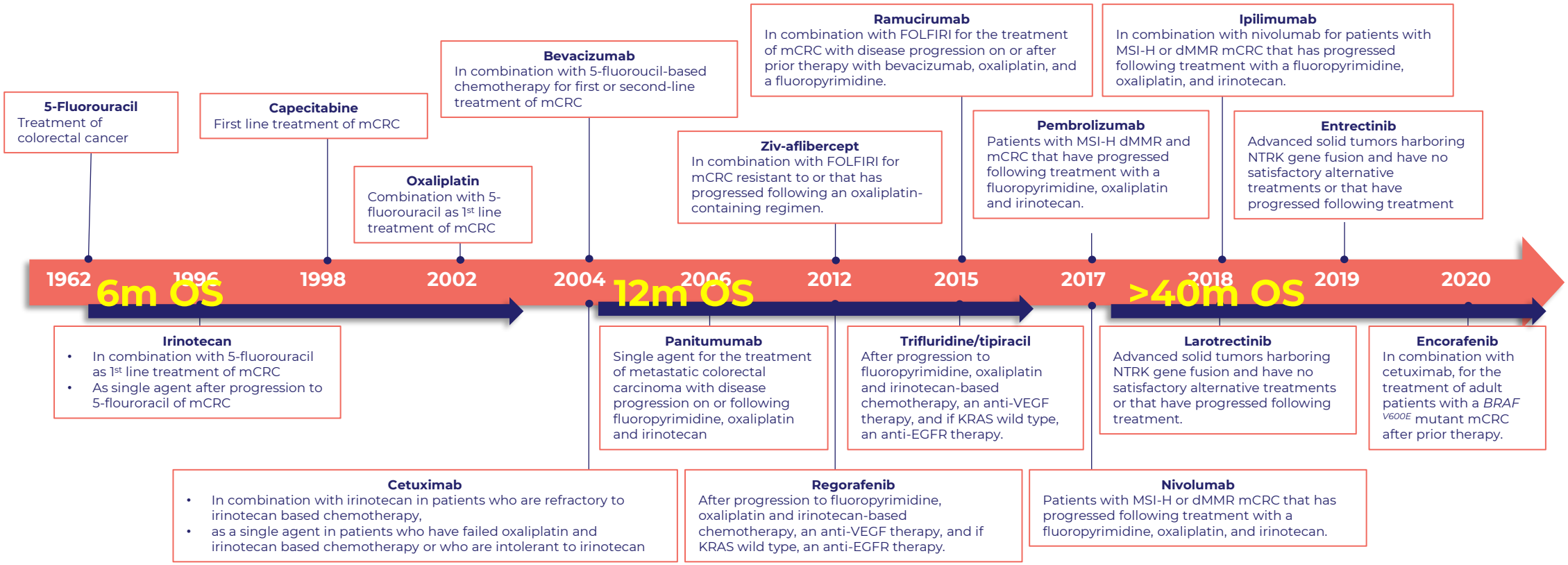
DECLARATION OF INTERESTS

Advisory Board Meetings or Speaker Fees:

Roche, Merck, MSD, BMS, Lilly, Amgen, Servier, Bayer, AstraZeneca, Incyte, Arcus Bio., Pierre Fabre, Taiho, Takeda, Sanofi, AiCME, Cor2Ed

Neue Arzneien haben die Prognose beim mKRK verbessert

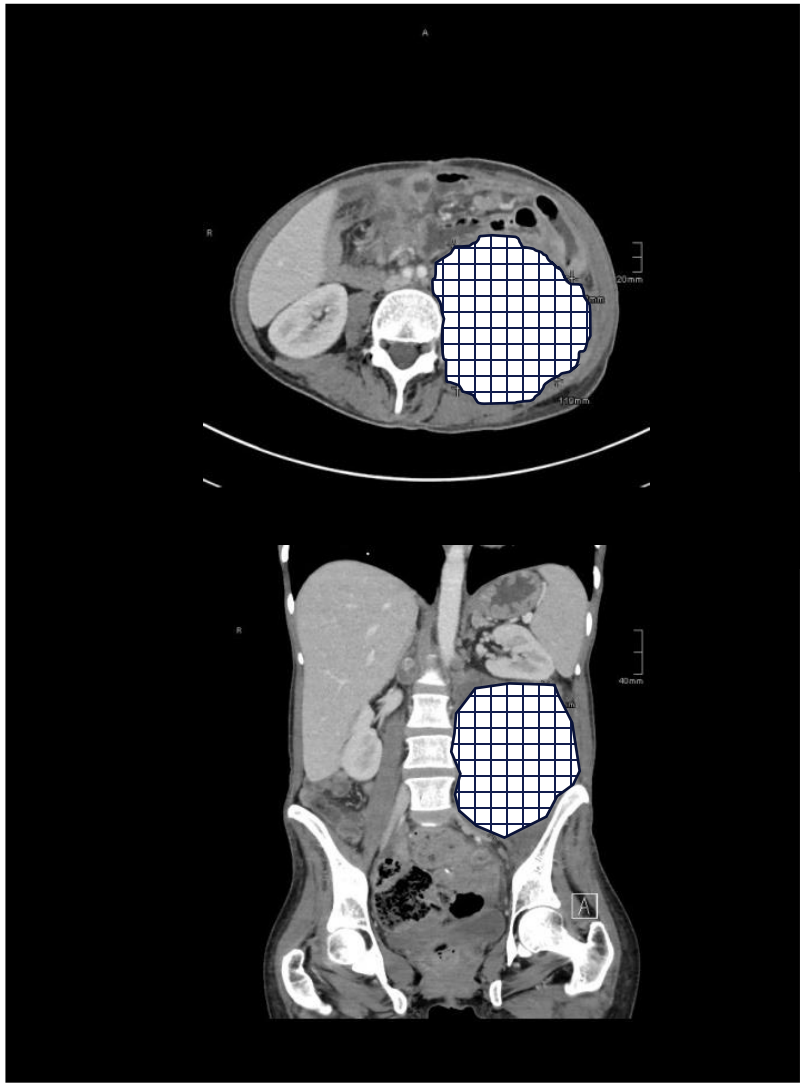


Adapted from Ciardiello et al[1]

mCRC, metastatic colorectal cancer; **MSI-H,** microsatellite instability high; **FOLFIRI**, leucovorin calcium (folinic acid), fluorouracil, and irinotecan hydrochloride; **OS,** overall survival. **Los medicamentos o combinaciones de medicamentos mencionados no están necesariamente registrados o reembolsados en España./Medicines or combinations of medicines mentioned are not necessarily registered or reimbursed in Spain.*

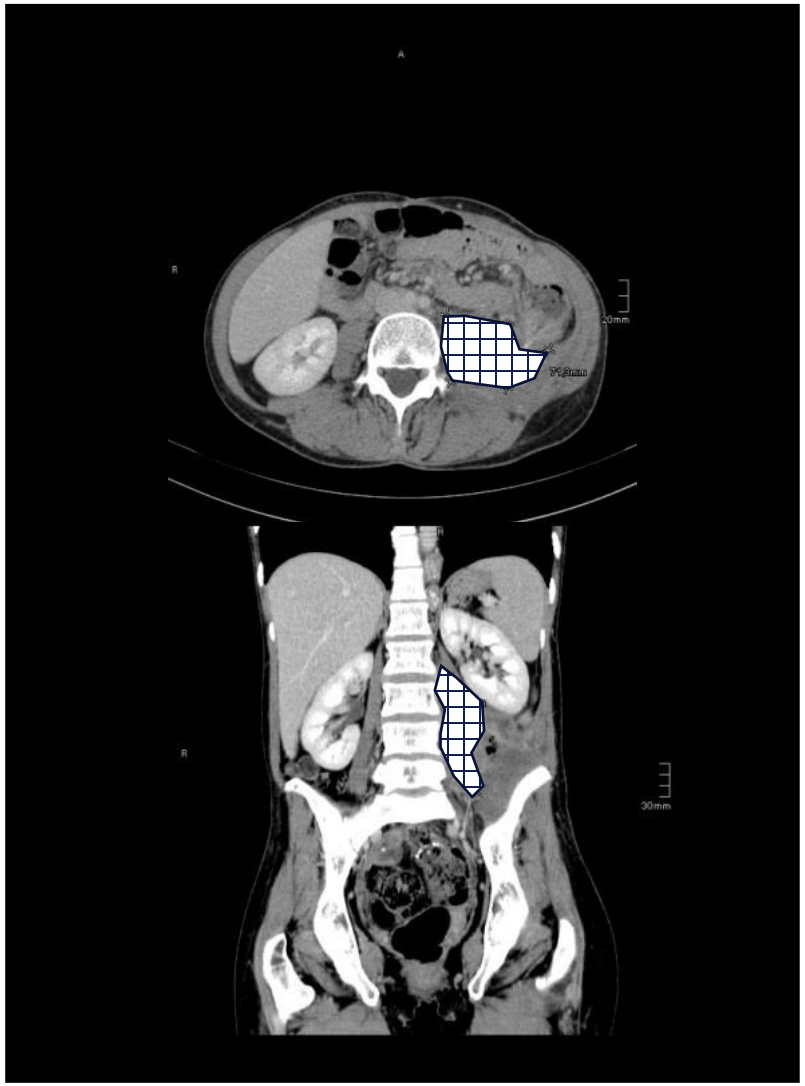
1. Ciardiello F, et al. *CA Cancer J Clin*. 2022;72(4):372-401

Case Study von 2015: Weibl. Pat. 42 Jahre, MMR-deficient



3 Mo

Impressive radiographic response: on the left showing the bulky metastasis before treatment and on the right after three months treatment with pembrolizumab



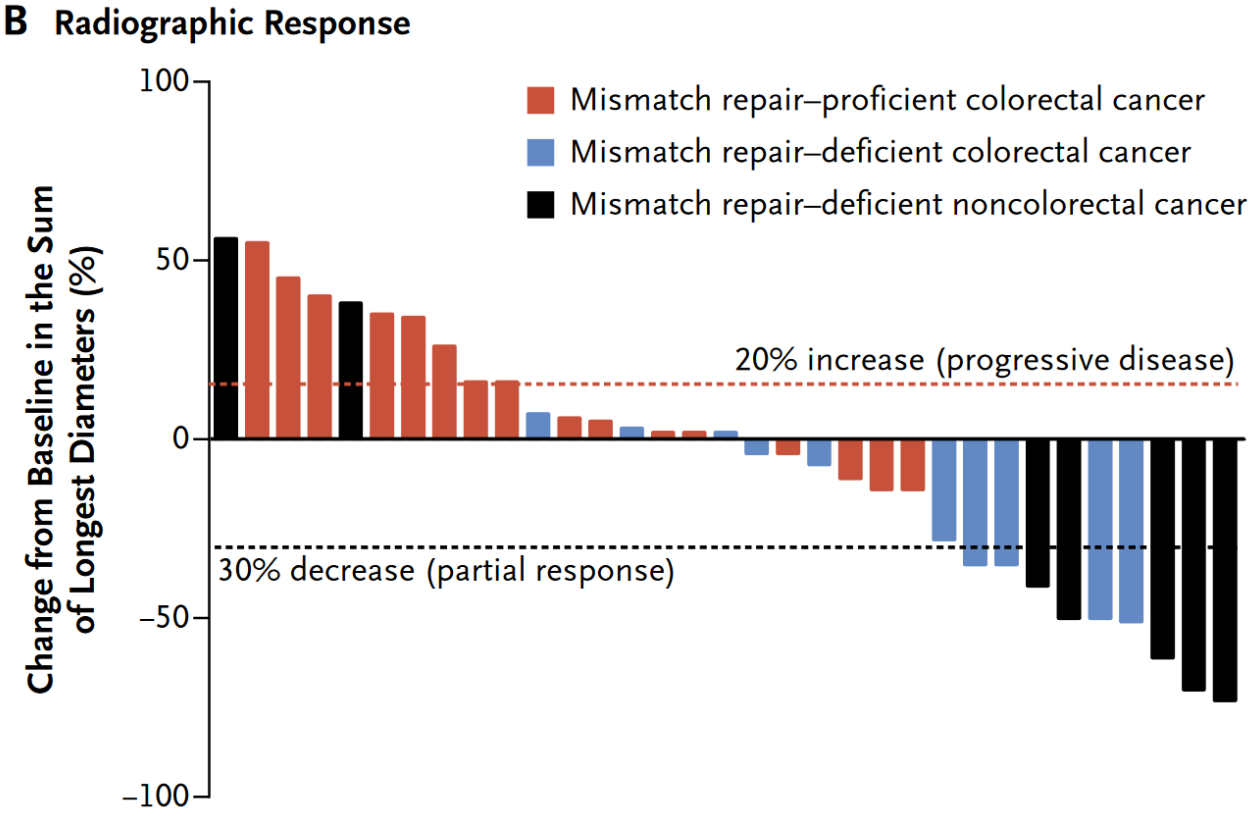
PD-1 BLOCKADE IN TUMORS WITH MISMATCH-REPAIR DEFICIENCY

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

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



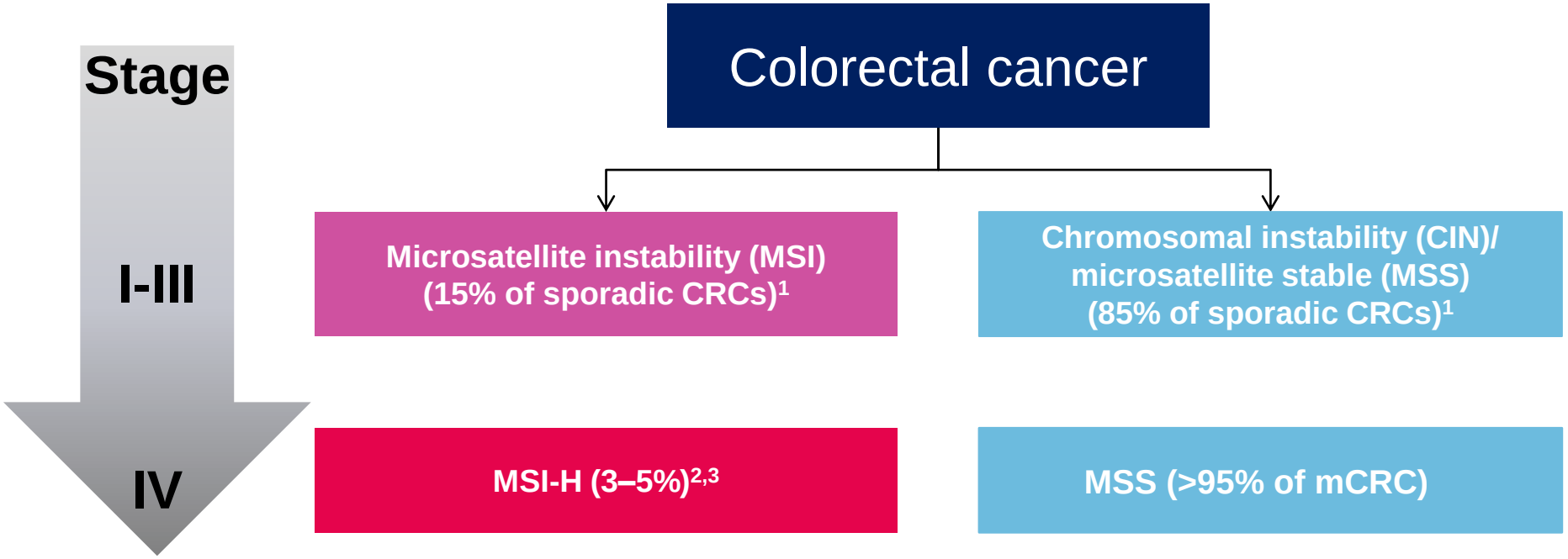
Dung T. Le et al.; N Engl J Med 2015;372:2509-2520

CHECKPOINT INHIBITORS IN MCRC

Targeting Immune Cells in mCRC

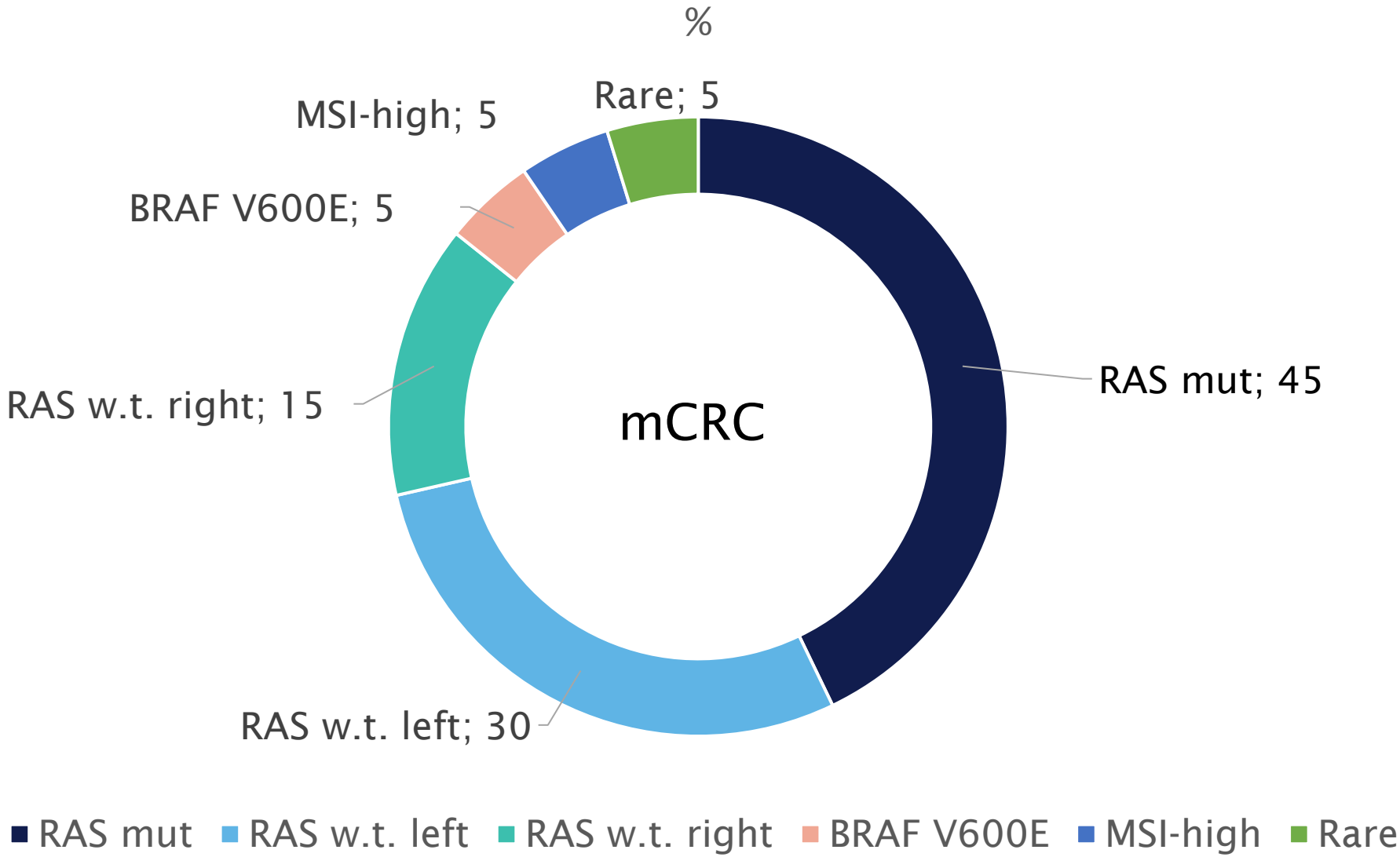
„Kid in the Candy-Shop“ phenomenon

THE TWO MAJOR GENETIC PATHWAYS FOR METASTATIC CRC TUMOUR DEVELOPMENT HAVE DISTINCT BIOLOGY WHICH AFFECTS PROGNOSIS

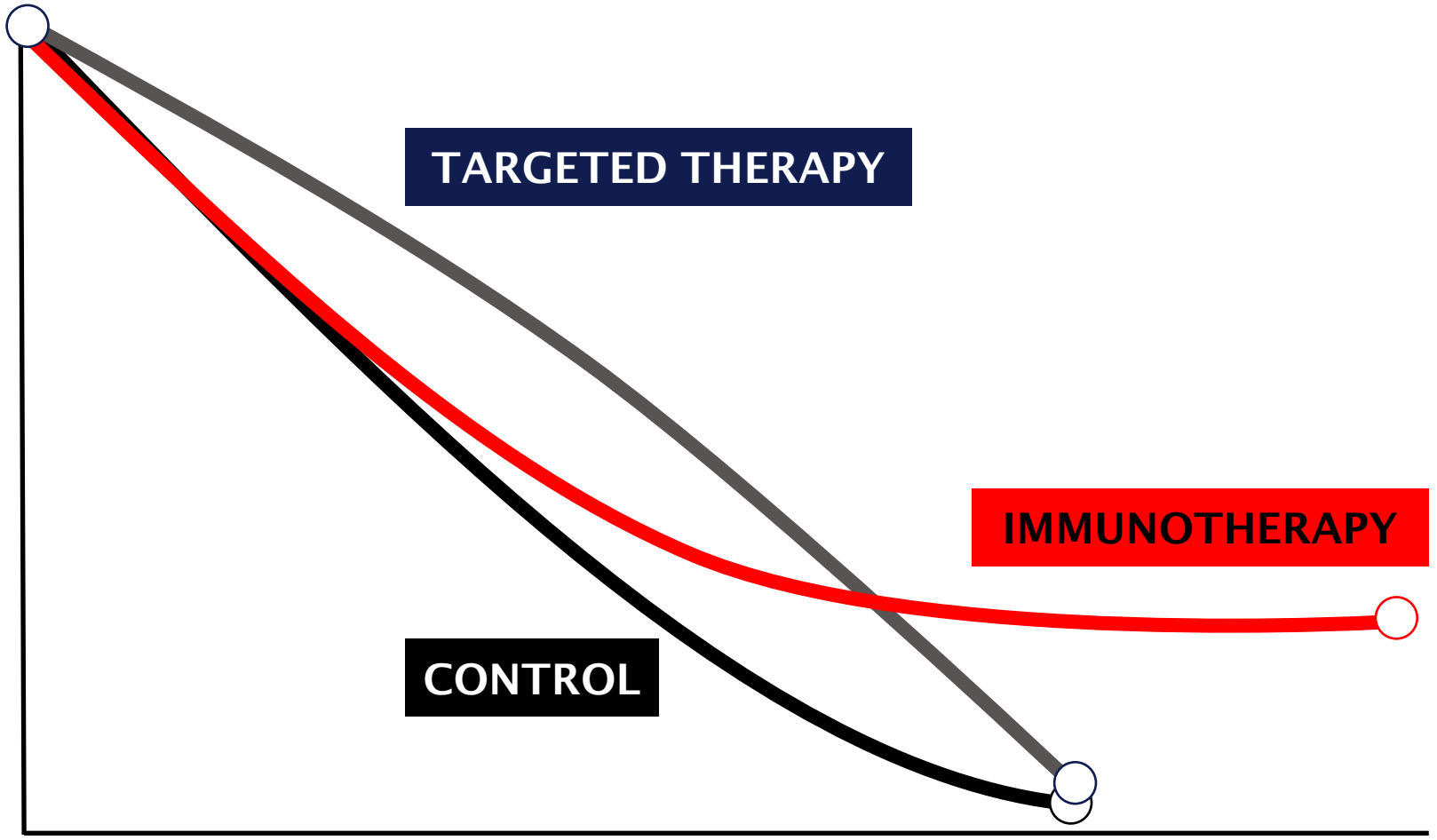


1. Grady and Markowitz. Dig Dis Sci 2015; 2. Koopman et al. Br J Cancer 20093. Fujiyoshi et al. Anticancer Res 2017

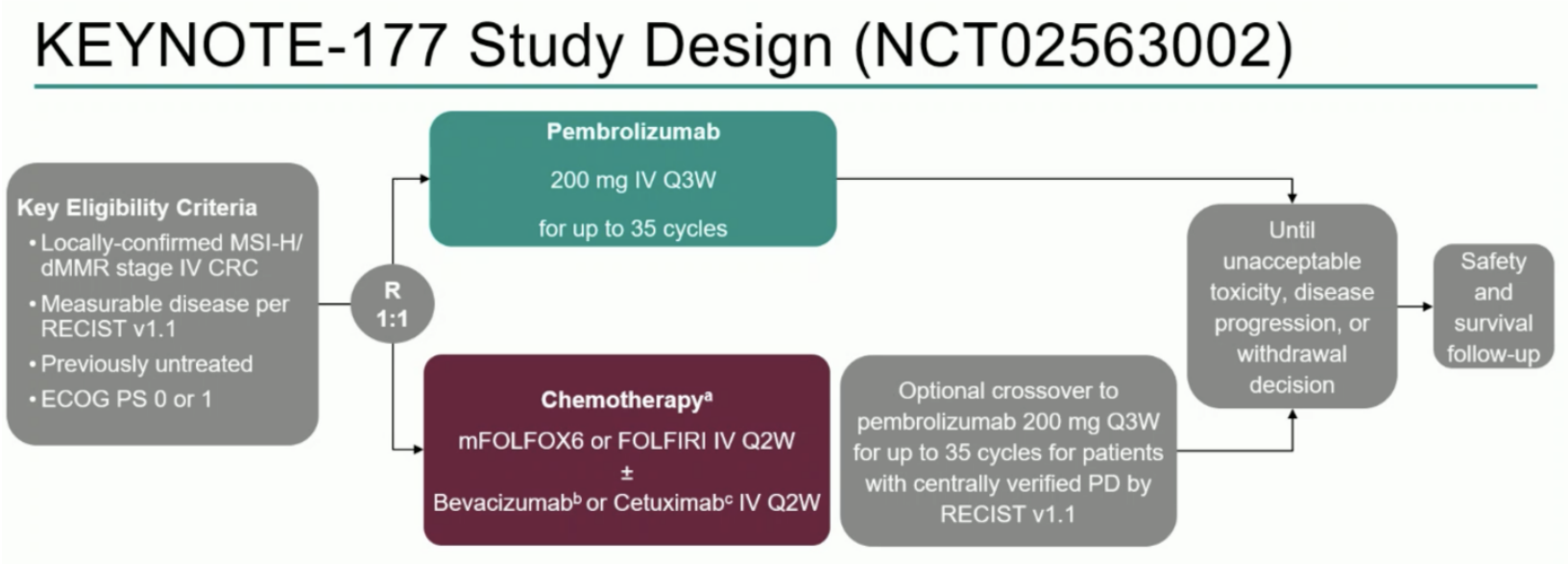
mCRC mol. subtypes with a therapeutic impact



Cancer immunotherapies may be able to improve survival



Pembrolizumab versus chemotherapy in microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) metastatic colorectal cancer (mCRC): 5-year follow-up of KEYNOTE-177

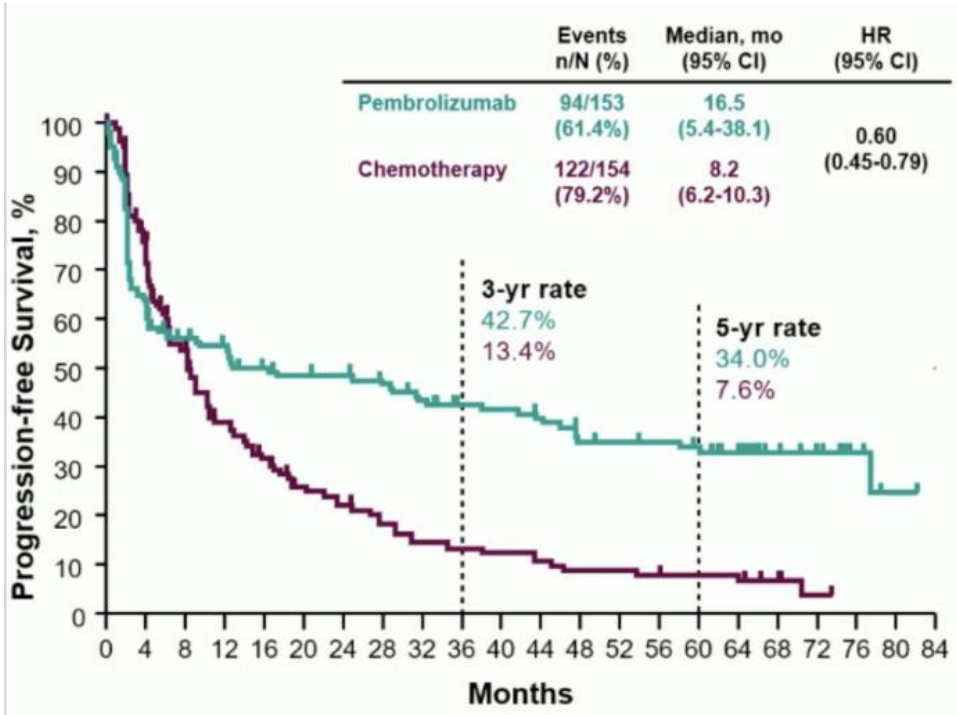


Rationale for this update:

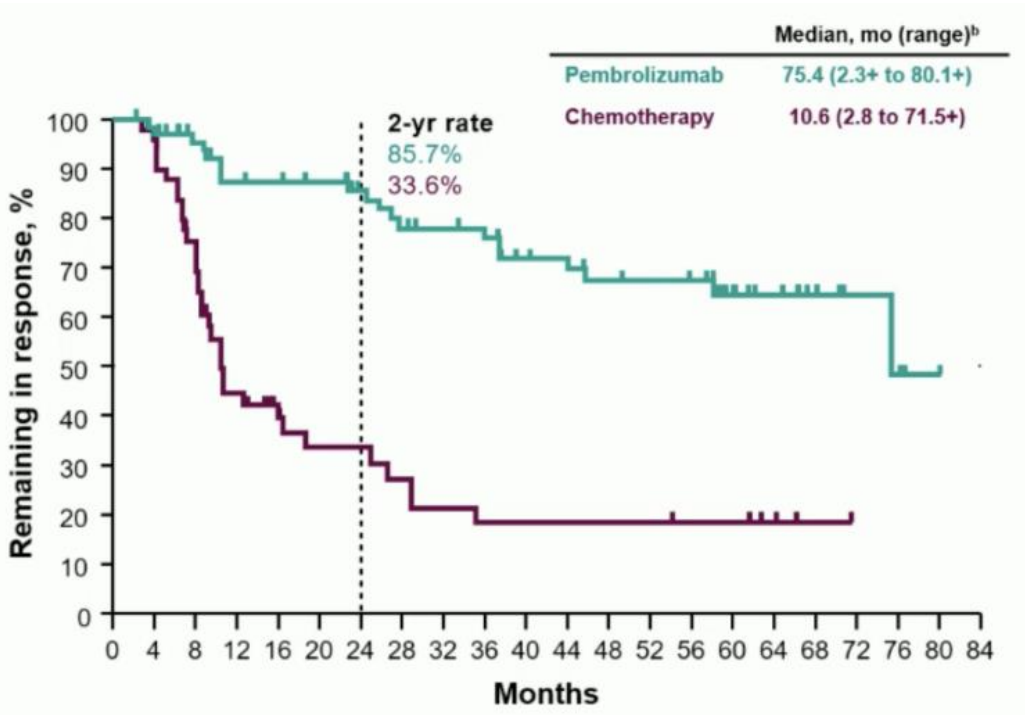
- This pivotal trial showed 1st line therapy with pembrolizumab led to a doubling in PFS (16.5 vs 8.2 months) compared to standard of care
- However, there was not a statistically significant OS benefit, likely due to a high crossover rate (62.3% - 37% on protocol and 25% off protocol)

Pembrolizumab versus chemotherapy in microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) metastatic colorectal cancer (mCRC): 5-year follow-up of the randomized phase III KEYNOTE-177 study.

Progression-Free Survival

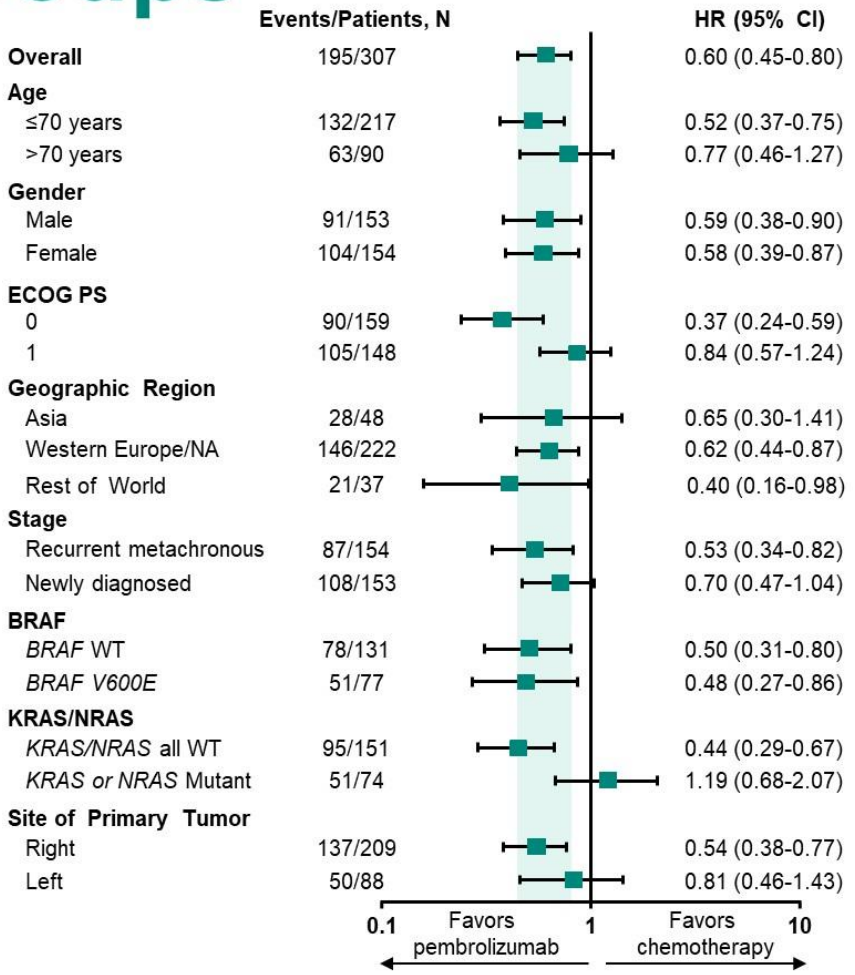


Duration of Response



Among those who respond, the duration of response can be very prolonged.

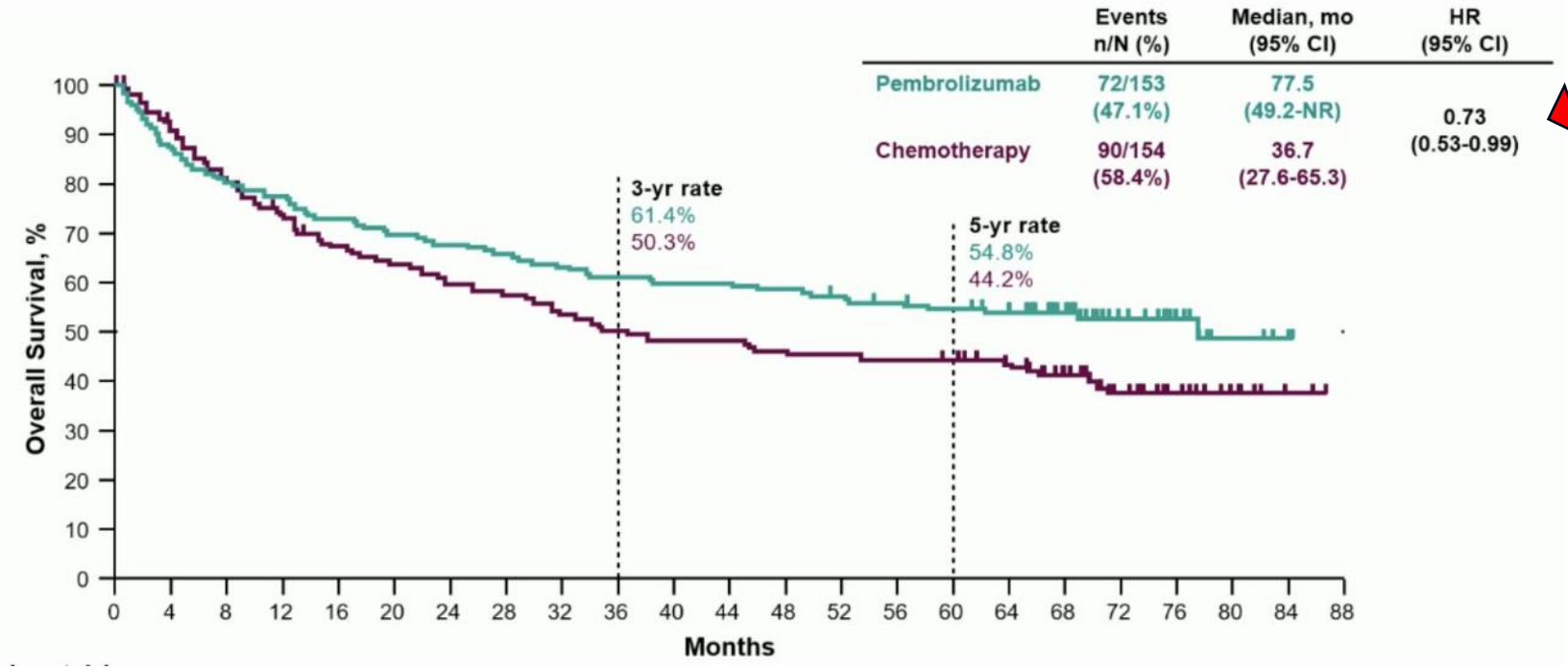
Progression-Free Survival in Key Subgroups



NA, North America; Data cut-off: 19Feb2020.

LBA32: Pembrolizumab versus chemotherapy in microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) metastatic colorectal cancer (mCRC): 5-year follow-up of the randomized phase III KEYNOTE-177 study.
Kai-Keen Shiu, et al.

Overall Survival Results after
73.3 months (6.1 years)



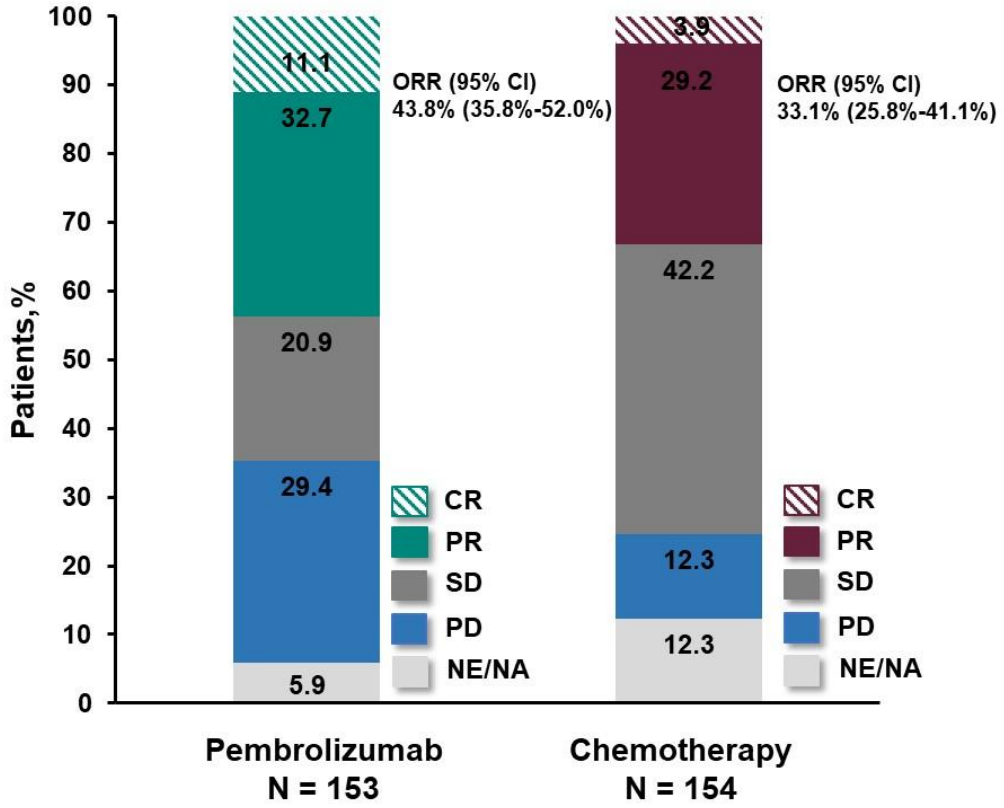
Cross Over and Subsequent Therapy

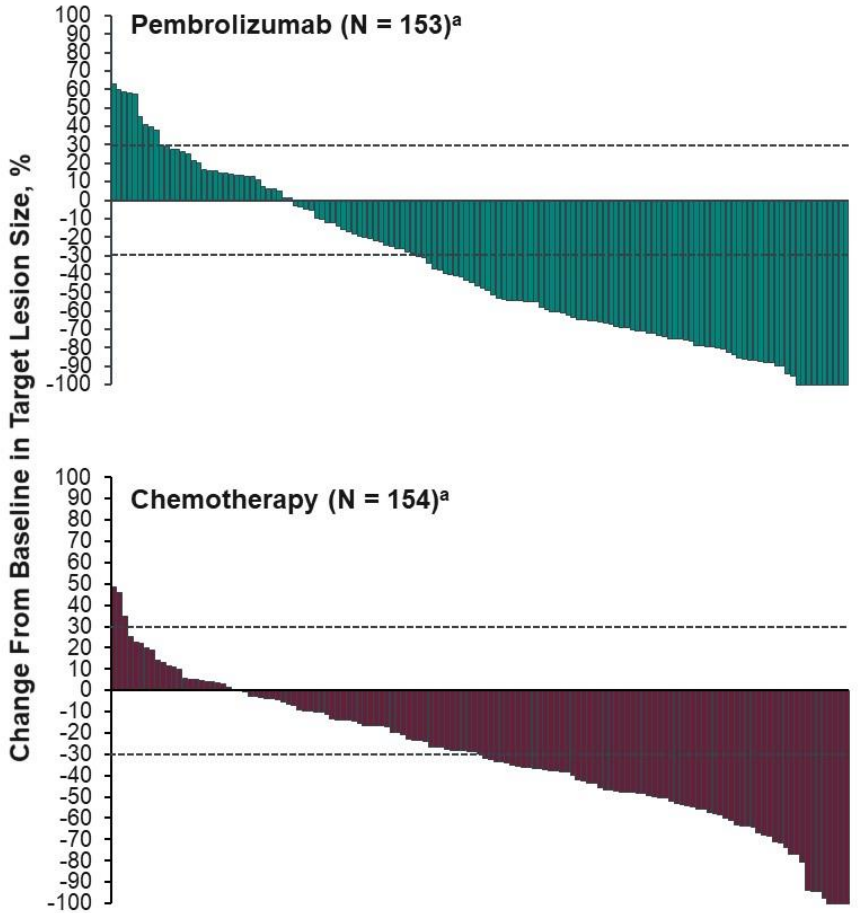
- 56 of 154 (36%) patients in the chemotherapy arm crossed over to receive pembrolizumab after confirmed disease progression
  - 37 additional patients received anti-PD-1/PD-L1 therapy outside of the study for an effective crossover rate of 60% in the ITT

	Pembrolizumab N = 153	Chemotherapy N = 154
Any anti-PD-1/PD-L1 therapy, n (%)	14 (9.2)	93 (60.4)
On protocol therapy - pembrolizumab[a]	8 (5.2)	56 (36.4)
Off protocol therapies	6 (3.9)	37 (24.0)
Any non-anti-PD-1/PD-L1 therapy, n (%)	38 (24.8)	28 (18.2
Chemotherapy	35 (22.9)	20 (13.0)
VEGF inhibitor	22 (14.4)	13 (8.4)
EGFR inhibitor	9 (5.9)	5 (3.2)
Nucleosoide analog/thymidine phosphorylase inhibitor	2 (1.3)	2 (1.3)
CTLA-4 inhibitor	0	5 (3.2)
ICOS agonist	1 (0.7)	1 (0.6)
LAG-3 inhibitor	1 (0.7)	0
TIM3 inhibitor	1 (0.7)	1 (0.6)
Vaccine/viral therapy	0	2 (1.3)

[a]Including 2nd course treatment for patients randomized to pembrolizumab arm. Data cut-off: 19Feb2021.

Summary of Best Anti-Tumor Response

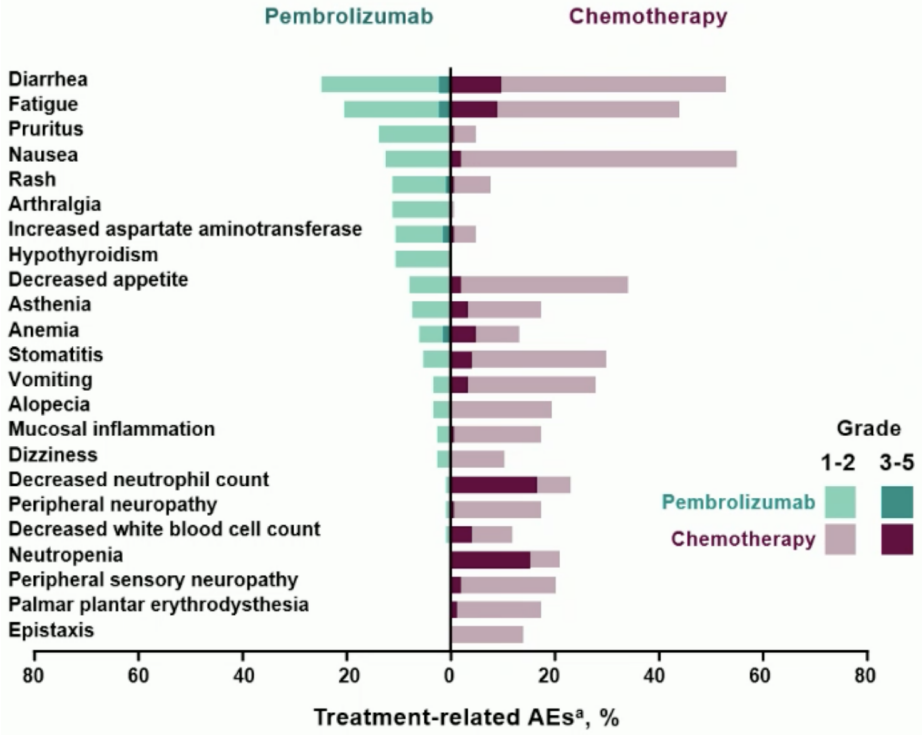




9 (6%) patients in the pembrolizumab arm and 19 (12%) in the chemotherapy arm were not evaluable (NE) or had no assessment (NA); [a]104 of 138 (75%) evaluable patients in the pembrolizumab arm and 111 of 135 (82%) evaluable patients in the chemotherapy arm had a reduction from baseline in target lesion size. Evaluable patients include those with ≥1 post-baseline target lesion imaging assessment in the intention-to-treat population; Data cut-off: 19Feb2020.

Pembrolizumab versus chemotherapy in microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) metastatic colorectal cancer (mCRC): 5-year follow-up of the randomized phase III KEYNOTE-177 study.

Adverse Events



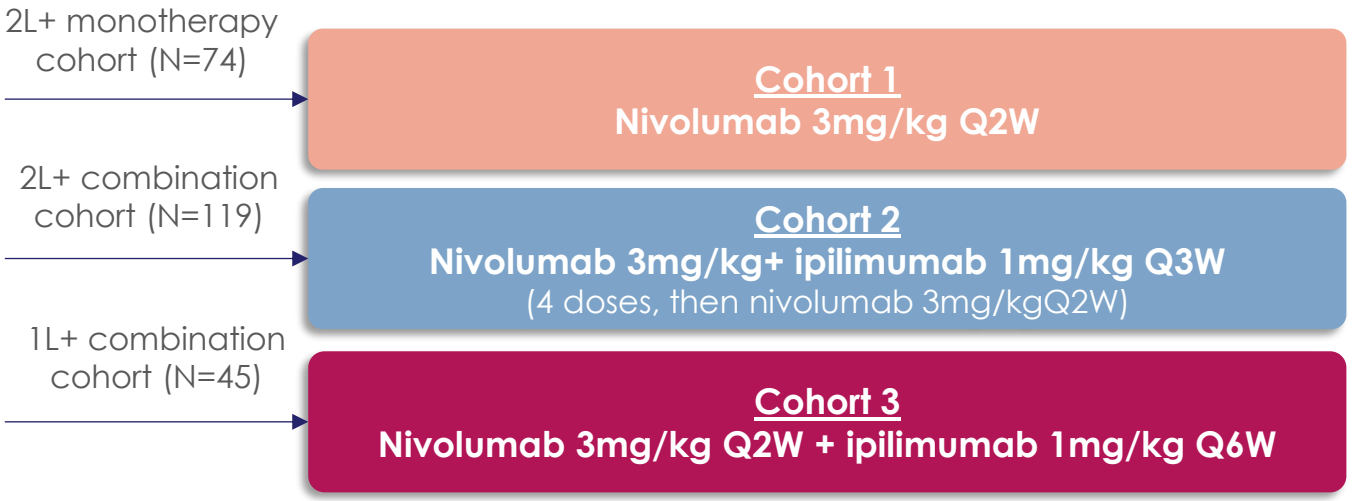
n (%)	Pembrolizumab N = 153	Chemotherapy N = 143
Any AE	**149 (97.4)**	**142 (99.3)**
Treatment-related AE	**122 (79.7)**	**141 (98.6)**
Grade 3-5	33 (21.6)	96 (67.1)
Led to treatment discontinuation	15 (9.8)	10 (7.0)
Led to death	0	1 (0.7)
Immune-mediated AEs and Infusion Reactions		
All	51 (33.3)	23 (16.1)
Grade 3-5	16 (10.5)	3 (2.1)
Led to death	0	0

Phase II CheckMate142 Trial: Nivo3+Ipi1 in First-Line MSI-High

Study Design

Key eligibility

- Histologically confirmed metastatic or recurrent CRC
- MSI-H/dMMR per local labratory

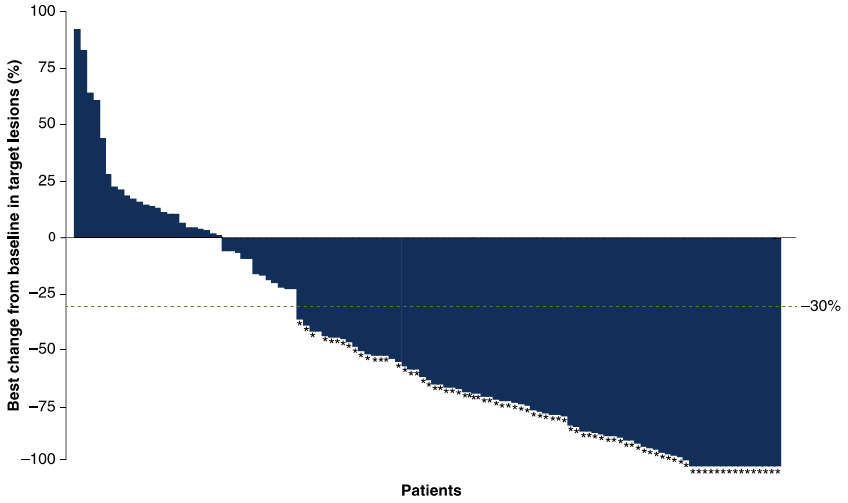


- **Primary endpoint:** ORR by RECIST v.1.1
- **Other key endpoints:** DCR, DOR, PFS, OS and safety

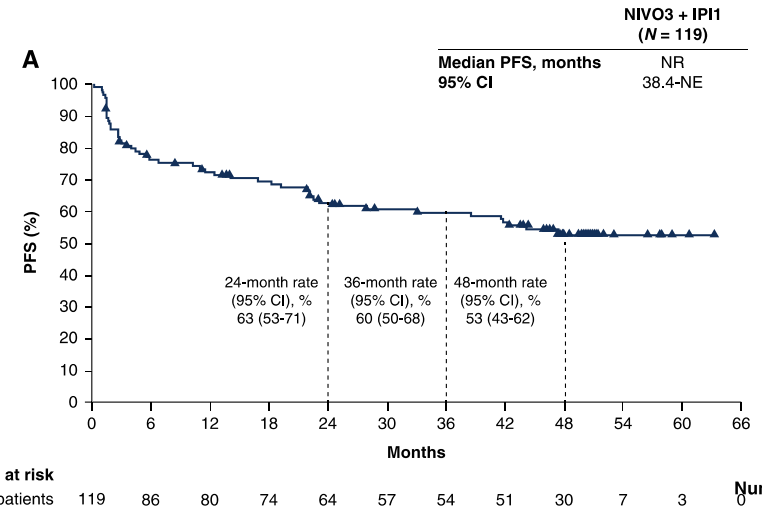
. Overman, M, et al. 2022 ASCO Annual Meeting I. Abstract 3510. *Nivolumab in combination with ipilimumab is indicated for the treatment of adult patients with metastatic colorectal cancer with mismatch repair system deficiency or high microsatellite instability after prior fluoropyrimidine-based combination chemotherapy.

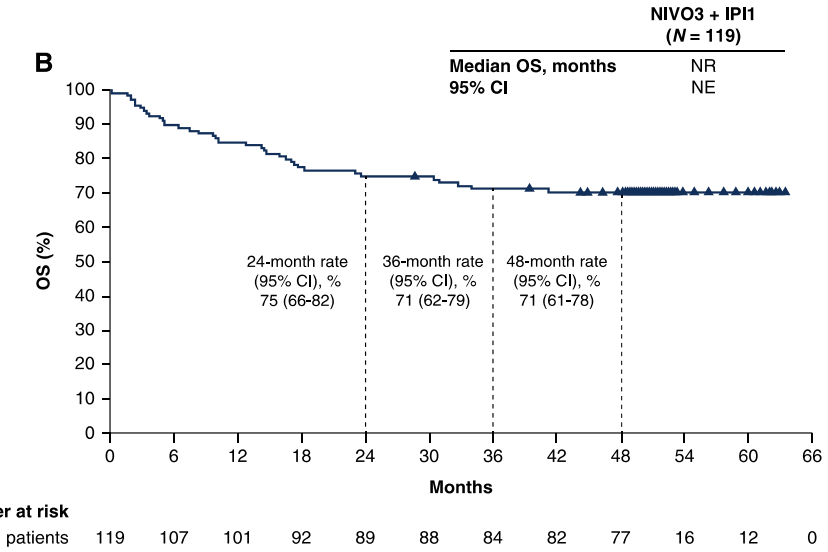
Phase II CheckMate142 Trial: Nivo3+Ipi1 in First-Line MSI-High

Median follow up: 50.9 months



ORR: 65%





mCRC, metastatic colorectal cancer; **PFS,** progression-free survival; **OS,** overall survival; **ORR,** objective response rate; **DOR,** duration of response; **DCR,** disease control rate; **RECIST,** response evaluation criteria in solid tumors; **ECOG PS,** Eastern Cooperative Oncology Group performance status; **CI,** confidence interval; **Q2W,** once every 2 weeks; **Q3W**, once every 3 weeks; **Q6W**, once every 6 weeks; **NIVO,** nivolumab; **IPI,** ipilimumab.

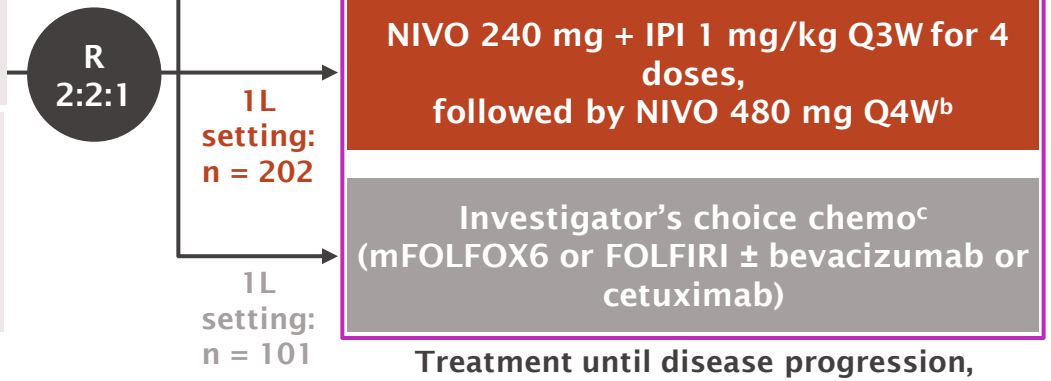
1. Andre T., et al. *Ann Oncol*. 2022 Oct;33(10):1052-1060. doi: 10.1016/j.annonc.2022.06.008

CheckMate 8HW study design

- CheckMate 8HW is a randomized, multicenter, open-label phase 3 study[a]

Key eligibility criteria:
- Histologically confirmed unresectable or metastatic CRC
- MSI-H/dMMR status by local testing
- ECOG PS 0 or 1

Stratification factors:
- Prior lines of treatment (0 vs 1 vs ≥ 2)
- Primary tumor location (right vs left)



Treatment until disease progression, unacceptable toxicity, withdrawal of consent (all arms), or a maximum treatment duration of 2 years (NIVO and NIVO + IPI arms only)

Dual primary endpoints in patients with centrally confirmed MSI-H/dMMR status[d]:
- PFS by BICR[e] (NIVO + IPI vs chemo in the 1L setting)
- PFS by BICR[e] (NIVO + IPI vs NIVO across all lines)

Other select endpoints:
- Safety
- OS; ORR by BICR[e]; PROs

- At data cutoff (October 12, 2023), the median follow-up[f] was 24.3 months

[a]ClinicalTrials.gov. NCT04008030. [b]Patients with ≥ 2 prior lines are randomized only to the NIVO or NIVO + IPI arms. [c]Patients receiving investigator's choice of chemotherapy are eligible to receive NIVO + IPI upon progression (crossover treatment). [d]Confirmed using either immunohistochemistry and/or polymerase chain reaction-based tests. [e]Evaluated using RECIST v1.1. [f]Time between randomization and last known date alive or death.

Baseline characteristics

Characteristic (1L all randomized patients)	Category	NIVO + IPI (n = 202)	Chemo (n = 101)
Age	Median (range), years	62 (21–86)	65 (26–87)
	< 65 years	117 (58)	46 (46)
Sex	Male	95 (47)	45 (45)
Region	US/Canada/Europe	133 (66)	71 (70)
	Asia	19 (9)	11 (11)
	Rest of world	50 (25)	19 (19)
ECOG PS	0	111 (55)	52 (51)
Disease stage at initial diagnosis[a]	Stage IV	85 (42)	49 (49)
Tumor sidedness	Right	138 (68)	68 (67)
Sites of metastases[b,c]	Liver	76 (38)	42 (42)
	Lung	44 (22)	25 (25)
	Peritoneum	84 (42)	43 (43)
Centrally confirmed MSI-H/dMMR status	Yes	171 (85)	84 (83)
	No	31 (15)	17 (17)
Tumor cell PD-L1[d,e]	< 1%	145 (72)	80 (79)
	≥ 1%	43 (21)	12 (12)
***BRAF, KRAS, NRAS* mutation status**[e,f]	*BRAF/KRAS/NRAS* all wild-type	47 (23)	23 (23)
	BRAF mutant	52 (26)	24 (24)
	KRAS or *NRAS* mutant	43 (21)	21 (21)
	Unknown	55 (27)	31 (31)
Clinical history of Lynch syndrome[e,g]	Yes	22 (11)	17 (17)
	No	135 (67)	49 (49)
	Reported as unknown	44 (22)	30 (30)
Prior surgery related to current cancer	Yes	174 (86)	84 (83)
	No	28 (14)	17 (17)

Data are shown as n (%) unless otherwise noted. [a]All patients had stage IV disease at study entry. [b]Per BICR. [c]Metastases not reported in 3 patients in the NIVO + IPI arm. [d]Tumor cell PD-L1 expression indeterminate, not evaluable, or not available: NIVO + IPI, n = 14; chemo, n = 9. [e]Percentages may not add up to 100% due to rounding. [f]*BRAF* and *KRAS/NRAS* mutant: NIVO + IPI, n = 5; chemo, n = 2. [g]Patients with Lynch syndrome not reported: NIVO + IPI, n = 1; chemo, n = 5.

Exposure and disposition

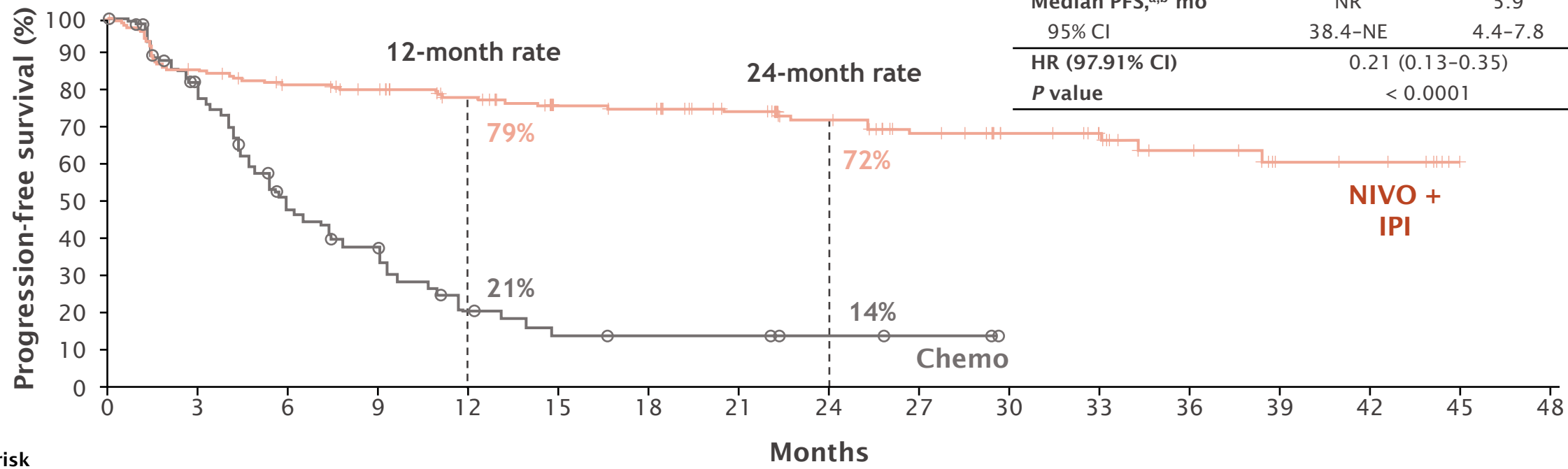
Disposition	NIVO + IPI	Chemo
All randomized patients, n	202	101
All treated patients, n	200	88
Ongoing treatment,[a] n (%)	42 (21)	6 (7)
Completed treatment,[a] n (%)	62 (31)	0
Discontinued treatment,[a] n (%)	96 (48)	82 (93)
Reasons for treatment discontinuation,[a] n (%)		
Disease progression	38 (19)	61 (69)
AE related to treatment	36 (18)	4 (5)
AE not related to treatment	12 (6)	5 (6)
Maximum clinical benefit	0	8 (9)
Other[b]	10 (5)	4 (5)

- Median duration of treatment was 13.5 months in the NIVO + IPI arm and 4.0 months in the chemo arm
  - In the NIVO + IPI arm, median duration of treatment for each component was 13.5 months for NIVO and 2.1 months for IPI
- Among patients treated with chemo, 66 patients (75%) received a biologic agent (bevacizumab, n = 56; cetuximab, n = 10)

In the chemo arm, 45 patients received crossover treatment upon disease progression by BICR. [a]Percentages shown are based on all treated patients. [b]Other reasons for discontinuation included death (n = 2),
withdrawal of consent (n = 1), pregnancy (n = 1), patient no longer met study criteria (n = 1), and other reasons (n = 9).

Progression-free survival

1L centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 171)	Chemo (n = 84)
Median PFS,[a,b] mo	NR	5.9
95% CI	38.4–NE	4.4–7.8
HR (97.91% CI)	0.21 (0.13–0.35)	
P value	< 0.0001	



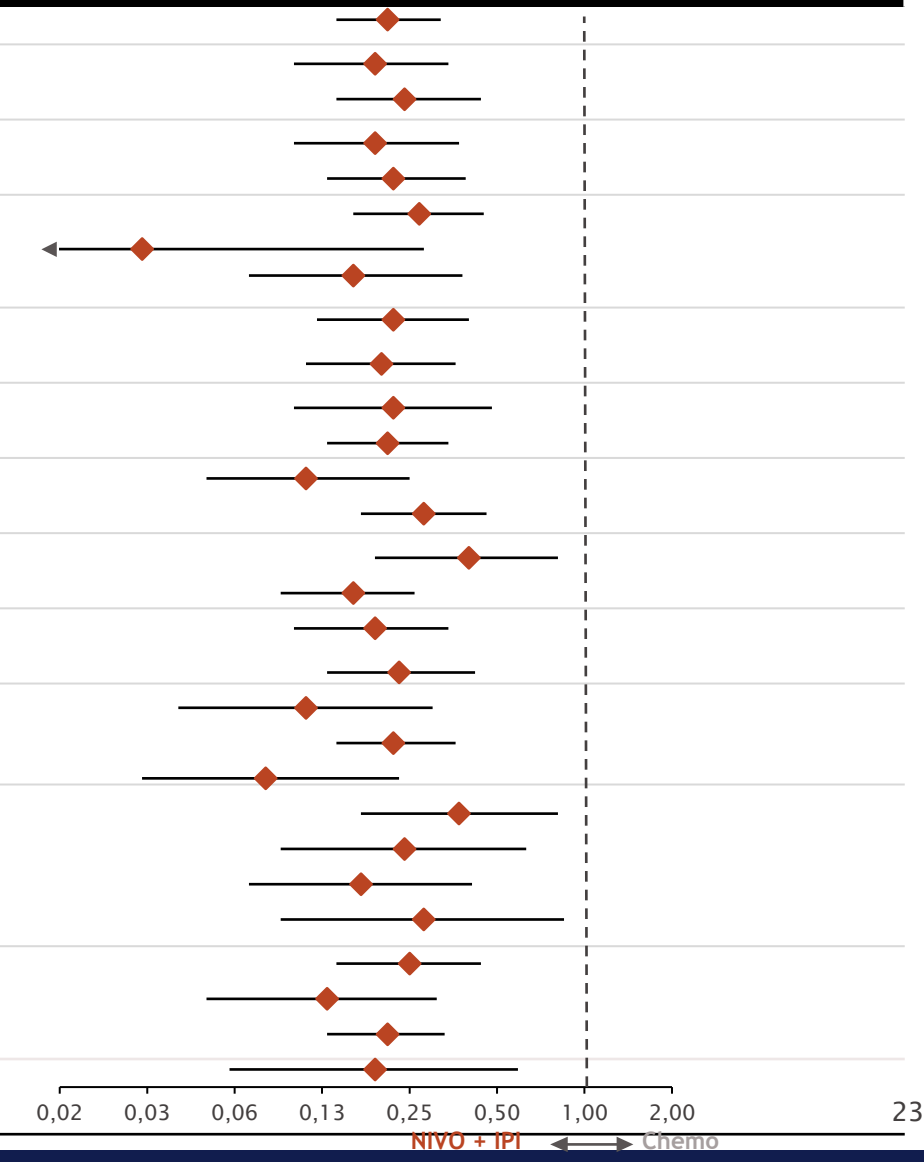
No. at risk																
NIVO + IPI	171	144	132	122	108	95	92	77	64	53	42	37	22	10	9	1	0
Chemo	84	53	29	20	10	6	5	5	3	2	0	0	0	0	0	0	0

- PFS benefit with NIVO + IPI vs chemo was robust and consistent across the sensitivity analyses, including PFS by BICR in 1L all randomized patients (HR, 0.32; 95% CI, 0.23–0.46)

[a]Per BICR. [b]Median follow-up, 24.3 months.

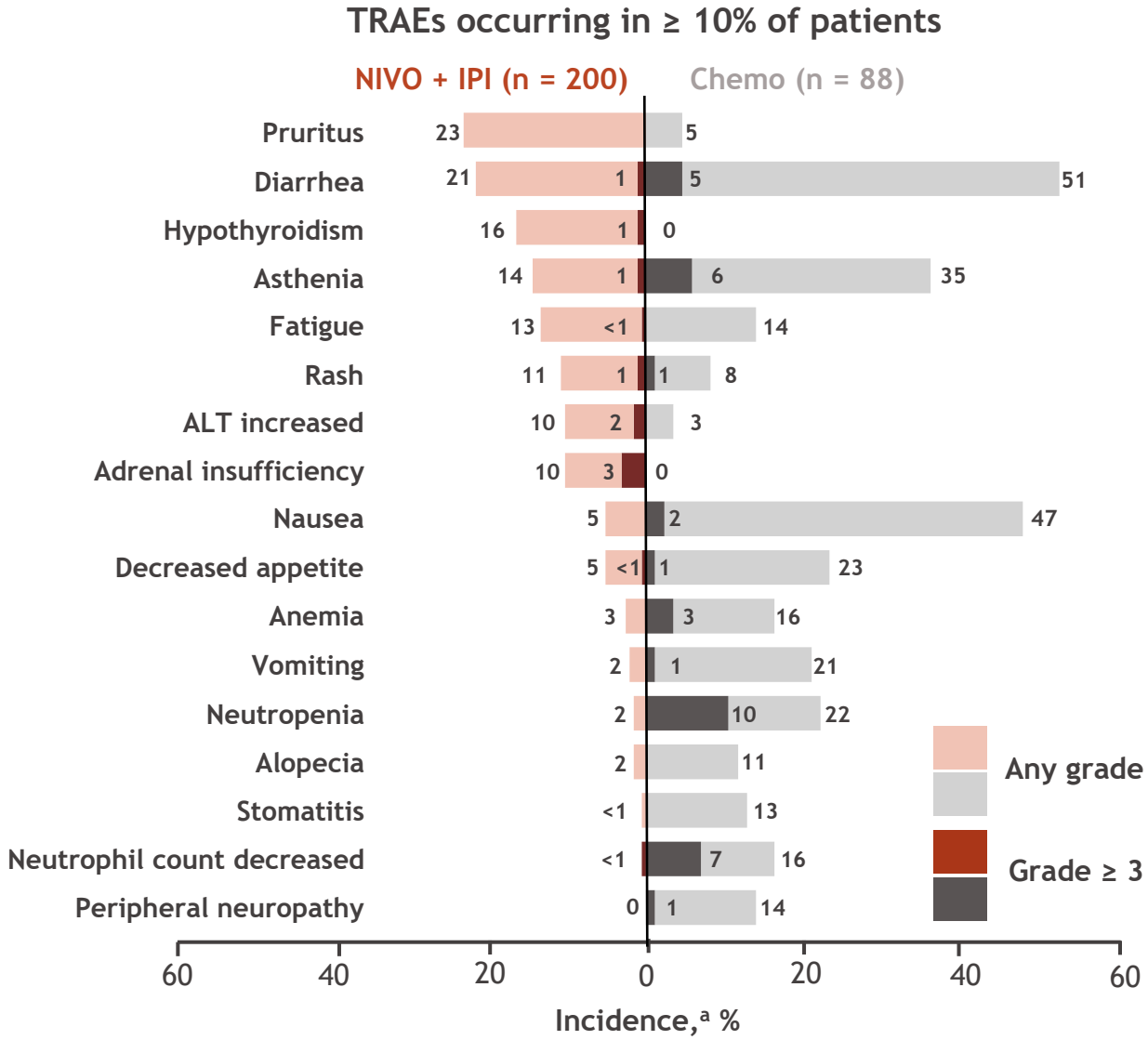
Progression-free survival subgroup analysis

Category (1L centrally confirmed MSI-H/dMMR)	Subgroup	Median PFS,[a] mo		Unstratified HR
		NIVO + IPI	Chemo	
Overall (N = 255)		NR	5.9	0.21
Age, years	< 65 (n = 138)	NR	5.7	0.19
	≥ 65 (n = 117)	NR	5.9	0.24
Sex	Male (n = 117)	NR	5.9	0.19
	Female (n = 138)	NR	6.2	0.22
Region	US/Canada/Europe (n = 167)	NR	5.7	0.27
	Asia (n = 28)	NR	7.4	0.03
	Rest of world (n = 60)	NR	6.2	0.16
ECOG PS	0 (n = 142)	NR	9.0	0.22
	≥ 1 (n = 113)	NR	4.2	0.20
Tumor sidedness	Left (n = 70)	NR	4.4	0.22
	Right (n = 185)	NR	7.1	0.21
Liver metastases[a]	Yes (n = 87)	NR	5.9	0.11
	No (n = 166)	NR	5.4	0.28
Lung metastases[a]	Yes (n = 53)	13.2	4.9	0.40
	No (n = 200)	NR	6.2	0.16
Peritoneal metastases[a]	Yes (n = 115)	NR	4.4	0.19
	No (n = 138)	NR	7.4	0.23
Tumor cell PD-L1 expression	≥ 1% (n = 55)	NR	3.4	0.11
	< 1% (n = 191)	NR	6.5	0.22
BRAF/*KRAS*/*NRAS* mutation status	*BRAF*/*KRAS*/*NRAS* all wild type (n = 58)	34.3	5.4	0.08
	BRAF mutant (n = 72)	NR	9.2	0.37
	KRAS or *NRAS* mutant (n = 45)	NR	5.7	0.24
	Unknown (n = 74)	NR	4.9	0.17
Lynch syndrome	Yes (n = 31)	NR	7.4	0.28
	No (n = 152)	NR	6.2	0.25
	Unknown (n = 66)	NR	5.5	0.13
Prior surgery related to current cancer	Yes (n = 222)	NR	7.1	0.21
	No (n = 33)	NR	3.0	0.19



[a]Per BICR.

Treatment-related adverse events



1L all treated patients	NIVO + IPI (n = 200)		Chemo (n = 88)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
TRAEs,[a] n (%)				
Any TRAEs	160 (80)	46 (23)	83 (94)	42 (48)
Serious TRAEs	38 (19)	32 (16)	17 (19)	14 (16)
TRAEs leading to discontinuation	33 (17)	23 (12)	28 (32)	9 (10)
Treatment-related deaths, n (%)	2 (1)[b]		0 (0)[c]	
IMAEs,[d] n (%)				
Non-endocrine events				
Diarrhea/colitis	13 (7)	9 (5)	1 (1)	0
Hepatitis	11 (6)	6 (3)	0	0
Rash	11 (6)	3 (2)	0	0
Pneumonitis	4 (2)	3 (2)	0	0
Endocrine events				
Hypothyroidism/thyroiditis	34 (17)	3 (2)	1 (1)	0
Adrenal insufficiency	21 (11)	7 (4)	0	0
Hyperthyroidism	18 (9)	0	1 (1)	0
Hypophysitis	10 (5)	5 (3)	0	0

[a]Includes events reported between first dose and 30 days after last dose of study therapy. [b]Includes 1 event each of myocarditis and pneumonitis. [c]One death (acute myocarditis) was related to crossover treatment. [d]Includes events reported within 100 days of last dose of study therapy reported in ≥ 2% of patients.

Offene Fragen MSI-high / dMMR

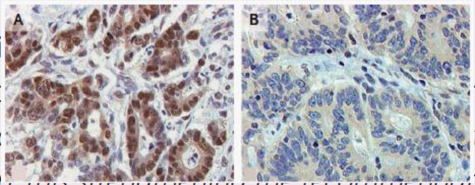
- Was ist die beste Kombination (brauchen wir eine Kombi?)
- Wie lange sollen wir therapieren?
- OMD: CPI und Chirurgie (Chirurgie noch notwendig?)
  - No surgery?
    - Wie lange sollte die systemische CPI Therapie erfolgen?
    - Wenn das eine Option ist, wie sieht die Nachsorge aus?

ESMO recommendations on MSI testing for immunotherapy in cancer

Table 1. Summary table of recommendations for MSI testing in the framework of immunotherapy and comments from the ESMO TR and PM WG consensus panel

Recommendation A: immunohistochemistry

The first test of choice is IHC, using antibodies recognising the four MMR proteins: MLH1, MSH2, MSH6 and PMS2.

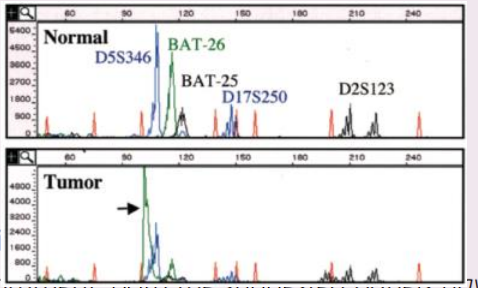


Coeffici

Main co… …ers; for a correct IHC interpretation, the consensus panel highlights that mutations in MLH1 are associated with IHC l… …tations in MSH2 are associated with IHC loss of both MSH2 and MSH6. There exist isolated losses of PMS2, MSH2 or MSH6, this strengthening the recommendation to use all four antibodies.

Recommendation B: polymerase chain reaction

In case of doubt of IHC, confirmatory molecular analysis is mandatory. The first-line of molecular analysis is represented by PCR. It can be carried out using two possible panels: (i) a panel with two mononucleotide (BAT-25 and BAT-26) and three dinucleotide (D5S346, D2S123 and D17S250) repeats and (ii) a panel with five poly-A mononucleotide repeats (BAT-25, BAT-26, NR-21, NR-24, NR-27). The five poly-A panel is the recommended panel given its higher sensitivity and specificity.



Coeffici

Main comment: both the suggested panels have been and are being used to assess MSI in clinical trials. Molecular tests guarantee the highest values of specificity and sensitivity in MSI testing.

Recommendation C: next-generation sequencing

NGS represents another type of molecular tests to assess MSI. Its main advantages are represented by the possibilities of coupling MSI analysis with the determination of tumour mutational burden (TMB).

Coefficient of agreement: very strong (9.0)

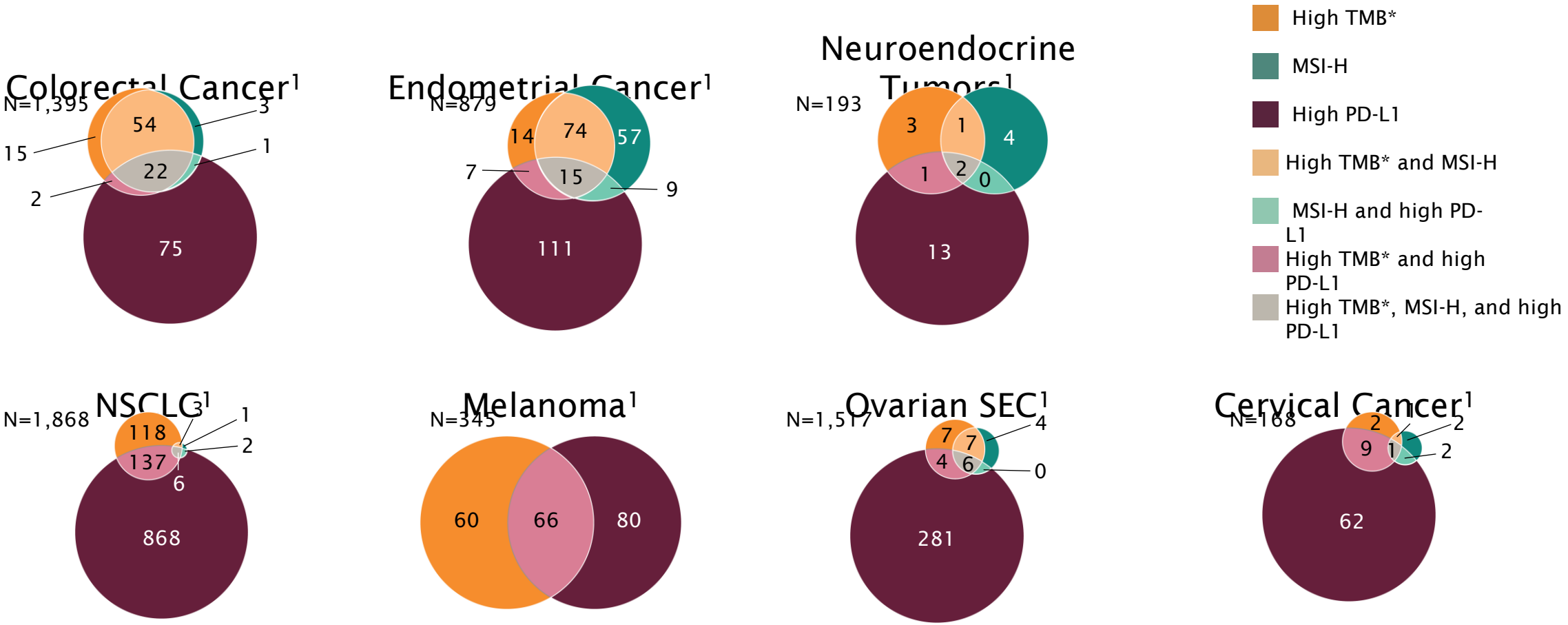
Main comment: NGS should be carried out only in selected centres devoted to these techniques.

Coefficient of agreement ranges from 0 = totally disagree, to 10 = totally agree.

IHC, immunohistochemistry; PCR, polymerase-chain reaction; NGS, next-generation sequencing.

Annals of Oncology 30: 1232–1243, 2

The Overlap of TMB With PD-L1 and MSI-H Depends on Tumor Type



*TMB cutoff was 17 mut/Mb.

MSI-H=microsatellite high; NSCLC=non-small cell lung cancer; PD-L1=programmed death ligand 1; SEC=synchronous endometrial cancer; TMB=tumor mutational burden.

1. Vanderwalde A, et al. *Cancer Med*. 2018;7:746-756.

Figures reproduced with permission from Vanderwalde A, et al. *Cancer Med*. 2018;7:746-756.

Other Ongoing Trials

MK C08[1]

Key Eligibility

- Stage IV mCRC
- MSI-H/dMMR
- Measurable disease per RECIST v1.1 by BIRC
- ECOG PS 0 or 1

Cohort A
Chemotherapy-refractory

R

1:1
N=120

- Pembrolizumab 400mg IV Q6W
- Coformulated Quavonlimab/Pembrolizumab 25 mg/400 mg IV Q6W

Cohort B
Previously untreated for metastatic disease

R

1:1:1:1:1
N=200

- Pembrolizumab 400mg IV Q6W
- Coformulated Quavonlimab/Pembrolizumab 25 mg/400 mg IV Q6W
- Coformulated Favezelimab/Pembrolizumab 800 mg/200 mg IV Q3W
- Coformulated Vibostolimab/Pembrolizumab 200 mg/200 mg IV Q3W
- MK-4830 800 mg + Prembrolizumab 200 mg IV Q3W

NRG GI004/SWOG 1610[2]

dMMR/MSI-H mCRC without prior systemic treatment for metastatic disease
(N = 211)

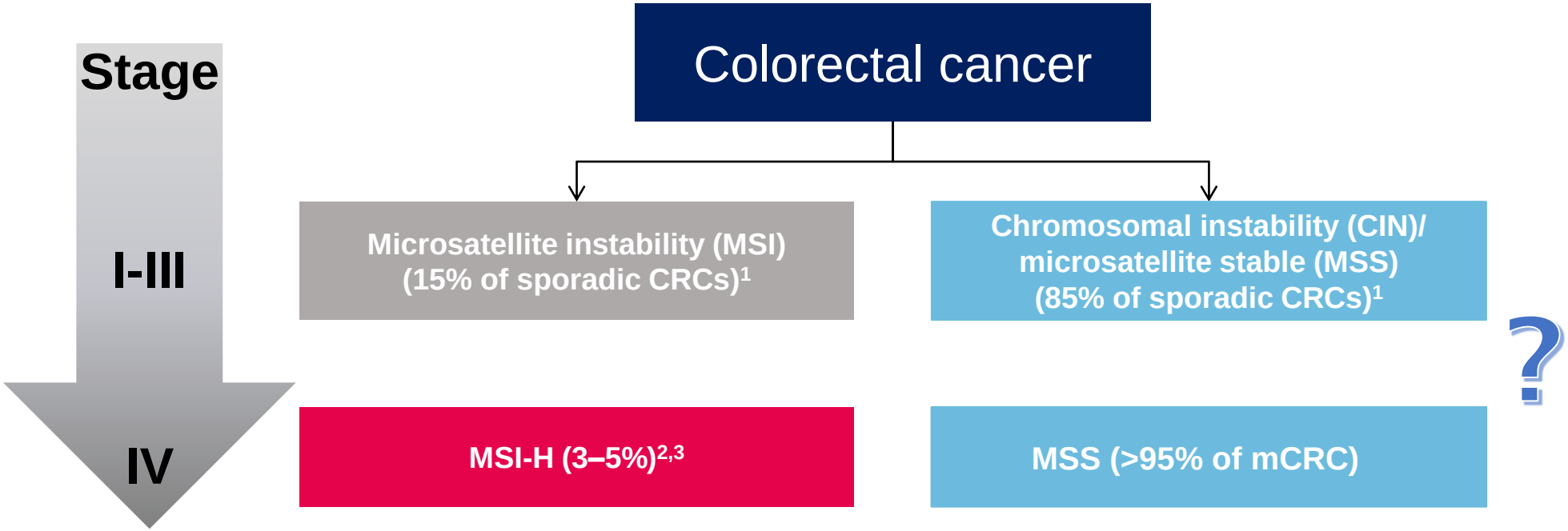
R

- Atezolizumab (Arm 2: Single Agent)
- mFOLFOX6/Bevacizumab (Arm 1: Control)
- mFOLFOX6/Bevacizumab Atezolizumab (Arm 3: Combination)

mCRC, metastatic colorectal cancer; **MSI-H**, microsatellite instability high; **dMMR**, mismatch repair deficiency; **BICR**, blinded independent review committee; **ECOG PS**, Eastern Cooperative Oncology Group Performance Score; **FOLFOX**,folinic acid, fluorouracil, oxaliplatin

1. ClinicalTrials.gov: NCT04895722. 2. ClinicalTrials.gov: NCT02997228

The two major genetic pathways for metastatic CRC tumour development have distinct biology which affects prognosis



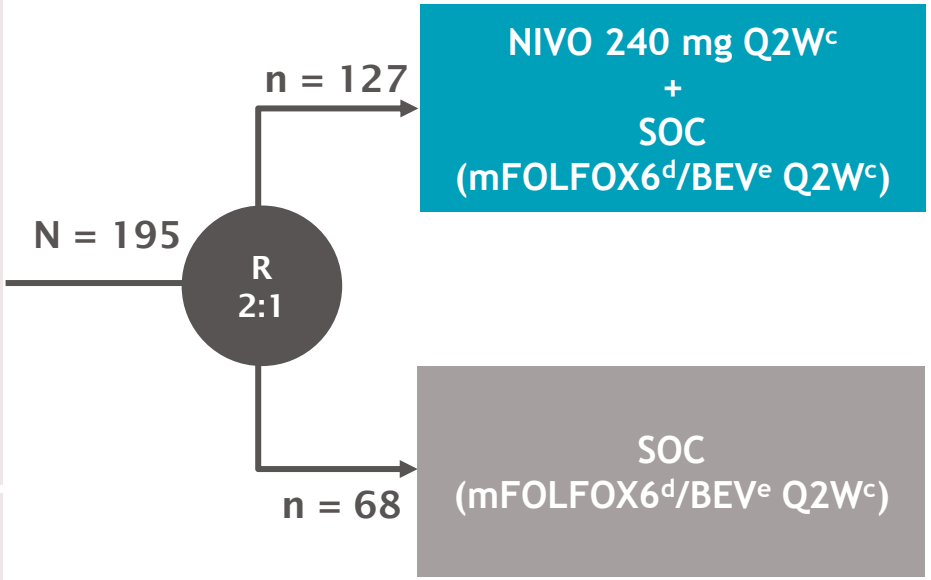
1. Grady and Markowitz. Dig Dis Sci 2015; 2. Koopman et al. Br J Cancer 20093. Fujiyoshi et al. Anticancer Res 2017

CheckMate 9X8 study design: *All-Comers !!!*

- CheckMate 9X8 is a randomized, open-label phase 2/3 study[a]

Key eligibility criteria
- Histologically confirmed mCRC not amenable to curative resection
- No prior chemotherapy for mCRC
- No prior treatment with checkpoint inhibitors[b]
- ECOG PS 0–1

Stratification factors
- Tumor sidedness (left, right, transverse, or unknown)
- Prior oxaliplatin-based chemotherapy (yes or no)



Primary endpoints
- PFS per BICR (RECIST v1.1)

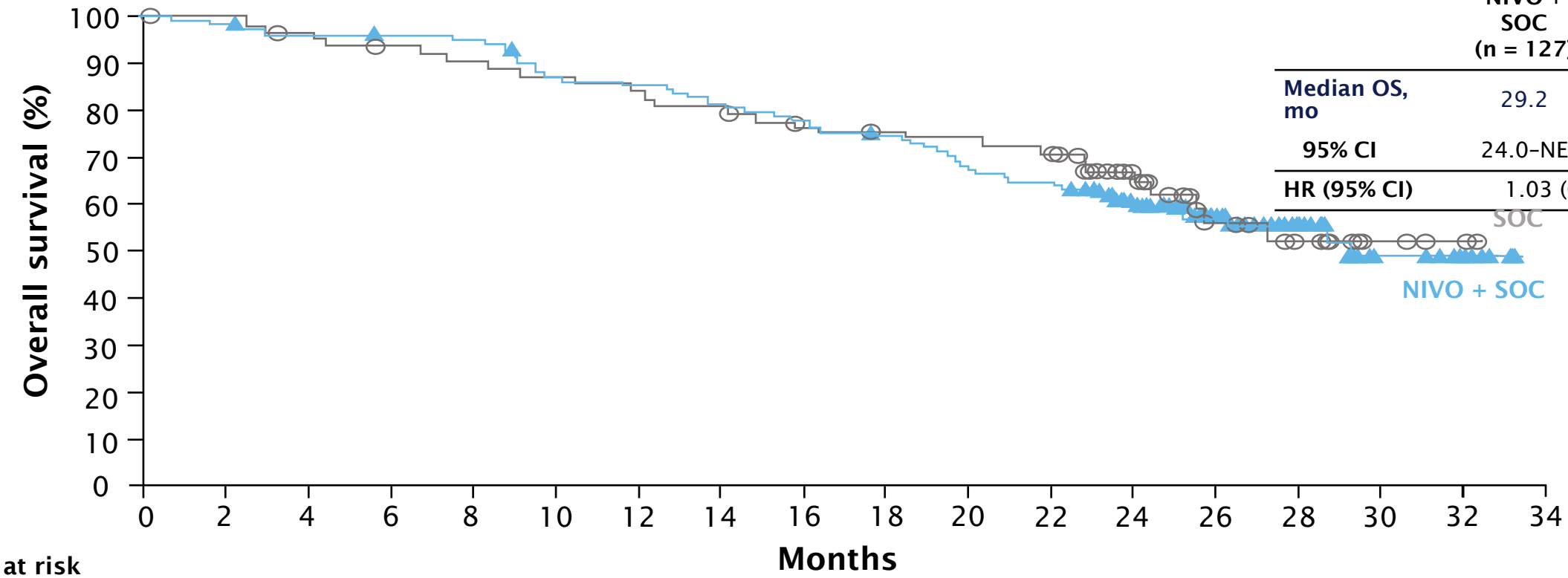
Secondary endpoints
- PFS per INV (RECIST v1.1)
- ORR, DCR, DOR, and TTR per BICR and per INV; OS; and safety

Exploratory endpoints
- Biomarker analyses

- At data cutoff (February 1, 2021), the minimum follow-up was 21.5 months[f]

[a]ClinicalTrials.gov. NCT03414983; [b]No prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways; [c]Until disease progression, unacceptable toxicity, withdrawal of consent, or end of study; NIVO treatment for ≤ 24 months; [d]Oxaliplatin, 85 mg/m^2; leucovorin, 400 mg/m^2 or 350 mg/m^2 per local standards; fluorouracil, bolus 400 mg/m^2, followed by 1200 mg/m^2 continuous infusion on day 1 (or 15) and day 2 (or 16), or 2400 mg/m^2 continuous infusion over 46–48 hours from day 1 (or 15) through day 2 (or 16) per local standards; [e]Bevacizumab, 5 mg/kg; [f]Time from randomization of the last patient to clinical data cutoff.

Overall survival

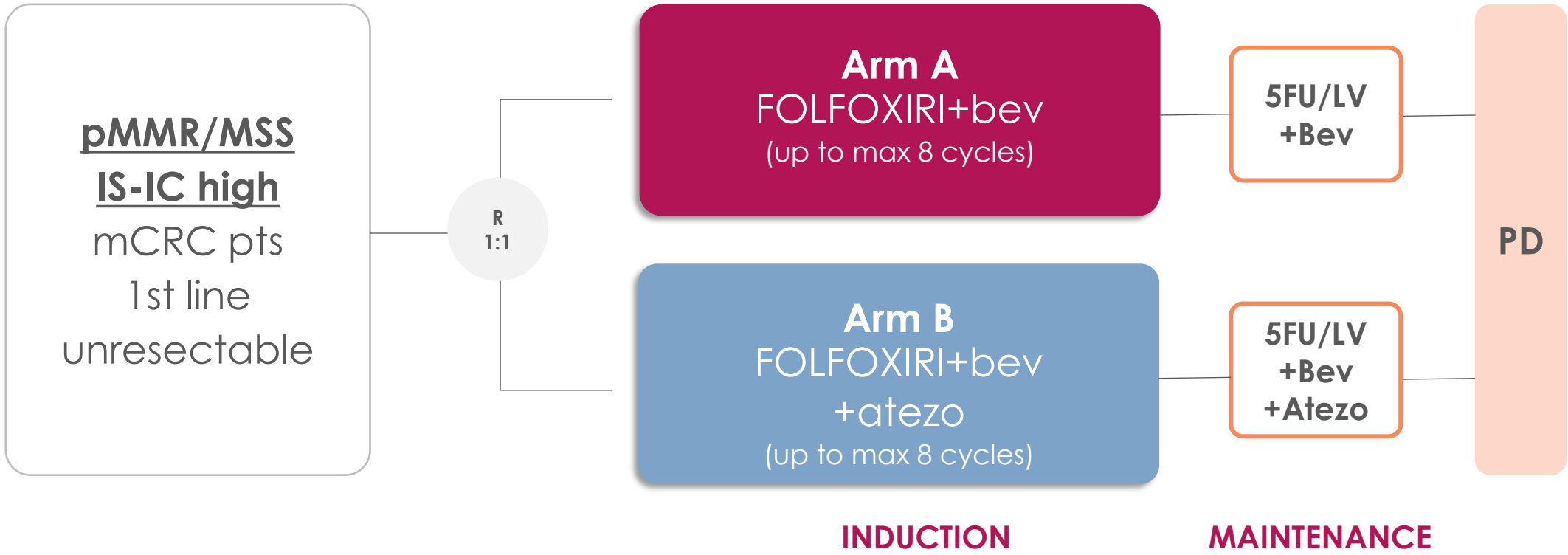


	NIVO + SOC (n = 127)	SOC (n = 68)
Median OS, mo	29.2	NR
95% CI	24.0–NE	24.4–NE
HR (95% CI)	1.03 (0.64–1.66)	

No. at risk																		
NIVO + SOC	127	123	119	118	117	106	104	99	93	90	82	78	60	39	23	10	6	0
SOC	68	64	61	58	56	54	52	49	46	44	43	41	28	17	12	5	3	0

- Minimum follow-up was 21.5 months; longer follow-up is warranted

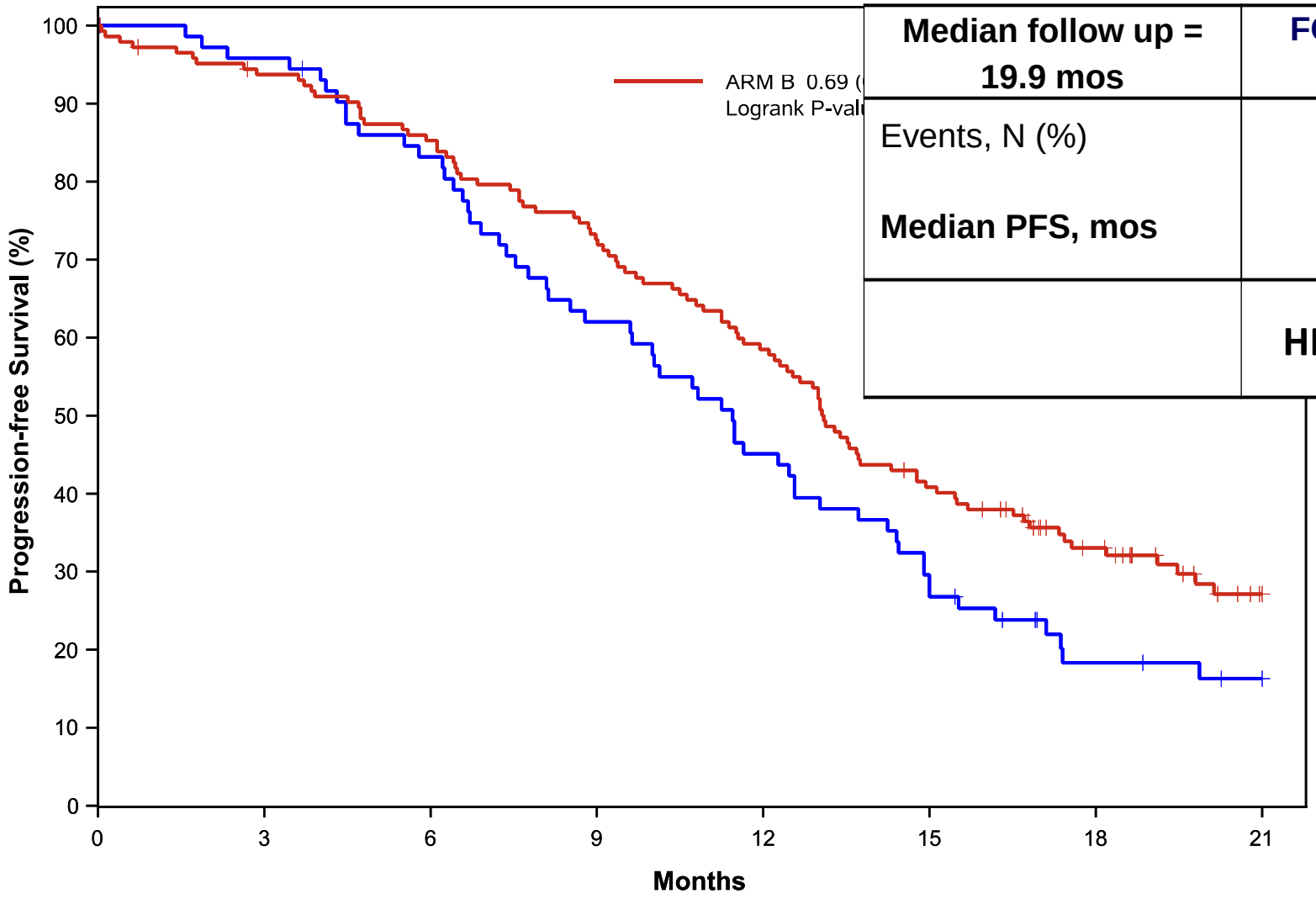
AtezoTRIBE2: Study Design



mCRC, metastatic colorectal cancer; **MMR**, mismatch repair;; **FOLFOXIRI**, folinic acid, fluorouracil, oxaliplatin, irinotecan; **PD**, progressive disease; **5FU/LV**, fluorouracil and leucovorin; **bev**, bevacizumab; **MSS**, microsatellite stable

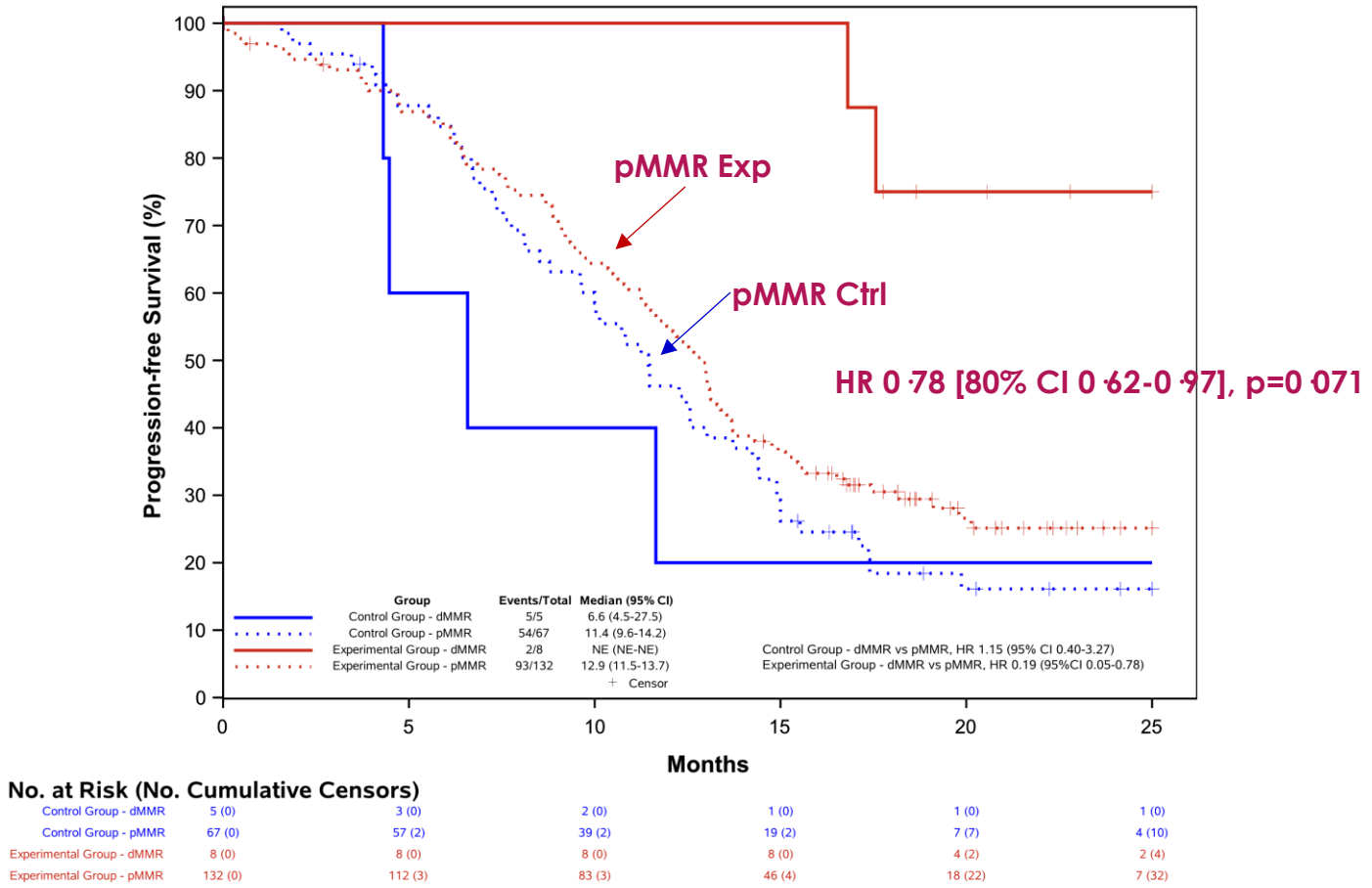
1. Antoniotti et al., *Lancet Oncol.* 2022 Jul;23(7):876-887. doi: 10.1016/S1470-2045(22)00274-1

Primary endpoint: Progression Free Survival



Median follow up = 19.9 mos	FOLFOXIRI/Bev N = 73	FOLFOXIRI/Bev/Atezo N = 145
Events, N (%)	60 (82%)	99 (68%)
Median PFS, mos	**11.5**	**13.1**
	HR = 0.69 [80% CI: 0.56-0.85] p=0.012	

AtezoTRIBE: Primary Endpoint – PFS



MMR, mismatch repair; **FOLFOXIRI**, folinic acid, fluorouracil, oxaliplatin, irinotecan; **Ctrl**, control; **exp**, experimental; **HR**, hazard ratio; **CI**, confidence interval; **PFS**, progression free survival

1. Antoniotti et al., *Lancet Oncol.* 2022 Jul;23(7):876-887. doi: 10.1016/S1470-2045(22)00274-1

Combinations with chemotherapy?

AtezoTRIBE – translational analyses on tumour specimens

- TMB[1] 
- Immunoscore[2] 
- Immunoscore IC[2] 
- PD-L1 TPS[2] 
- Tumour infiltrating lymphocytes[3] 
- Determa IO gene signature[4] 

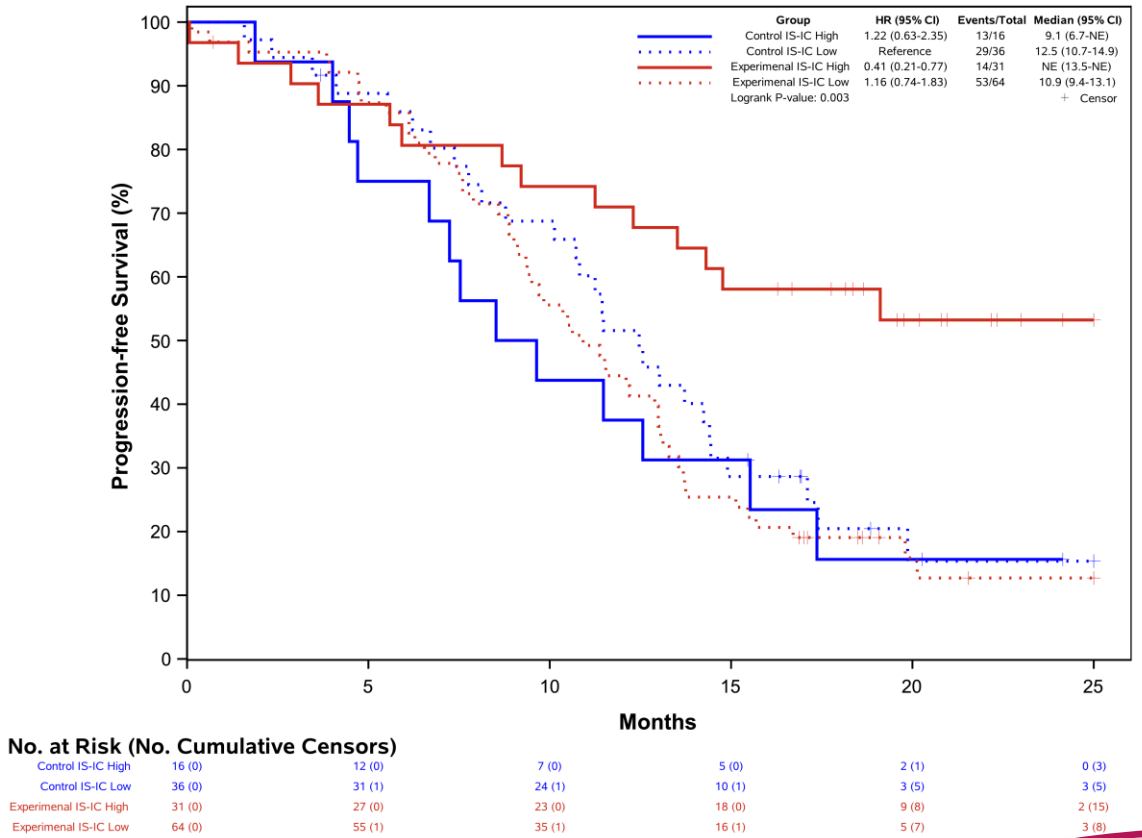
Biomarker description	Assessable population
Number of mutations per megabase	**141** (65%)
Densities of CD8+ and CD3+ cells into the tumour core and at the invasive margin*	**77** (35%)
Densities of CD8+ and PD-L1+ cells and their proximity into the tumour core	**157** (72%)
Density of PD-L1+ tumour cells	**162** (74%)
Density of tumour epithelium infiltrating lymphocytes	**181** (83%)
Immune-related 27-gene targeted panel	**122** (56%)

1: FoundationOne CDx assay, US; 2: Veracyte; US; 3: University of Pisa, Italy; 4: Oncocyte inc, US. *assessed only on tumour surgical resection (no biopsies).

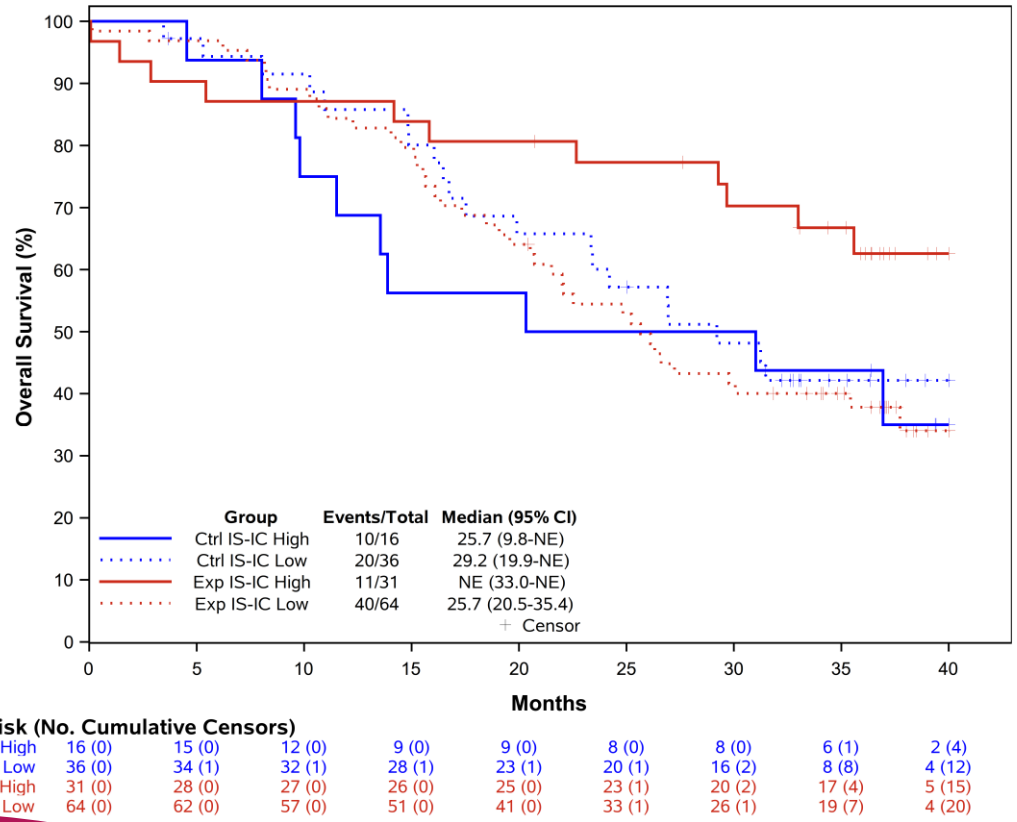
Antoniotti C et al. ASCO 2023

AtezoTRIBE: pMMR cohort – subgroup analysis according to IS-IC

PFS[1]



OS[2]



IS-IC high prevalence: 32%

OS, overall survival; **PFS**, progression free survival

1. Antoniotti et al., *Lancet Oncol.* 2022 Jul;23(7):876-887. doi: 10.1016/S1470-2045(22)00274-1. 2. Antoniotti et al., *ASCO Annual Meeting 2023.*

Fruquintinib plus sintilimab in refractory repair-proficient (pMMR)/microsatellite stable (MSS) metastatic colorectal cancer (mCRC): preliminary clinical results and biomarker analyses from a phase II study

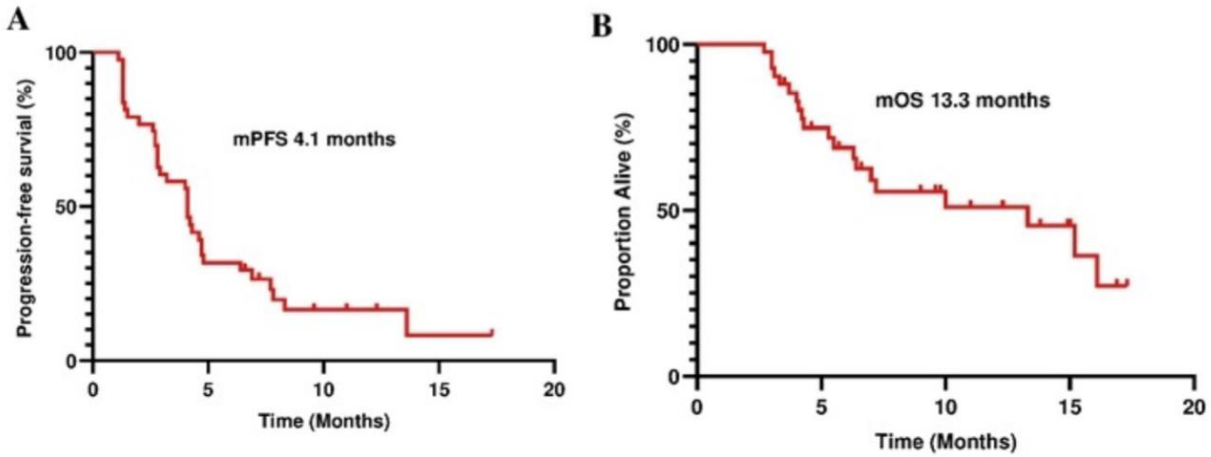
Wen Zhang[1], Yongkun Sun[1], Zhichao Jiang[1], Tianyi Liu[1], Caifeng Gong[1], Lin Yang[1], Ying Xin[2], Depei Huang[2], Aiping Zhou[1]

[1] Department of Medical Oncology, National Cancer Center, Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China;
[2] The Medical Department, 3D Medicines Inc.

423P

Characteristic	No. (%)
Site of metastases	
Liver-only	15 (34.88%)
Lung-only	8 (23.26%)
Both liver and lung	13 (30.23%)
Neither liver or lung	5 (11.63%)
Lines of prior chemotherapy	
Two lines	30 (69.77%)
Three or more lines	13 (30.23%)
Previous Bevacizumab treatment	
Yes	43 (100%)
No	0
Previous anti-EGFR treatment	
Yes	11 (25.58%)
No	32 (74.42%)

Figure 1. Kaplan–Meier curves of PFS (A) and OS (B) in patients with MSS mCRCs treated with fruquintinib plus sintilimab (43 patients were eligible for efficacy analysis).



Subgroup analysis

Figure 2.ORR (A) and PFS (B) analysis of patients with or without liver metastases. Patients with liver metastases had lower ORR than those without (7.1% vs 33.3%, P=0.0398) and were associated with shorter PFS (4.1 vs 6.4 m, P=0.0364).

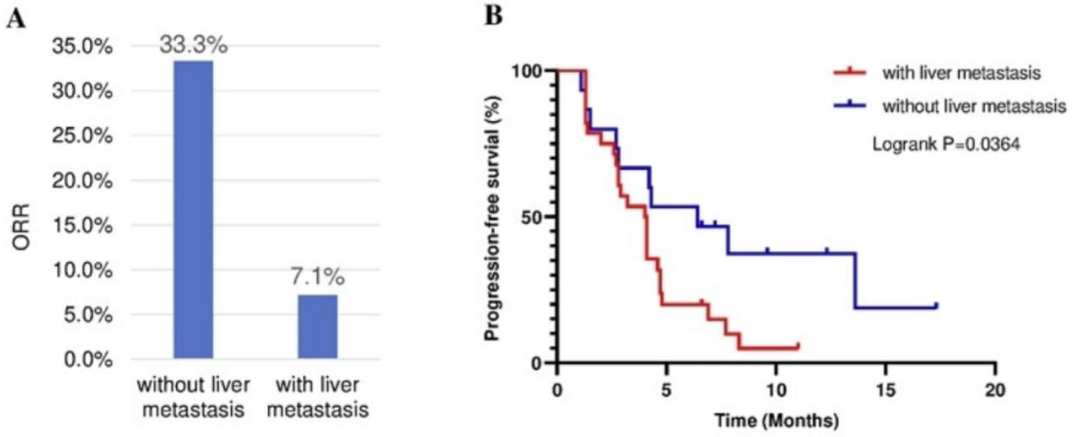
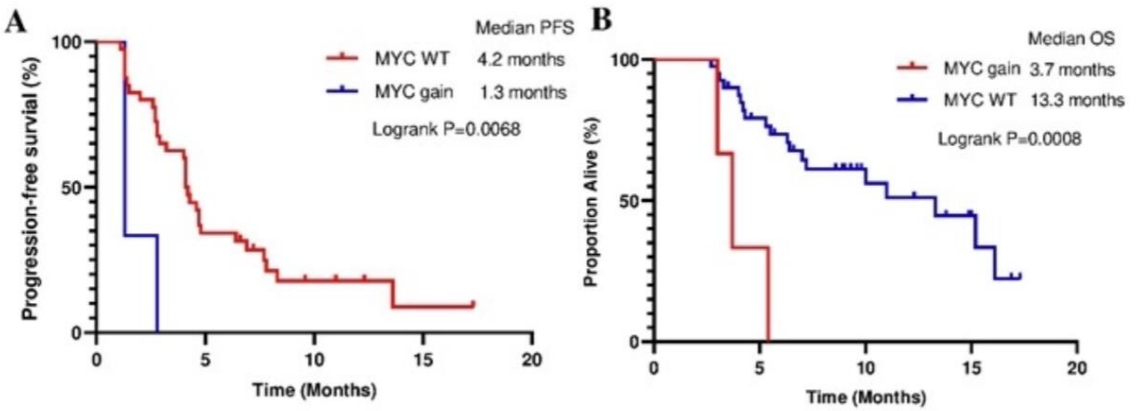


Figure 5. Exploratory analysis of progression-free (A) and overall (B) survival by *MYC* status. Three pts with *MYC* amplification in ctDNA seemed to have worse PFS (1.3 m, 1.3 m, 2.1 m) and OS (3.0 m, 3.7 m, 5.4 m).



Zusammenfassung

Die Immunotherapie ist der Chemotherapie bei MSI-h/dMMR mKRK Patienten überlegen;

Der MMR/MSI-Status MUSS daher erhoben werden!

Derzeit ist es noch immer unklar wie MSS Tumore immunogen “heiß” gemacht werden können.

Pembrolizumab (1st line) oder Nivolumab/Ipilimumab (1st and 2nd line) sind in Europa by EMA in mCRC.


Critik
der
reinen Vernunft
von
Immanuel Kant
Professor in Königsberg.
Riga,
verlegts Johann Friedrich Hartknoch
1781.


Immanuel Kant (Photo from a steel engraving)

“The one who knows more, may decide better”