Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

MSI Current Data and Approvals

Neil H. Segal MD PhD

Associate Attending, Gastrointestinal Oncology Service
Memorial Sloan Kettering Cancer Center
Associate Professor of Medicine
Weill Cornell Medical College, Cornell University
New York, NY

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Disclosures

- Consulting Fees: Immunocore, PsiOxus, Roche/Genentech, Boehringer Ingelheim, Revitope, ABL Bio, Novartis, GSK

- Contracted Research: Regeneron, Immunocore, Incyte, AstraZeneca, BMS, Merck, Pfizer, Roche/Genentech

- I will be discussing non-FDA approved indications during my presentation.

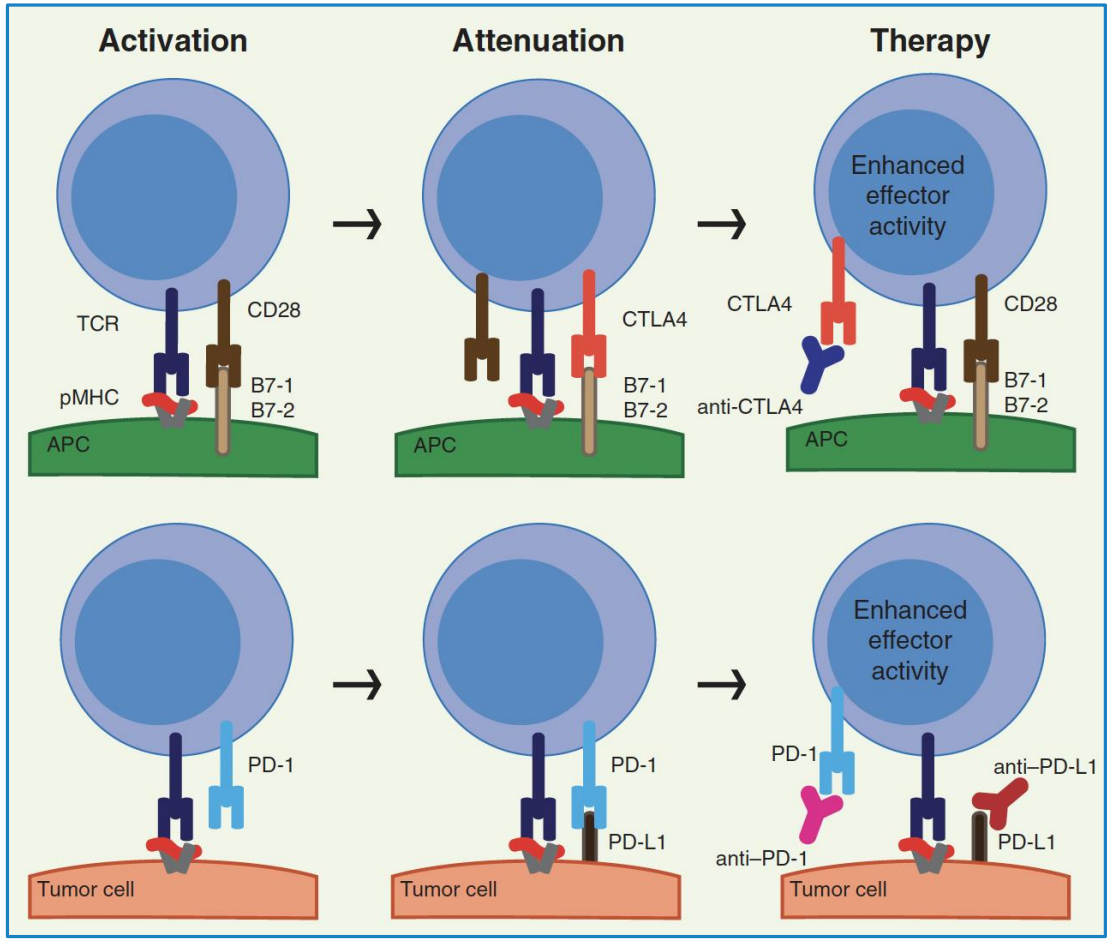
We will talk about…

Ipilimumab:

- Recombinant human, IgG1 monoclonal antibody
- Binds CTLA-4 with high affinity
- Preventing its interaction with B7-1/2
- Increasing B7-1/2 co-stimulation of CD28 → T-cell activation

Pembrolizumab, Nivolumab and Dostarlimab-gxly:

- Humanized or fully human, IgG4 monoclonal antibodies
- Bind PD-1 with high affinity
- Preventing its interaction with PDL-1/PDL-2
- Thus, allowing immune recognition and response



Wei. Can Disc. 2018

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Microsatellite instability (MSI)

- Frequent polymorphisms in short repetitive DNA sequences
  - Due to deficiency of DNA mismatch repair protein/s (dMMR)
  - Leads to multiple frame shift and point mutations

- Usually sporadic: *MLH1 promoter hypermethylation*
- Lynch syndrome: *Germline defect in MLH1, MSH2, MSH6, PMS2, or EPCAM*

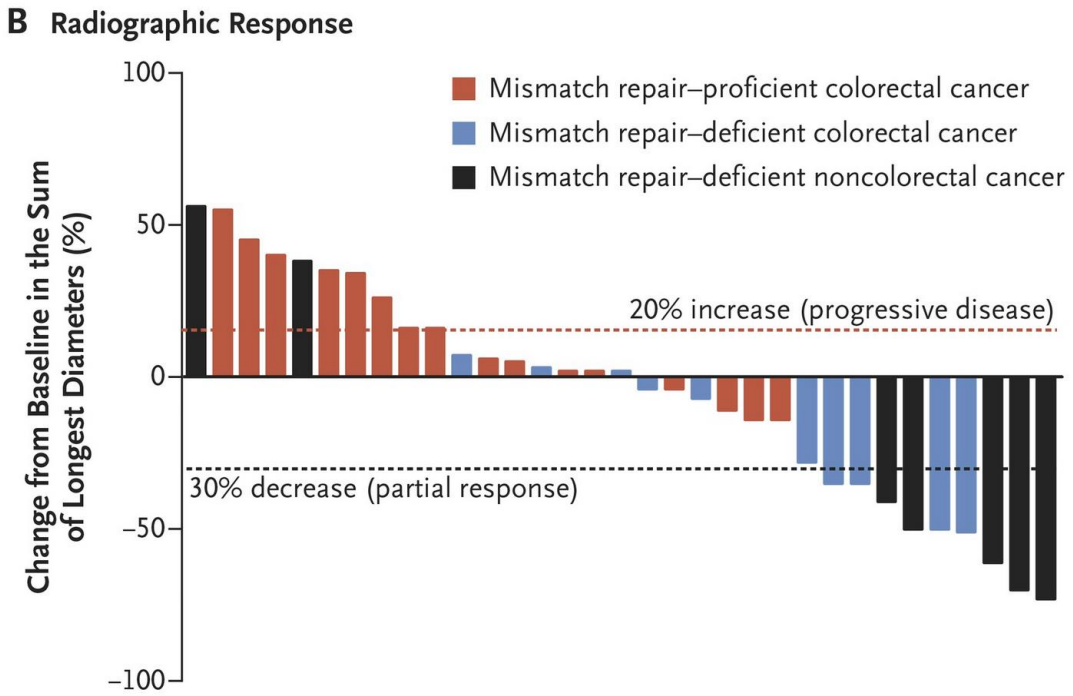
- Identified by IHC (dMMR), PCR (MSI-H) and NGS (MSIsensor)

- Predicted to have thousands of somatic mutations → very large number of mutation associated neo-antigens that might be recognized by the immune system

Stadler. Hem Onc Clin N Am. 2015

Pembrolizumab in dMMR tumors

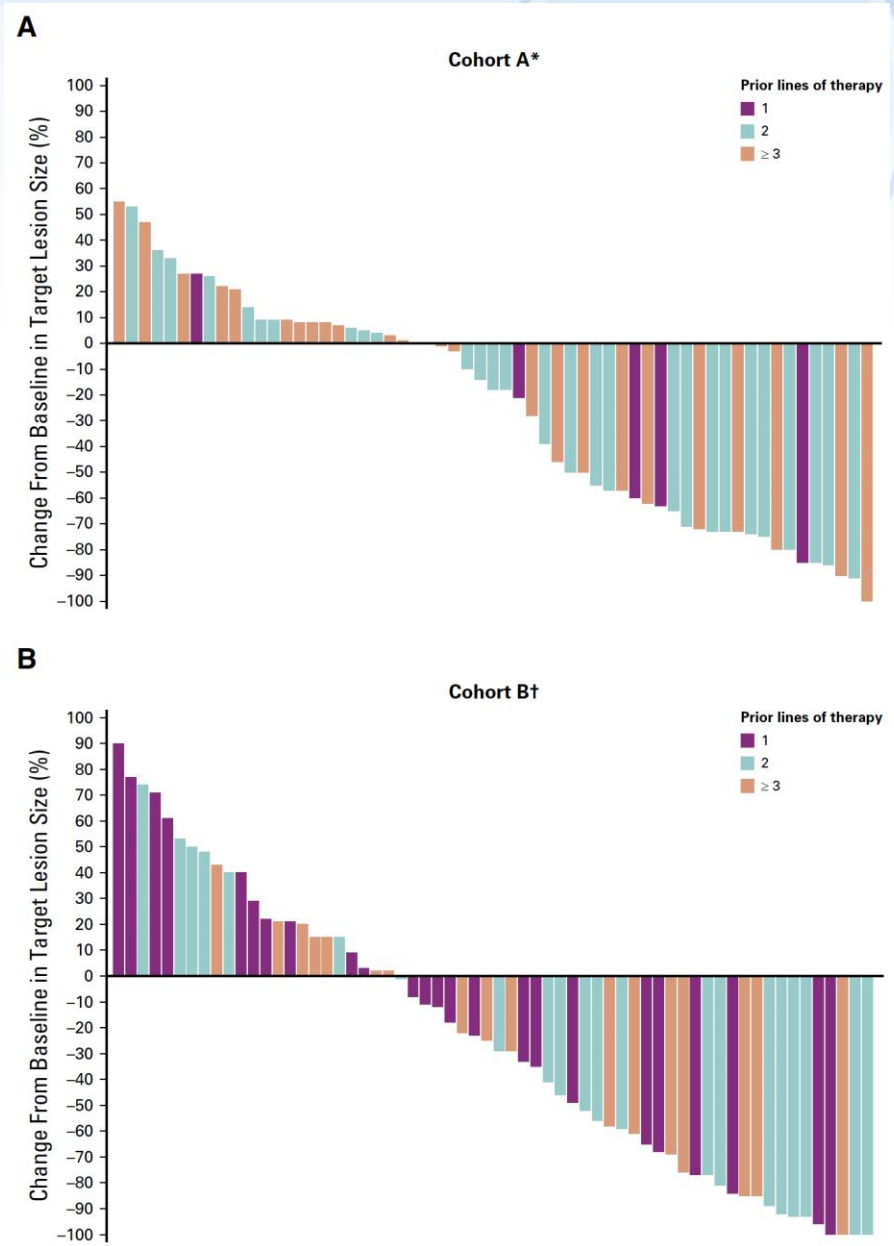
- Phase II study, including 11 pts with dMMR CRC
- Pembrolizumab 10 mg/kg Q2W
- **irORR** = 40%
- **20-week irPFS rate** = 78%
- Median PFS and OS not reached



Le. NEJM. 2015

KEYNOTE-164

- Phase II study: 124 pts with MSI-H/ dMMR CRC
  - Cohort A (n=61): ≥ 2 prior lines
  - Cohort B (n=63): ≥ 1 prior line
- Pembrolizumab 200 mg Q3W for up to 2 years
- **ORR** = 33% (both cohorts)
- Median PFS = 2.3 mo and 4.1 mo
- Median Survival = 31.4 mo and NR
- Grade 3/4 treatment-related AE = 16%/13% [pancreatitis, fatigue, ALT, lipase (2 pts each)]



Data from KEYNOTE-164 confirm the durable clinical benefit of pembrolizumab in patients with previously treated MSI-H/dMMR metastatic CRC

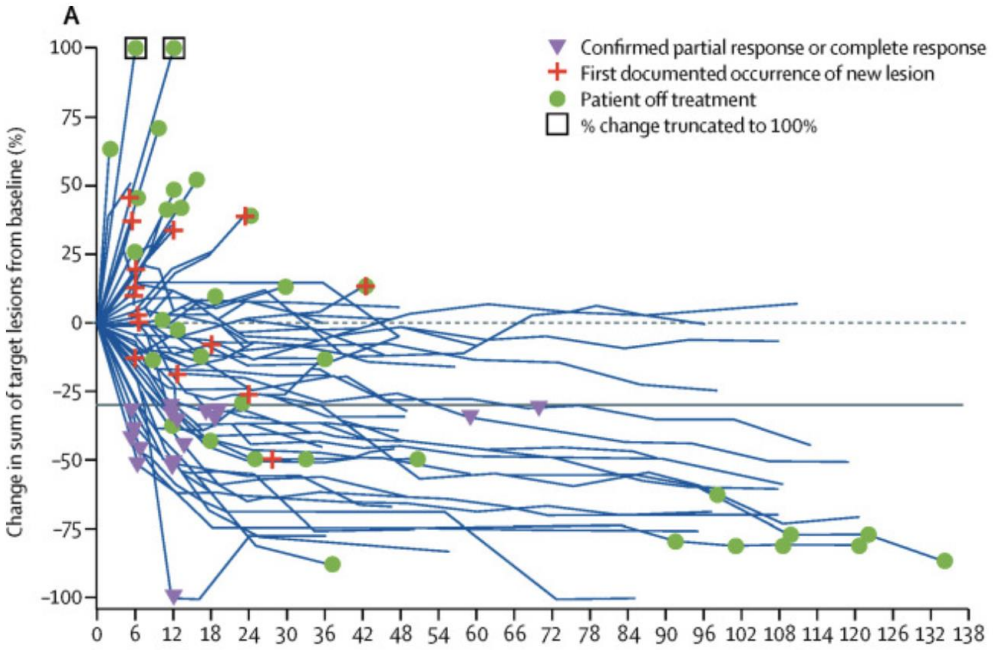
Le. JCO. 2020

Checkmate-142

Phase II, multi-cohort, multi-center study

<u>Cohort 1: 74 pts with dMMR, ≥ 1 prior line</u>

- **Nivolumab** 3 mg/kg every 2 weeks



- **Investigator assessed ORR** = 31.1%
- 12-mo PFS = 50%
- 12-month OS = 73%

- Grade 3/4 treatment-related AE = 20% pts [lipase (8%), amylase (3%)]

Overman. Lancet. 2017

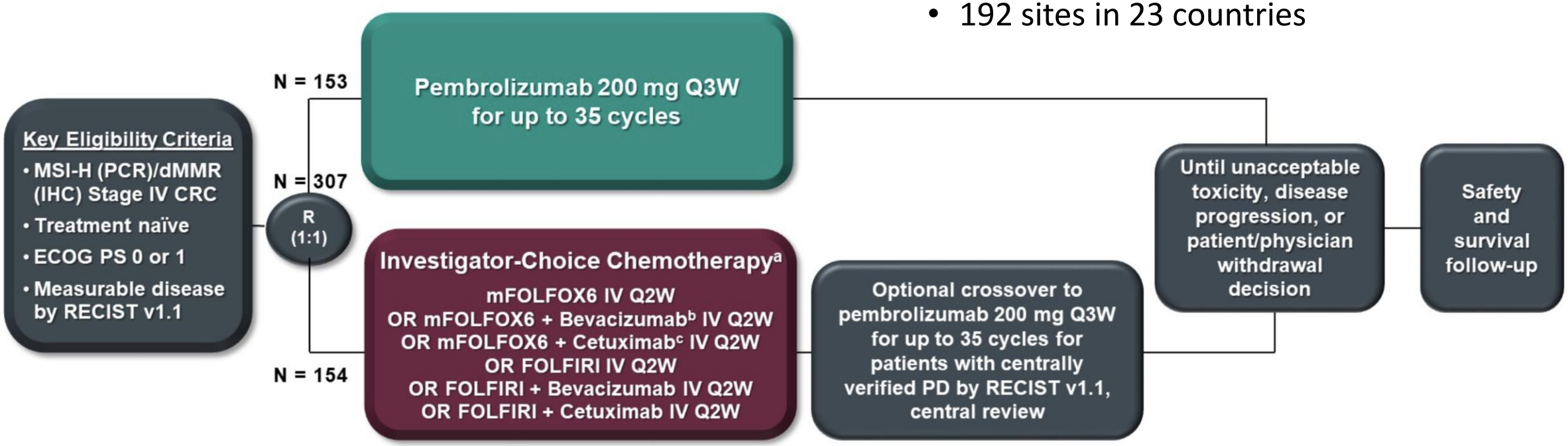
Benefit across patient subgroups

	Objective response	Disease control for ≥12 weeks
Tumour PD-L1 expression		
≥1% (n=21)	6 (29%)	11 (52%)
<1% (n=47)	13 (28%)	35 (75%)
Immune cell PD-L1 expression		
Rare (n=24)	5 (21%)	14 (58%)
Intermediate (n=21)	5 (24%)	17 (81%)
Numerous (n=23)	9 (39%)	15 (65%)
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%)
Clinical history of Lynch syndrome*		
Yes (n=27)	9 (33%)	19 (70%)
No (n=28)	8 (29%)	21 (75%)

Overman. Lancet. 2017

KEYNOTE-177 Study Design
(NCT02563002)

- Phase III, open-label, randomized study
- 192 sites in 23 countries



- Dual-Primary endpoints: PFS per RECIST v1.1, BICR; OS
- Secondary endpoints: ORR per RECIST v1.1 by BICR, PFS2, HRQoL, safety
- Tumor response assessed at week 9 and Q9W thereafter per RECIST v1.1 by BICR

[a]Chosen before randomization; [b]Bevacizumab 5 mg/kg IV; [c]Cetuximab 400 mg/m2 over 2 hours then 250 mg/mg^2 IV over 1 hour weekly.
BICR, blinded independent central review; IHC: immunohistochemistry with hMLH1, hMSH2, hMSH6, PMS2; PCR: polymerase chain reaction; PFS, progression-free survival; OS: overall survival; ORR: overall response rate; Q9W: every 9 weeks.

Andre. NEJM. 2020; Andre. ASCO. 2021

Baseline Characteristics

Characteristic	Pembrolizumab N = 153 (100%)	Chemotherapy N = 154 (100%)
Age, median (range), years	63.0 (24-93)	62.5 (26-90)
Male	71 (46.4%)	82 (53.2%)
ECOG PS 0	75 (49.0%)	84 (54.5%)
Recurrent disease	80 (52.3%)	74 (48.1%)
Liver Metastasis	71 (46.4%)	54 (35.0%)
Asia region	22 (14.4%)	26 (16.9%)
Western Europe/North America region	109 (71.2%)	113 (73.4%)
Rest of World	22 (14.4%)	15 (9.7%)
Right-sided tumor	102 (66.7%)	107 (69.5%)
Left-sided tumor	46 (30.1%)	42 (27.3%)
Other/unknown tumor location	5 (3.2%)	5 (3.2%)
Prior adjuvant therapy only	33 (21.6%)	37 (24.0%)
Prior neoadjuvant therapy (perioperative)	5 (3.2%)	8 (5.2%)
No prior therapy	115 (75.2%)	109 (70.8%)
BRAF, KRAS, NRAS all wildtype	43 (28.1%)	38 (24.7%)
BRAF V600E	35 (22.9%)	44 (28.6%)
KRAS or NRAS mutant	33 (21.6%)	39 (25.3%)
BRAF V600E mutant and KRAS/NRAS mutant	0	2 (1.3%)
Unknown[a]	42 (27.5%)	31 (20.1%)

[a] Defined as when KRAS/NRAS or BRAFV600E one or two or all are missing or if only one or two are missing and the other one are WT; Data cut-off: 19Feb2021.

Andre. NEJM. 2020; Andre. ASCO. 2021

Antitumor Response

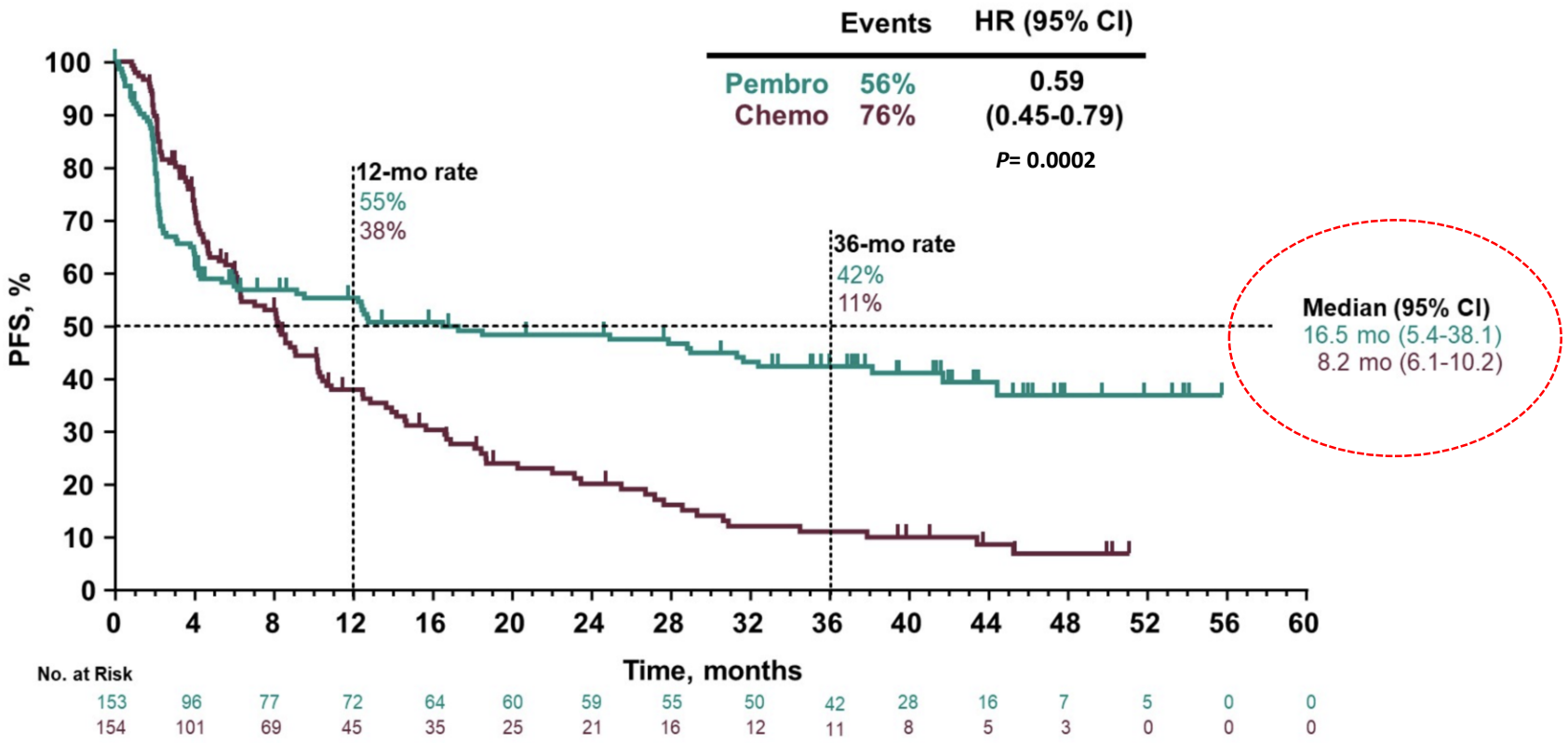
	Pembrolizumab N = 153	Chemotherapy N = 154
ORR, n (%)	**69 (45.1)[a]**	**51 (33.1)**
Best Overall Response, n (%)		
Complete response	20 (13.1)[b]	6 (3.9)
Partial response	49 (32.0)[c]	45 (29.2)
Stable disease	30 (19.6)	65 (42.2)
Disease control rate (CR+PR+SD)	99 (64.7)	116 (75.3)
Progressive disease	45 (29.4)	19 (12.3)
Not evaluable	3 (2.0)	2 (1.3)
No assessment	6 (3.9)	17 (11.0)
Median duration or response (range), mo	NR (2.3+ to 53.5+)	10.6 (2.8 to 48.3+)
≥ 24 months response duration, %	83.5	33.6

[a]ORR 43.8%; [b]CR rate 11.1%; [c]PR rate 32.7% at IA2 (data cut-off 19Feb2020).
Data cut-off: 19Feb2021.

Andre. NEJM. 2020; Andre. ASCO. 2021

Andre KN177FA ASCO 2021

Progression-Free Survival



Data cut-off: 19Feb2021.

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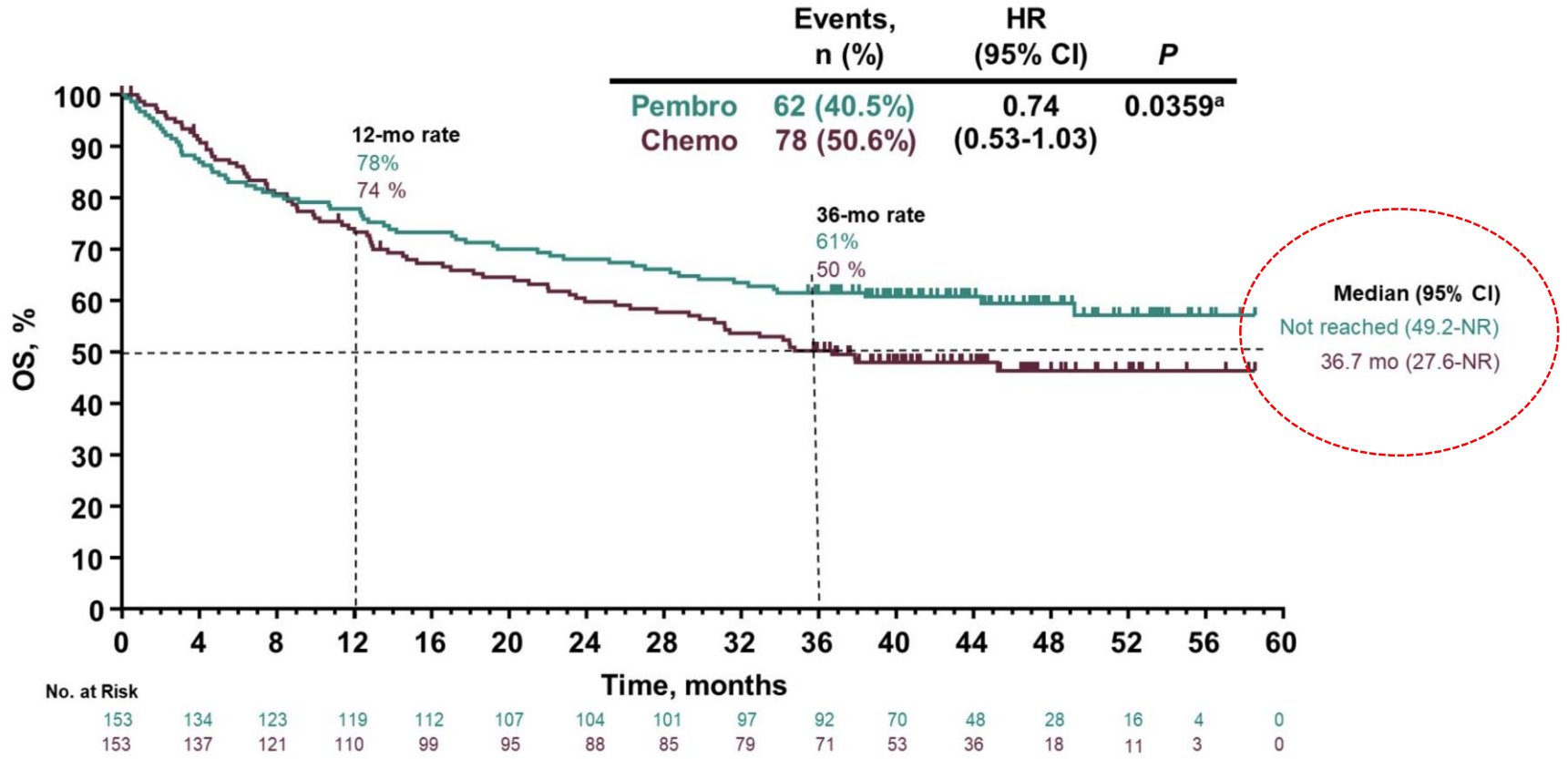
Andre. NEJM. 2020; Andre. ASCO. 2021

Overall Survival



[a]Pembrolizumab was not superior to chemotherapy for OS as one-sided α > 0.0246. Pre-specified sensitivity analyses to adjust for crossover effect by rank-preserving structure failure time model and inverse probability of censoring weighting showed OS HRs of 0.66 (95% CI 0.42-1.04) and 0.77 (95% CI 0.44-1.38). Data cut-off: 19Feb2021.

- Treatment with pembrolizumab versus chemotherapy is associated with a non-statistically significant reduction in mortality
  - HR for OS: 0.74 (*P* = 0.0359; did not meet threshold for significance)
  - High crossover rate from chemotherapy to anti-PD-1/PD-L1 therapies in second line of 60%

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Andre. NEJM. 2020; Andre. ASCO. 2021

Summary of Events in All Treated Patients

Events[a]	Pembrolizumab N = 153	Chemotherapy N = 143
All adverse events (AEs)	149 (97.4%)	142 (99.3%)
Treatment-related	122 (79.7%)	141 (98.6%)
Grade ≥3	33 (21.6%)	95 (66.4%)
Discontinued	15 (9.8%)	10 (7.0%)
Died	0	1 (0.7%)
Immune-mediated AEs and Infusion Reactions		
All	47 (30.7%)	21 (14.7%)
Grade ≥3	14 (9.2%)	3 (2.1%)
Discontinued	10 (6.5%)	1 (0.7%)
Died	0	0

[a]Percentages similar to those previously published: André T et al; *N Eng J Med* 2020;383:2207-18.
Data cut-off: 19Feb2021.

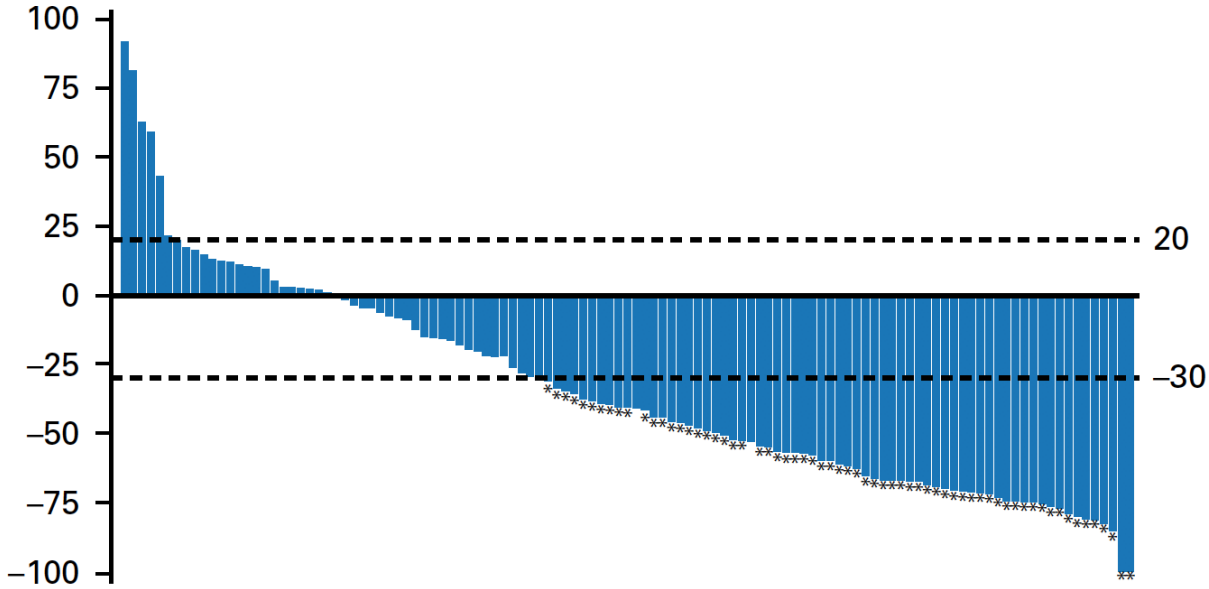
- Fewer treatment-related adverse events observed with pembrolizumab versus chemotherapy: grade ≥3 treatment-related events (22% vs 66%)[1]

Andre. NEJM. 2020; Andre. ASCO. 2021

Checkmate-142: Ipi + Nivo

Cohort 2: 119 pts with dMMR, **≥ 1 prior line**

- **Nivolumab** 3 mg/kg + **ipilimumab** 1 mg/kg Q3W x 4 → nivolumab 3 mg/kg Q2W



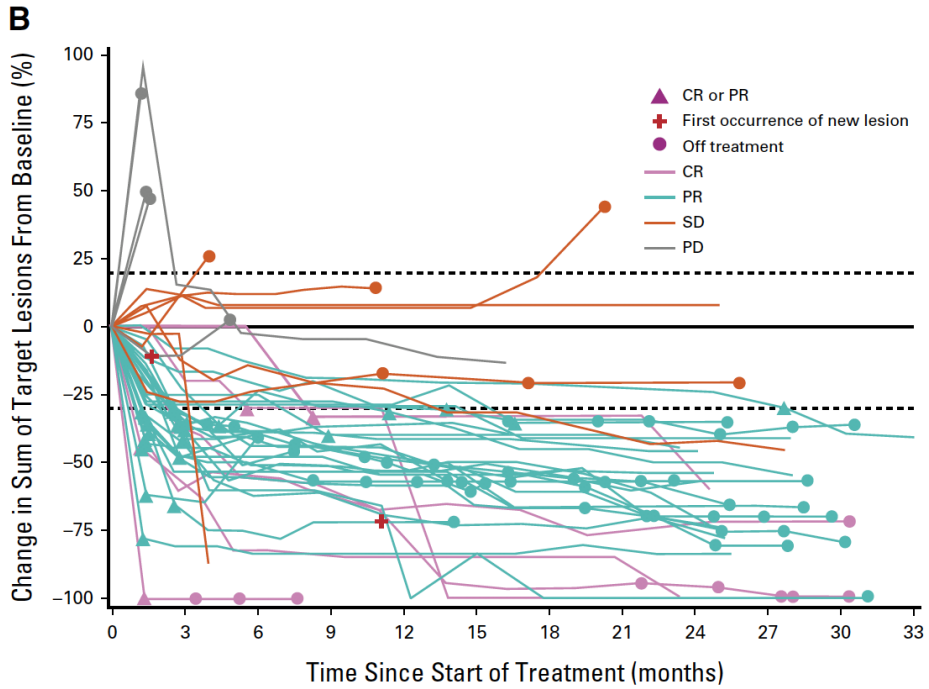
- **Investigator assessed ORR** = 55%
- 12-mo PFS = 71%
- 12-month OS = 85%
- Grade 3/4 treatment-related AE = 32% [AST/ALT (11%)]

Overman. JCO. 2019

Checkmate-142: Ipi + Nivo 1st line

Cohort 3: 45 pts with dMMR, treatment naïve (18 sites)

- Nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W
- **INV assessed ORR = 69% (95% CI, 53-82)** and 62% (BICR)
  - 71% of responders had responses lasting at least 12 months
  - PD rate 13%
- 24-mo PFS rate = 73.6%. Median PFS NR
- 24-mo OS rate = 79.4%. Median OS NR
- Grade 3/4 treatment-related AE = 22% [colitis (n=2, 4%)]



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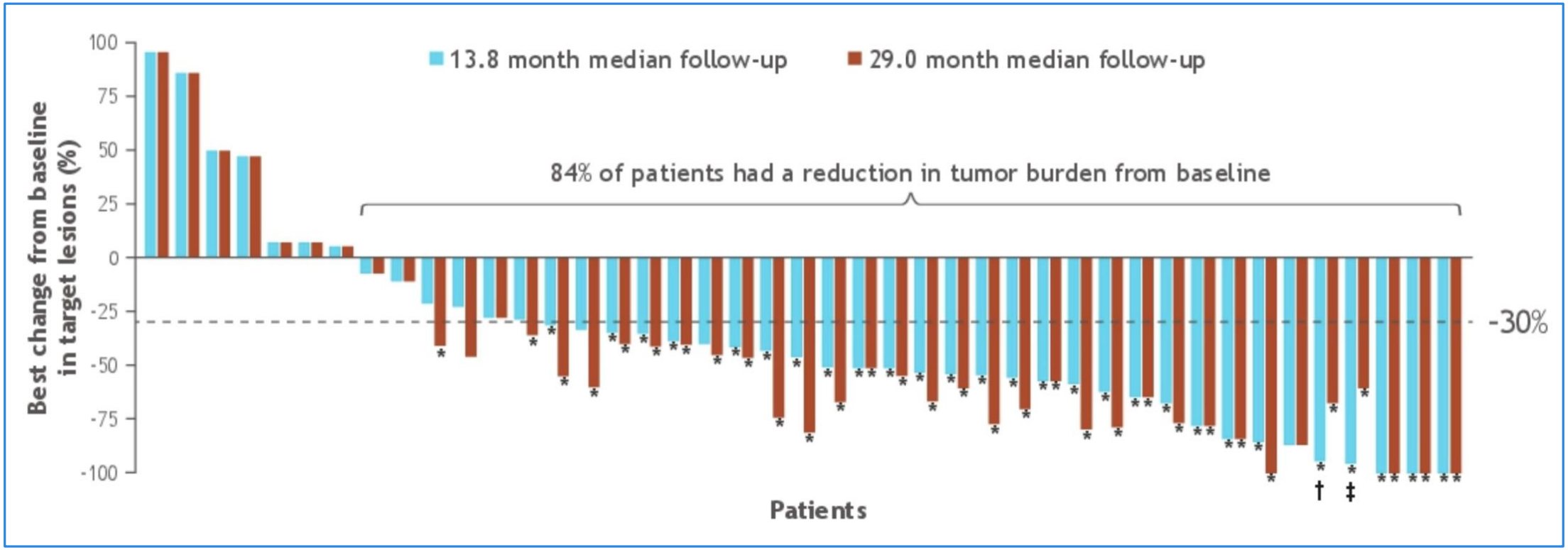
Lenz. JCO. 2021

Deepening of response with longer follow-up



ORR: 60% → 69%
CR rate: 7% → 13%

Lenz. ASCO. 2020

Current immunotherapy approvals (FDA/ NCCN)

- **Metastatic colorectal cancer**
  - Subsequent treatment (no prior ICI)
    - Pembrolizumab [preferred], Nivolumab ± Ipilimumab
  - First line setting
    - Pembrolizumab [preferred], Nivolumab ± Ipilimumab

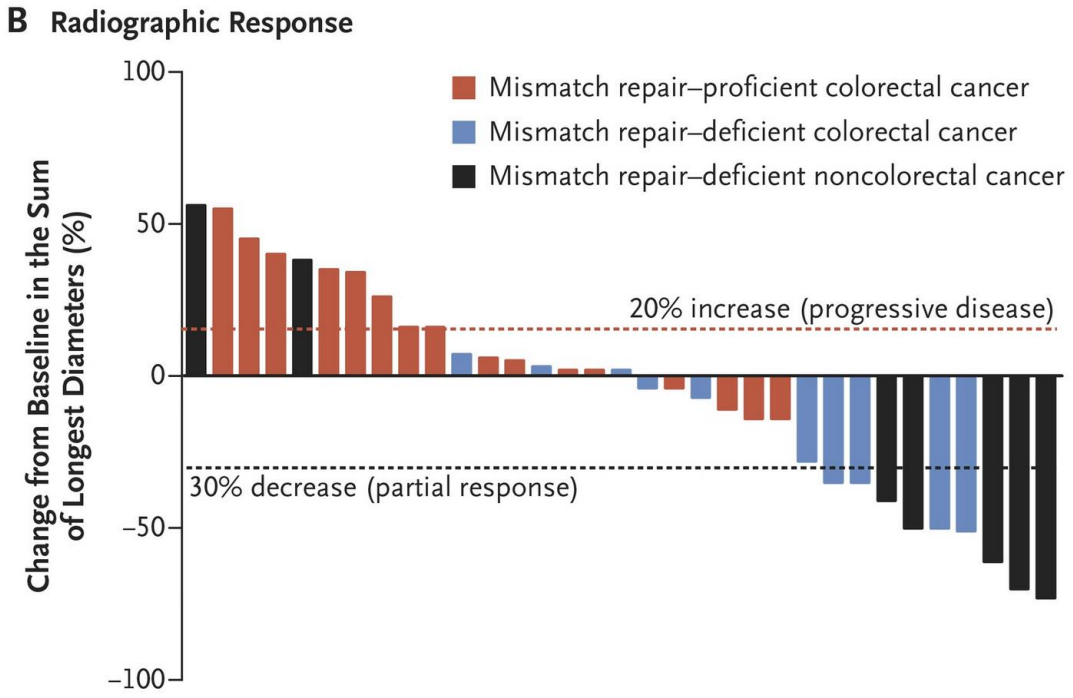
- **Metastatic tumor agnostic** (disease specific guidelines)
  - Subsequent treatment (no prior ICI)
    - Pembrolizumab, Dostarlimab-gxly

- Trials in progress (select):
  - PD-1 v. PD-1 plus CTLA-4 v. chemo (NCT04008030)
  - Adjuvant therapy in colorectal cancer (NCT02912559)
  - Adjuvant therapy in ctDNA+ (NCT03832569)
  - Neoadjuvant rectal cancer (NCT04165772)

https://www.nccn.org/professionals/drug_compendium/content/

Pembrolizumab in dMMR non-CRC

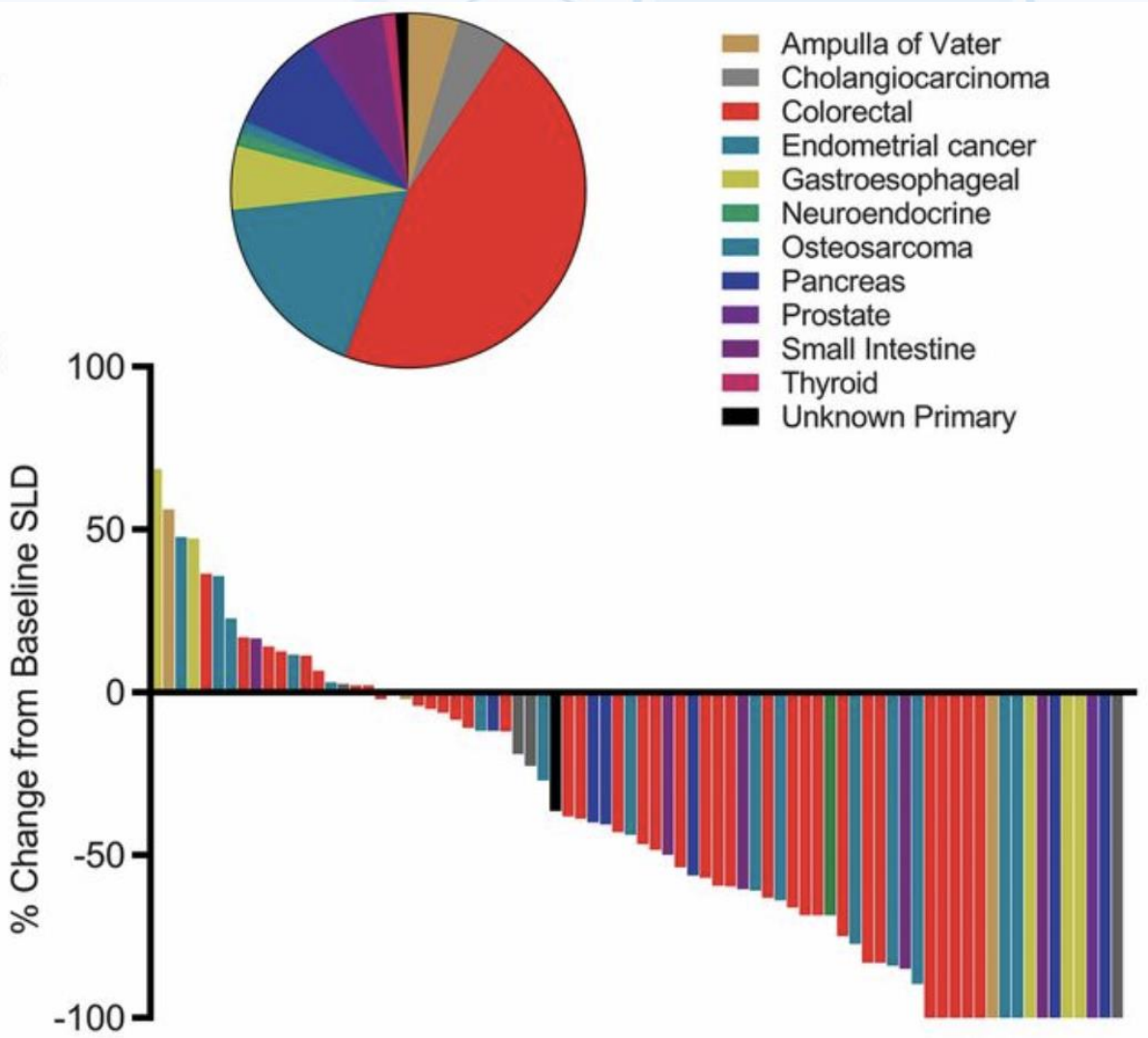
- Phase II study, inc. 7 pts with dMMR non-CRC
- Pembrolizumab 10 mg/kg Q2W
- irORR = 5/7 (71%)



Le. NEJM. 2015

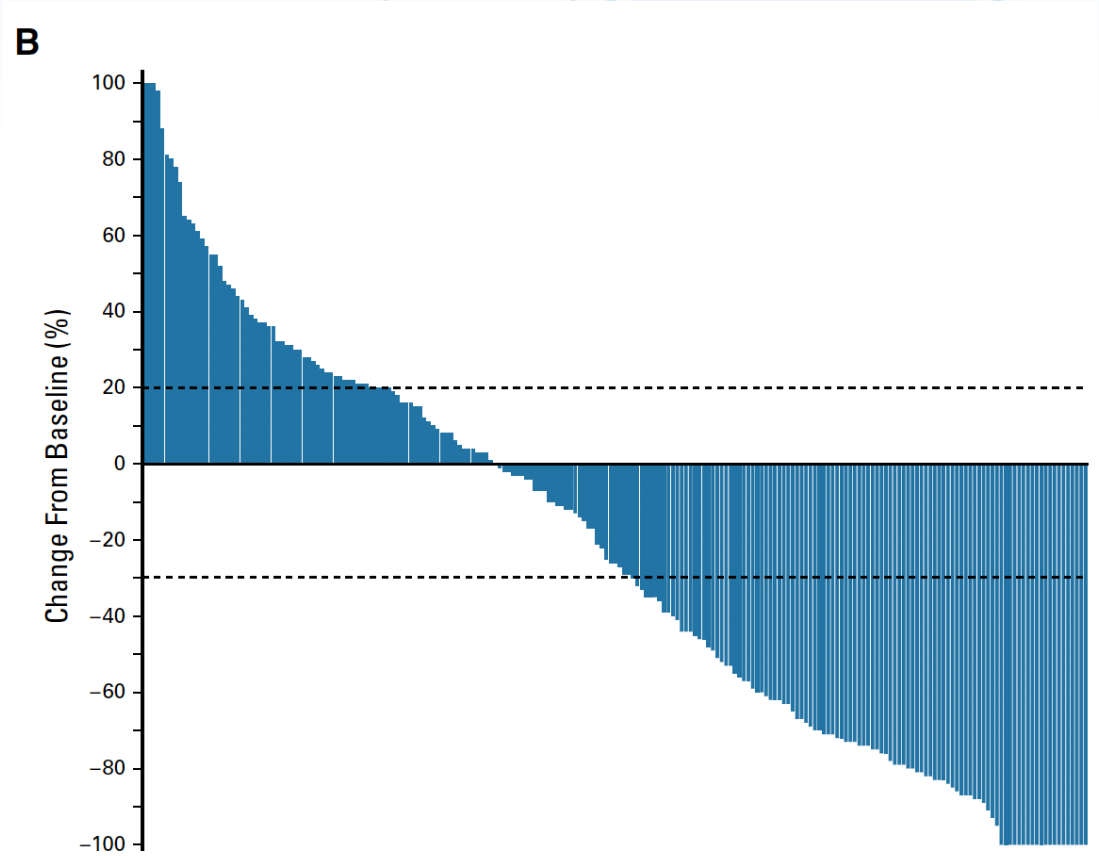
Tumor Agnostic

- Phase II study: 86 pts : ≥ 1 prior line of therapy
- Pembrolizumab 200 mg Q3W for up to 2 years
- **ORR** = 53% (21% CR)
  - CRC = 52%
  - Non-CRC = 54%
- 2-year PFS rate = 53%
- 2-year survival rate = 64%



Le. Science. 2017

KEYNOTE-158



- Phase II study: 233 pts with MSI-H/ dMMR non-CRC
  ≥ 1 prior line of therapy
- Pembrolizumab 200 mg Q3W for up to 2 years
- **ORR = 34.3%**
- Median PFS = 4.1 mo
- Median OS = 23.5 mo
- Grade 3/4 treatment-related AE = 14.6% [GGT and pneumonitis (1.3%)]

Marabelle. JCO. 2019

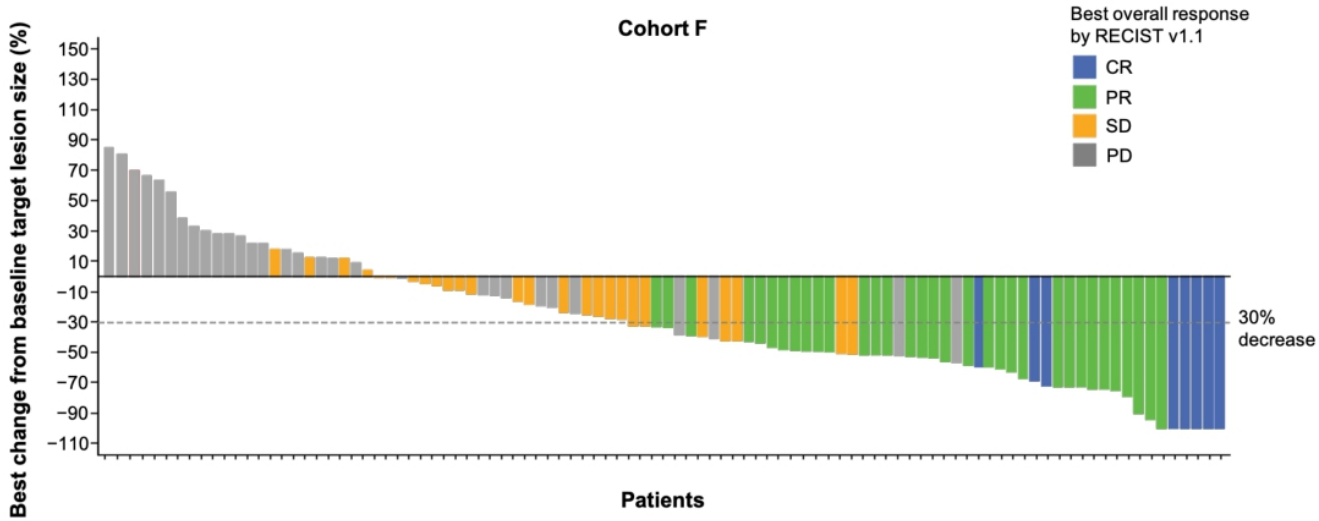
TABLE 3. Antitumor Activity for Tumor Types With Greatest Enrollment

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

Marabelle. JCO. 2019

GARNET study

- Phase 1 Dose Escalation and Cohort Expansion Study
- Cohort F (n=106) non-endometrial dMMR/MSI-H & POLE-Mut cancers, ≥ 1 prior line
- Dostarlimab-gxly 500 mg Q3W x 4 → 1,000 mg every 6 weeks.
- **ORR** = 38.7%.
- **DoR** = NR
- Grade ≥3 TRAE = 8.3%. [lipase (1.4%)]



Andre. ASCO GI. 2021, Berton.ASCO. 2021

Tumor type	N	Confirmed ORR (RECIST v1.1)	
		n (%)	95% CI*
Overall	**106**	**41 (38.7)**	**29.4–48.6**
CRC	**69**	**25 (36.2)**	**25.0–48.7**
Non-CRC	**37**	**16 (43.2)**	**27.1–60.5**
Small Intestinal Cancer	12	4 (33.3)	(9.9–65.1)
Gastric Cancer	8	3 (37.5)	(8.5–75.5)
Pancreatic Carcinoma	4	0	(0.0–60.2)
Liver Cancer	2	PR, PD	
Ovarian Cancer	2	PR, SD	
Adrenal Cortical	1	PR	
Biliary Neoplasm	1	CR	
Breast Cancer	1	CR	
Esophageal Cancer	1	PD	
Gallbladder	1	1	CR
Genital Neoplasm Malignant Female	1	PR	
Pleural	1	PR	
Renal Cell Carcinoma	1	SD	
Unknown Origin (Possibly GI tract)	1	PR	

Andre. ASCO GI. 2021

Current immunotherapy approvals (FDA/ NCCN)

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    - Pembrolizumab [preferred], Nivolumab ± Ipilimumab, Dostarlimab-gxly
  - First line setting
    - Pembrolizumab [preferred], Nivolumab ± Ipilimumab

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- Trials in progress (select):
  - PD-1 v. PD-1 plus CTLA-4 v. chemo (NCT04008030)
  - Adjuvant therapy in colorectal cancer (NCT02912559)
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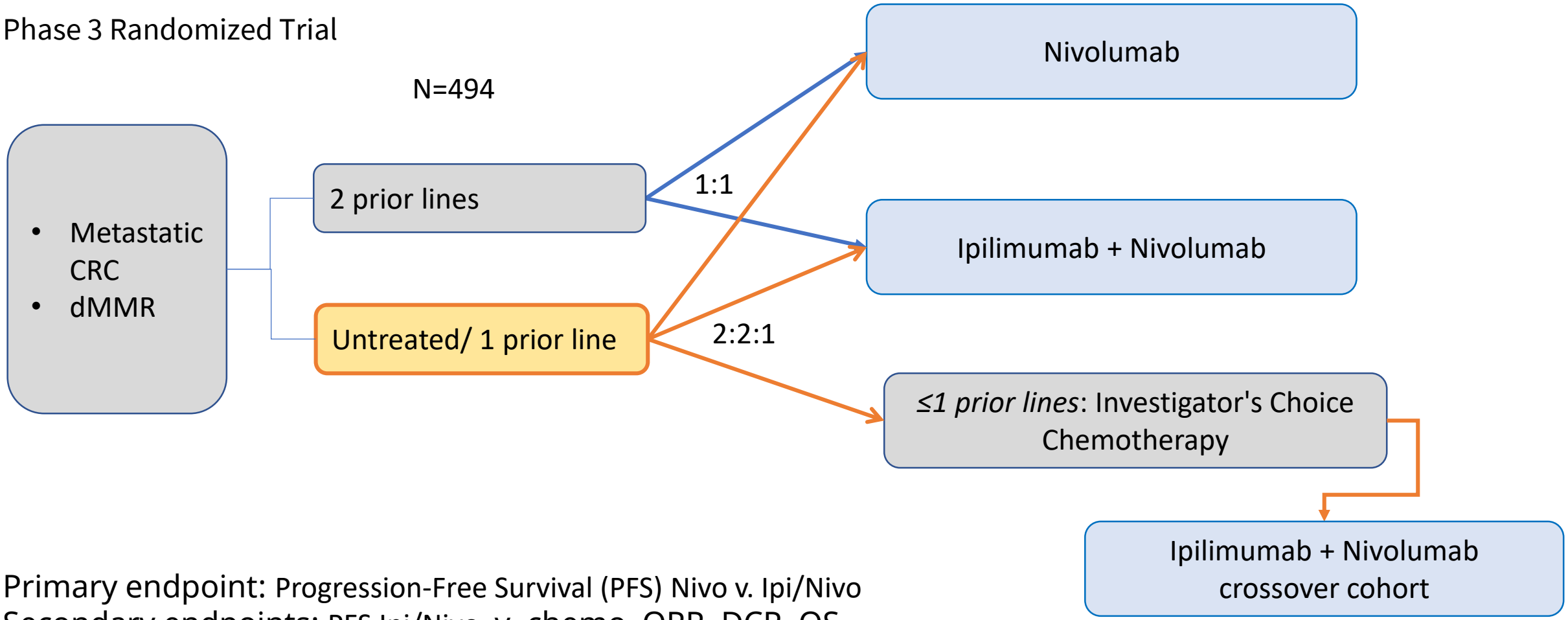
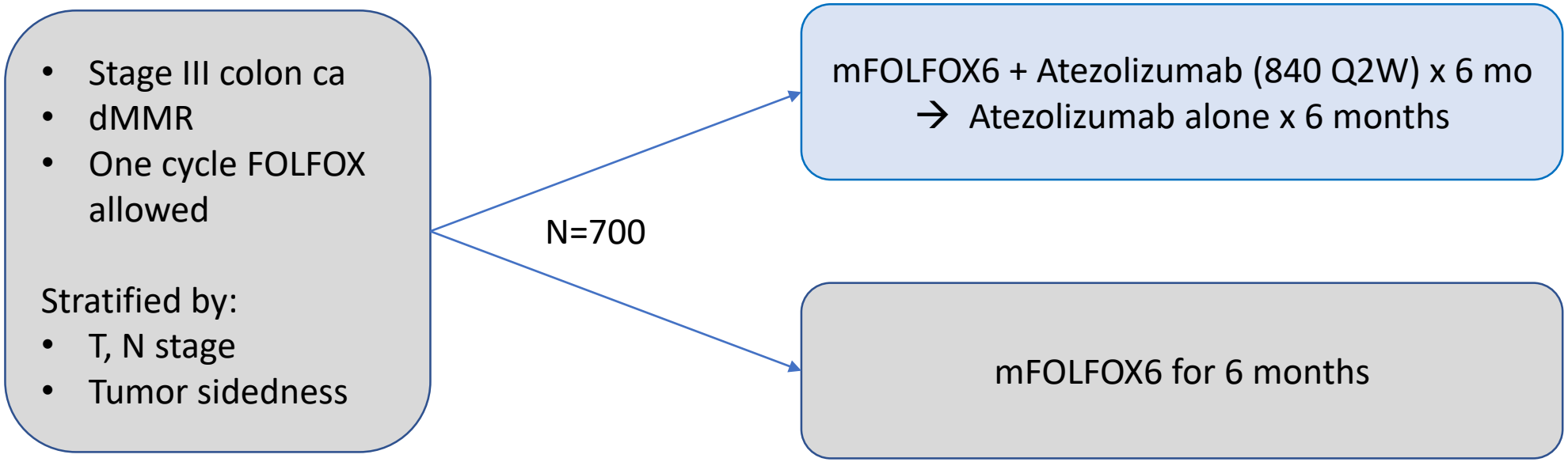
Phase III randomized study of Nivolumab, Nivolumab Plus Ipilimumab, or Investigator's Choice Chemotherapy for the Treatment of Patients With dMMR/ MSI-H Metastatic Colorectal Cancer (CheckMate 8HW) (NCT04008030)



Primary endpoint: Progression-Free Survival (PFS) Nivo v. Ipi/Nivo
Secondary endpoints: PFS Ipi/Nivo v. chemo, ORR, DCR, OS

https://clinicaltrials.gov/ct2/show/NCT04008030

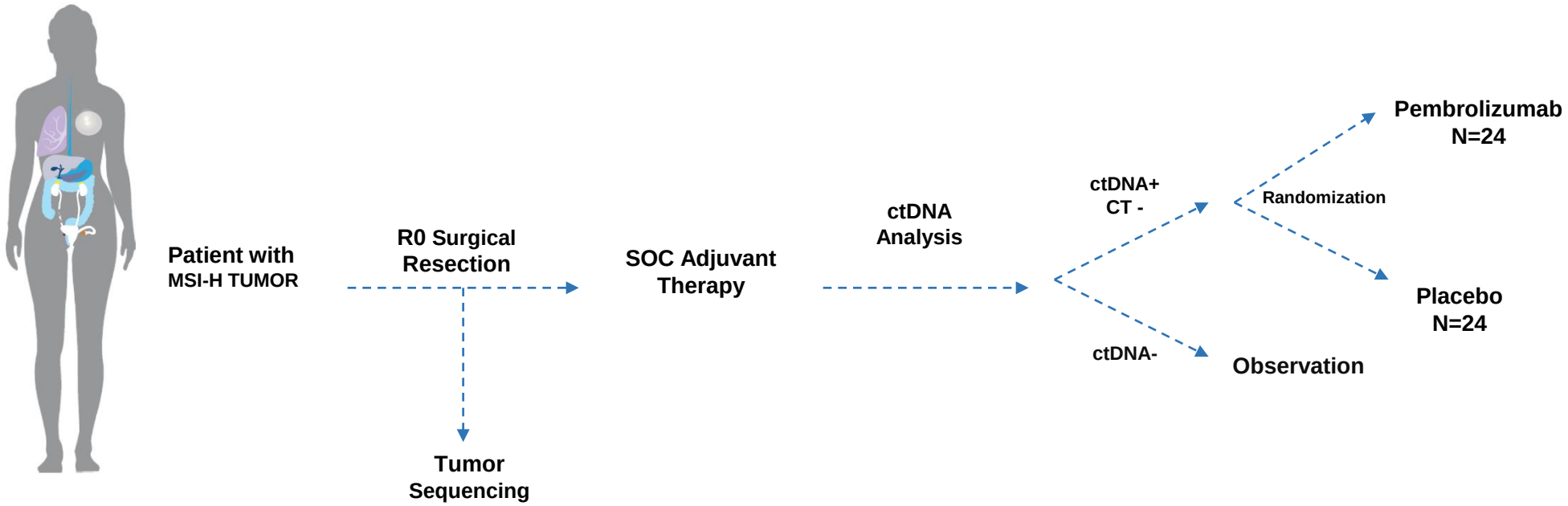
Combination Chemotherapy With or Without Atezolizumab in Treating Patients With Stage III Colon Cancer and Deficient DNA Mismatch Repair (Alliance A021502, NCT02912559)



Primary endpoint: DFS at two-sided alpha of 0.05.
Secondary endpoints: overall survival, treatment tolerability, and quality of life.

https://clinicaltrials.gov/ct2/show/NCT02912559

Study of Pembrolizumab Following Surgery in Patients With Microsatellite Instability High (MSI-H) Solid Tumors (NCT03832569)



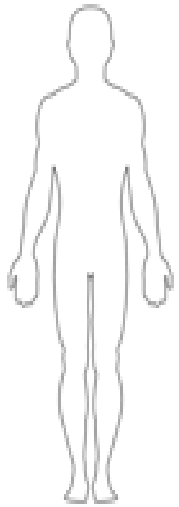
***Year 1 Objective*: To demonstrate clearance of ctDNA at 12 months.**

***Year 2, 3 and 5 Objectives*: To demonstrate improvement in DFS and OS.**

https://clinicaltrials.gov/ct2/show/NCT03832569

Study of Induction PD-1 Blockade in Subjects With Locally Advanced Mismatch Repair Deficient Solid Tumors (NCT04165772) - dostarlimab-gxly

Locally advanced solid tumor, that would be treated with neoadjuvant therapy



TSR042 500mg Q3W

0 — 6 wks. — 3 mos. — 6 mos.

Rectal MRI
PET CT
Endoscopic Exam
ctDNA
Biopsy

Conventional ChemoRT → **Surgery**

Rectal MRI
PET CT
Endoscopic Exam
ctDNA
Biopsy

Endoscopic Exam
Biopsy
ctDNA

Rectal MRI
PET CT
Endoscopic Exam
ctDNA
Biopsy

N=30

Primary endpoint: Pathologic complete response (pCR) or complete clinical response (cCR) at 12 months.

https://clinicaltrials.gov/ct2/show/NCT04165772

Summary

- Immune checkpoint blockade has led to unprecedented benefit in many patients with dMMR/MSI-H tumors

dMMR/MSI-H colorectal cancer

- 'Universal MMR or MSI testing is recommended in all newly diagnosed patients' (NCCN)
- Pembrolizumab, nivolumab +/- ipilimumab may be used as initial or subsequent therapy
- Dostarlimab-gxly may be used as subsequent therapy
- Combination ICI shows higher RR compared to PD-1 blockade alone. Limitation of cross cohort/ trial comparison. Many benefit from PD-1 blockade alone (KN-177: RR 45.1%, CR 13.1%, PFS 16.5 mo)
- Ongoing trials include: Nivolumab +/- ipilimumab, adjuvant, ctDNA+, neo-adjuvant solid tumors

dMMR/MSI-H Tumor agnostic

- Pembrolizumab or dostarlimab-gxly may be considered as subsequent therapy (re. cancer specific guidelines)

Thank you for your attention