XXXIII SIMPOSIO INTERNACIONAL
INTERNATIONAL SYMPOSIUM
11 - 12 DE DICIEMBRE DE 2025
OVIEDO

Inmunoterapia en CCRm dMMR/MSI
Qué opciones y para quien?

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Declaration of Interests

- Consultant or Speaker Role: Novartis, Advanz Pharma, Astellas, Bayer, BMS, Boerhinger, Crinetics, Esteve, GSK, Hutchmed, Ipsen, ITM, MSD, Novocure, PharmaMar, Pierre Fabre, Sanofi, Servier, Takeda

- Research Funding: MSD, Fundación CRIS Contra el Cancer

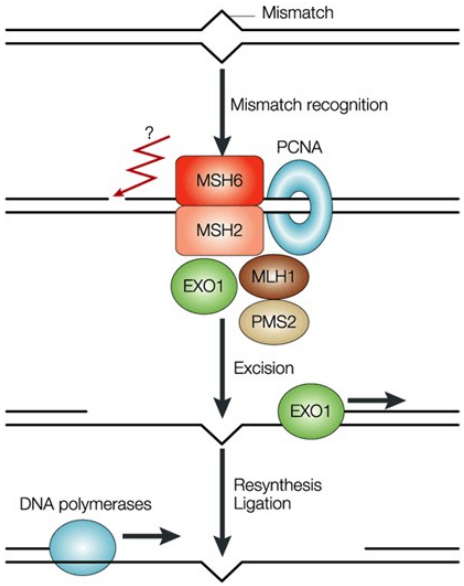
Outline

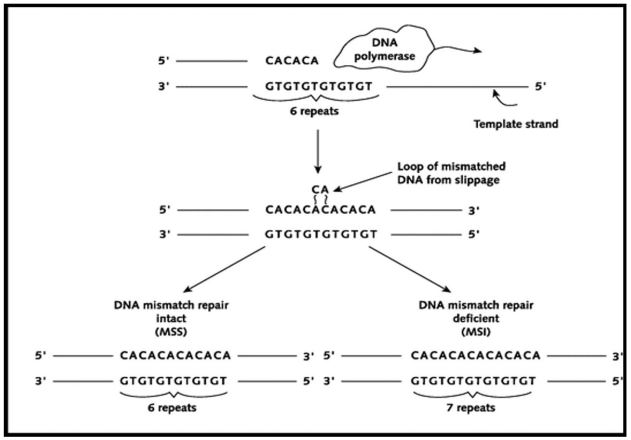
- Proof of concept trials of ICI tumor-agnostic efficacy in dMMR/MSI solid tumors
- Pivotal studies of ICI in dMMR/MSI metastatic CRC
- Dual versus single immune checkpoint blockade
  - ✓ Efficacy
  - ✓ Safety
  - ✓ QoL
  - ✓ Predictive markers?
- Clinical guidelines

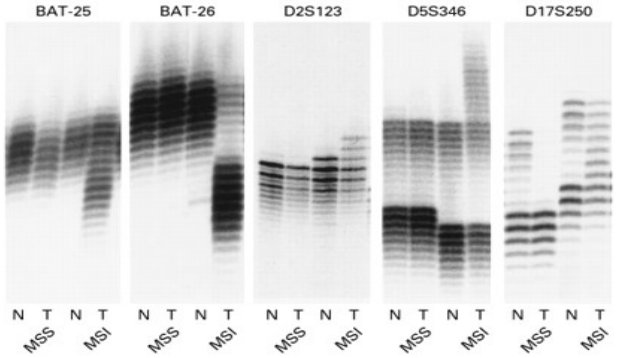
Defficient MMR leads to highly mutated and immunogenic tumors

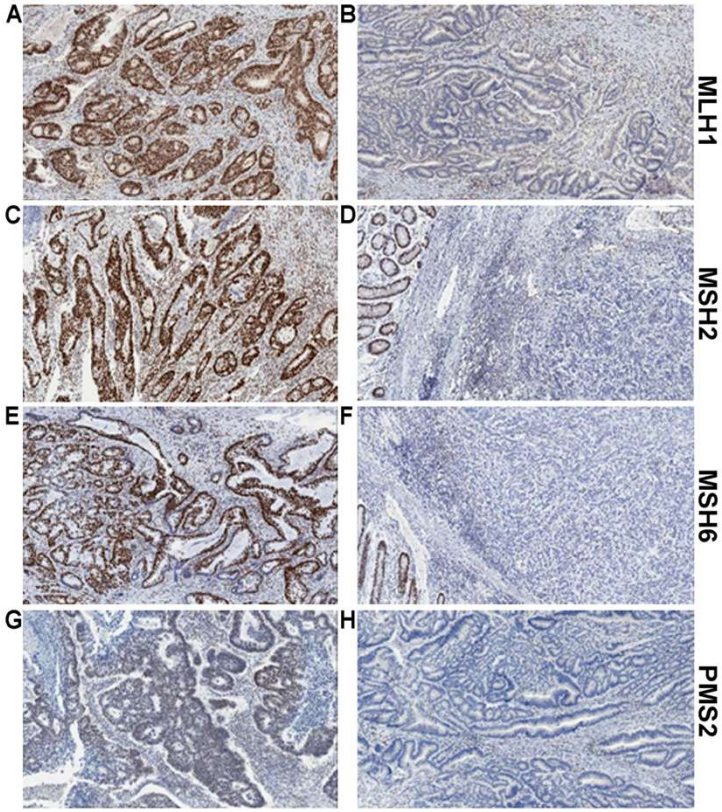
- ✓ dMMR/MSI in CRC: 15% of all cases, 4-7% of mCRC
- ✓ Tumors accumulate thousands of predominantly frameshift mutations that are highly immunogenic

DNA Mismatch Repair









KEYNOTE-16 - Proof of Concept Clinical Trial

FDA granted **tumor agnostic** approval (May 2017)

Colorectal Cancers

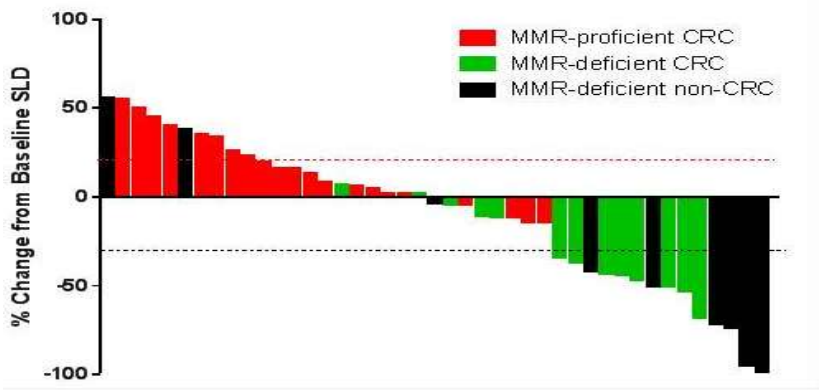
Cohort A
Deficient in Mismatch Repair

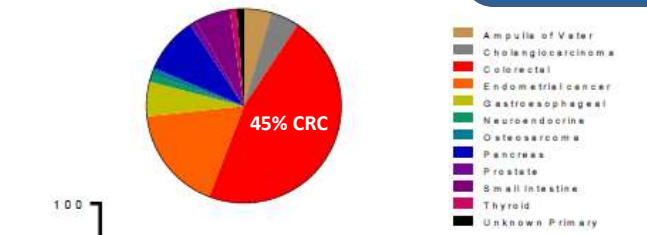
Cohort B
Proficient in Mismatch Repair

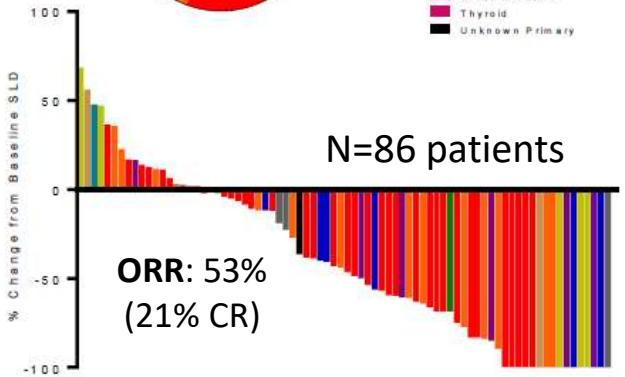
Non-Colorectal Cancers

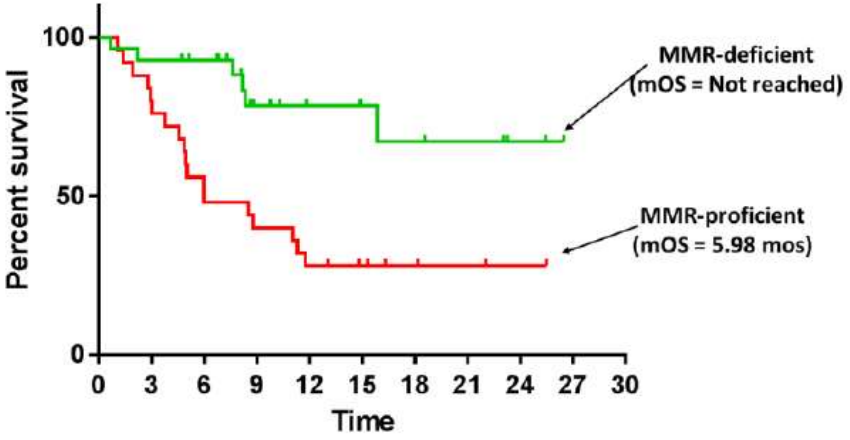
Cohort C
Deficient in Mismatch Repair

	MSI CRC	MSS CRC	MSI non-CRC
N	28 (54% Lynch)	25	10
ORR	**57%**	**0%**	**57%**
DCR	89%	16%	71%









Le D, et al. NEJM 2015, Science 2017

GARNET trial: **Dostarlimab** basket trial in dMMR solid tumors

Antitumor Activity

Primary Endpoint Analysis

Characteristic	Cohort A1 dMMR EC N=141	Cohort F dMMR non-EC solid tumors N=186	Overall dMMR solid tumors N=327[a]
Median follow-up time, mo	27.6	29.8	27.7
Confirmed responses, n	64	80	144
ORR, % (95% CI)	45.4 (37.0–54.0)	43.0 (35.8–50.5)	44.0 (38.6–49.6)
CR, n (%)	22 (15.6)	21 (11.3)	43 (13.1)
PR, n (%)	42 (29.8)	59 (31.7)	101 (30.9)
SD, n (%)	21 (14.9)	26 (14.0)	47 (14.4)
PD, n (%)	51 (36.2)	63 (33.9)	114 (34.9)
NE, n (%)	5 (3.5)	17 (9.1)	22 (6.7)
Disease control rate, % (95% CI)	60.3 (51.7–68.4)	57.0 (49.5–64.2)	58.4 (52.9–63.8)
Response ongoing, n (%)	53 (82.8)	70 (87.5)	123 (85.4)
Duration of response, median (range), mo	NR (1.18+ to 47.21+)	NR (2.76 to 41.49+)	NR (1.18+ to 47.21+)
Duration ≥12 months, n (%)	51 (79.7)	53 (66.3)	104 (72.2)

[a]341 patients were included in the overall safety population. 327 patients had measurable disease at baseline by BICR and ≥6 months of follo
population because they had no measurable disease at baseline by BICR.
BICR, blinded independent central review; CR, complete response; CRC, colorectal cancer; dMMR, mismatch repair deficient; EC, endome
response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

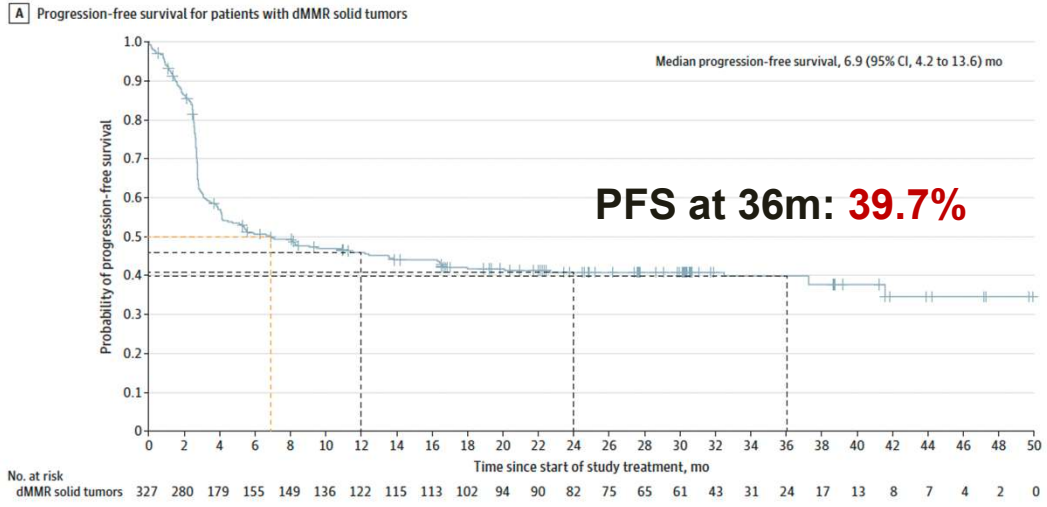
2022 ASCO ANNUAL MEETING #ASCO22

PRESENTED BY:
Thierry André, MD

dMMR CRC Cohort
N=115
ORR 43.5% (12% CR)
mPFS 8.4m, mOS NR

FDA granted **tumor agnostic** approval Aug 2021

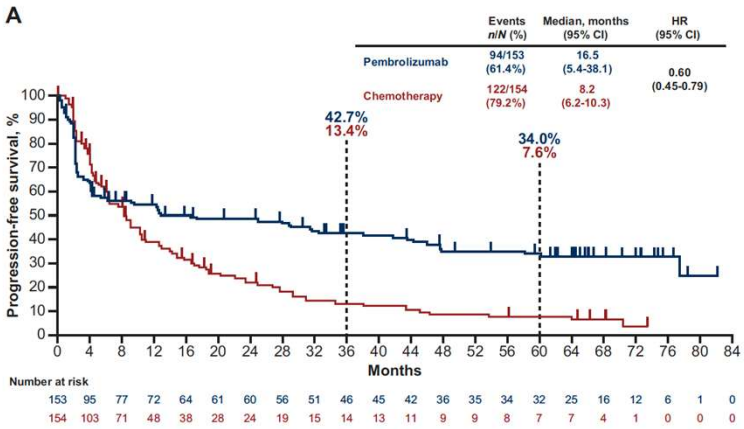
Figure 2. Progression-Free Survival and Overall Survival for Patients With Mismatch Repair Deficient (dMMR) Solid Tumors



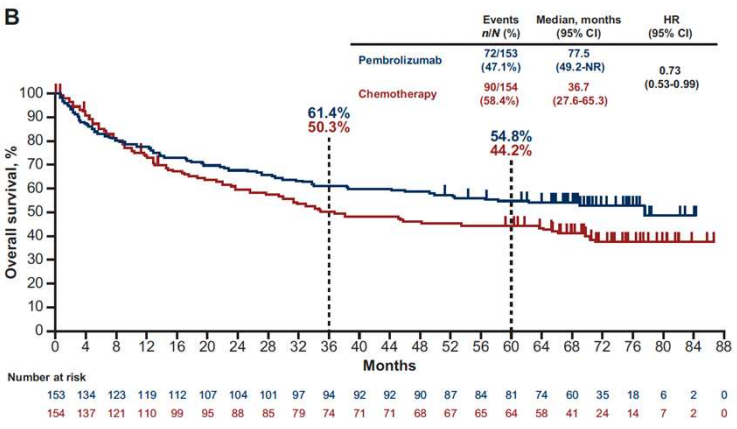
Andre T et al, JAMA Network Open 2023

KEYNOTE-177: 1L Pembrolizumab vs CT +/- MAb (INV choice) in MSI mCRC

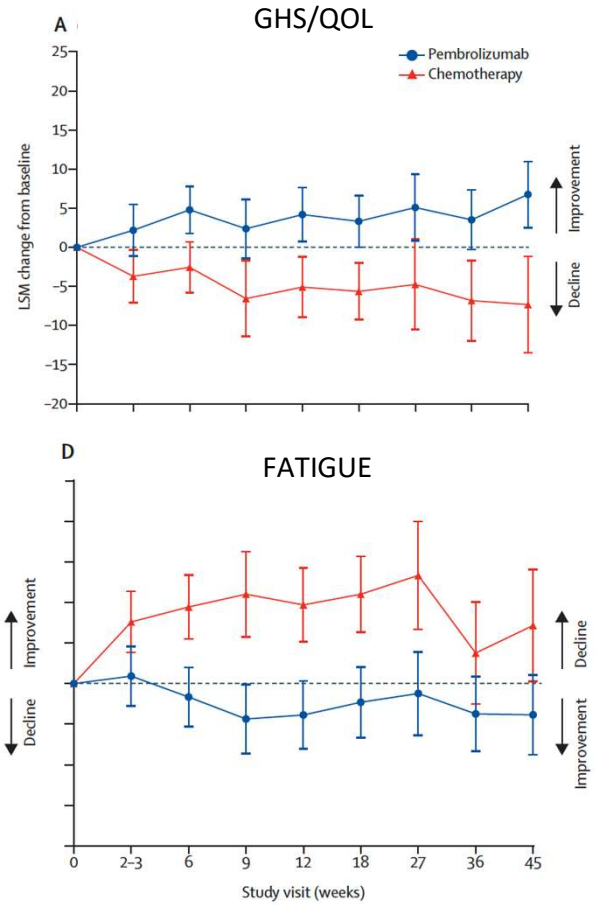
Progression-Free Survival



Overall Survival



HR-QoL



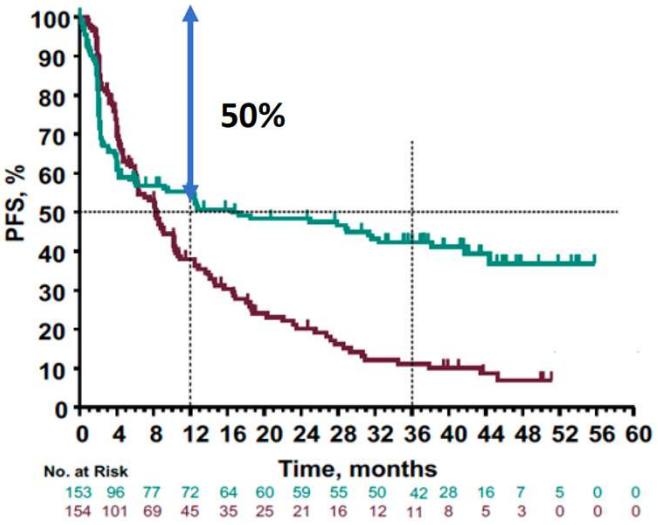
- ✓ Long-term improvement in PFS (34% vs 8% progression-free at 5y)
- ✓ Strong trend towards improved OS (▲10%) despite >60% crossover
- ✓ Lower toxicity (22% vs 67% G3-5 AEs) and improved QoL

Andre T, NEJM 2020 & Lancet 2021 & Ann Oncol 2025; Diaz L, Lancet 2022

How can we overcome resistance?

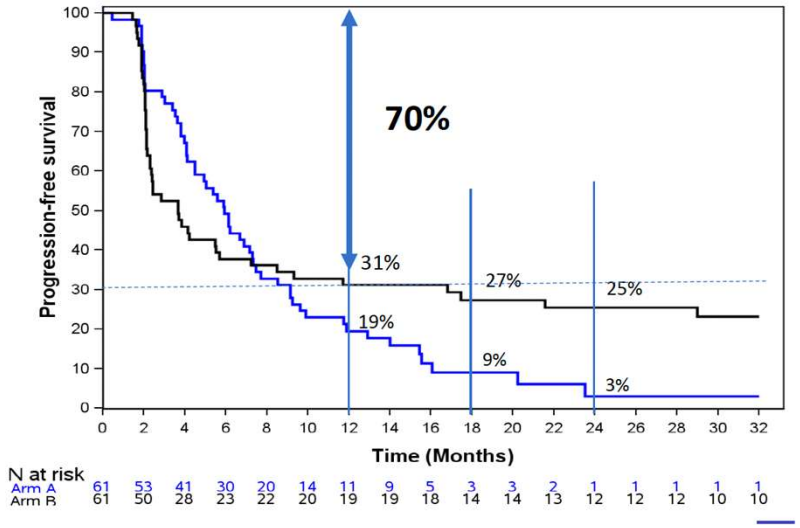
KEYNOTE 177

First line Pembrolizumab



PRODIGE 54-SAMCO

2nd-line Avelumab



Addition of:

- ✓ Anti-CTLA4
- ✓ CT +/- MAbs
- ✓ Targeted Ther
- ✓ Other ICI

Reasons for early PD (29% Pembro vs 12% CT):

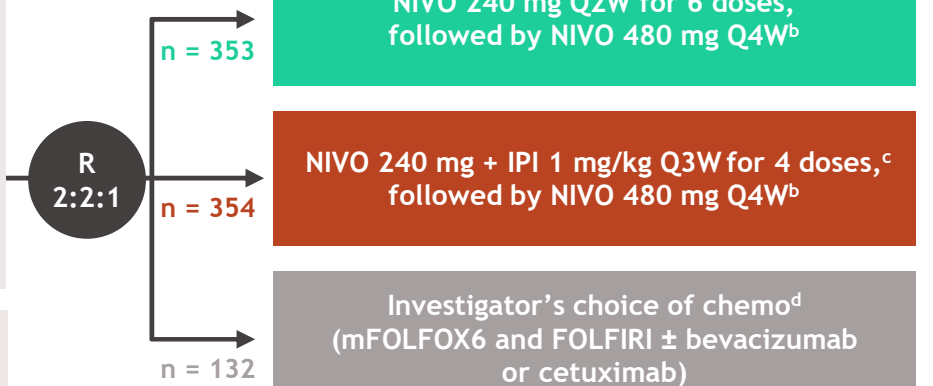
- ✓ Mis-diagnosis (or missinterpretation of IHC)
- ✓ Pseudo-PD
- ✓ True primary resistance

Study design: CheckMate 8HW

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

Key eligibility criteria:
- Histologically confirmed unresectable or metastatic CRC
- MSI-H/dMMR status by local testing
- Immunotherapy-naïve
- 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[e]:
- PFS by BICR[f] (NIVO + IPI vs chemo in 1L)
- PFS by BICR[f] (NIVO + IPI vs NIVO across all lines)

Secondary endpoints in patients with centrally confirmed MSI-H/dMMR status[e]:
- PFS by BICR[f] (NIVO + IPI vs NIVO in 1L)
- ORR by BICR[f] (NIVO + IPI vs NIVO in 1L)
- OS (NIVO + IPI vs NIVO across all lines)
- ORR by BICR[f] (NIVO + IPI vs NIVO across all lines)

Other key endpoints in 1L treated patients
- Safety

[a]ClinicalTrials.gov. NCT04008030. [b]Patients with ≥ 2 prior lines are randomized only to the NIVO or NIVO + IPI arms. [c]Patients can continue NIVO treatment upon early IPI discontinuation. [d]Patients receiving investigator's choice of chemo are eligible to receive NIVO + IPI upon progression (crossover treatment). [e]Confirmed using either immunohistochemistry and/or polymerase chain reaction-based tests. [f]Evaluated using RECIST v1.1. [g]Time between randomization and data cutoff across all 3 treatment arms. [h]Median follow-up was 55.1 (range 24.7-68.5) months in all lines.

Baseline characteristics

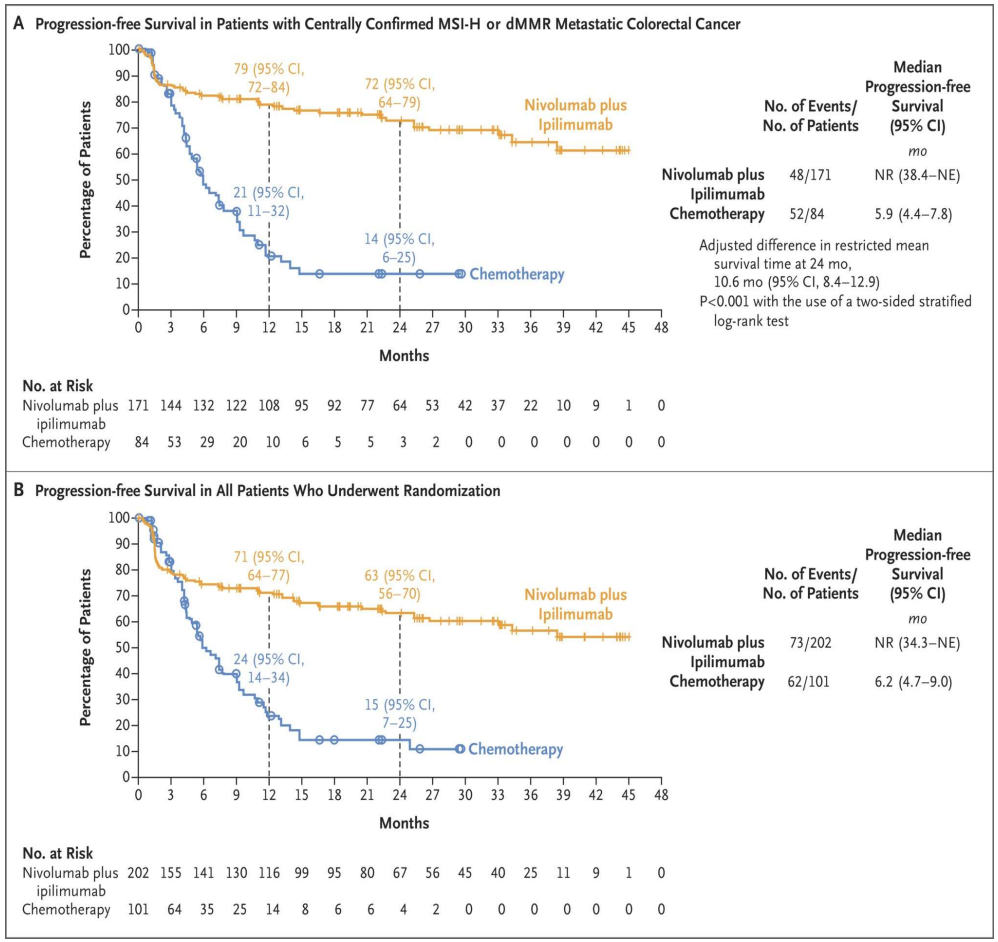
Characteristic (all randomized patients)	Category	NIVO + IPI (n = 354)	NIVO (n = 353)	Chemo (n = 132)
Age	Median (range), years	62 (21-86)	63 (20-87)	65 (26-87)
Sex	Female	192 (54)	163 (46)	68 (52)
	Male	162 (46)	190 (54)	64 (48)
Region	US/Canada/Europe	251 (71)	246 (70)	95 (72)
	Asia	26 (7)	33 (9)	13 (10)
	Rest of world	77 (22)	74 (21)	24 (18)
ECOG PS	0	192 (54)	183 (52)	61 (46)
Number of prior lines of therapy per IRT	0	202 (57)	201 (57)	101 (77)
	1	67 (19)	67 (19)	31 (23)
	≥ 2	85 (24)	85 (24)	0
Tumor sidedness	Right	244 (69)	244 (69)	89 (67)
Sites of metastases[a-c]	Liver	140 (40)	149 (42)	57 (43)
	Peritoneum	143 (40)	126 (36)	59 (45)
Centrally confirmed MSI-H/dMMR status	Yes	296 (84)	286 (81)	113 (86)
	No	58 (16)	67 (19)	19 (14)
	MSS and pMMR	41 (12)	40 (11)	13 (10)
	MSS or pMMR[d]	8 (2)	10 (3)	0
	Not available[e]	9 (3)	17 (5)	6 (5)
BRAF, *KRAS*, *NRAS* mutation status[f,g]	*BRAF*/*KRAS*/*NRAS* all wild type	83 (23)	103 (29)	34 (26)
	BRAF mutant	106 (30)	85 (24)	34 (26)
	KRAS or *NRAS* mutant	83 (23)	89 (25)	31 (23)
	Unknown	73 (21)	74 (21)	31 (23)

Data are shown as n (%) unless otherwise noted. [a]Per BICR. [b]Patients may have had more than 1 site of metastasis. [c]Sites of metastases not reported: NIVO + IPI, n = 3; NIVO, n = 2; chemo = 1. [d]Patients with either centrally confirmed MSS tumors that could not be evaluated or were not tested for MMR status or centrally confirmed pMMR tumors that could not be evaluated or were not tested for MSI status. [e]Patients with tumors that could not be evaluated or were not tested centrally for both MSI and MMR status. [f]Percentages may not add up to 100% due to rounding. [g]*BRAF* and *KRAS*/*NRAS* mutant: NIVO + IPI, n = 9; NIVO, n = 2; chemo, n = 2.

Lenz H-J, ASCO 2025

Primary Endpoint: NIVO + IPI vs Chemotherapy in the 1L setting

PFS by BICR in centrally confirmed dMMR/MSI mCRC

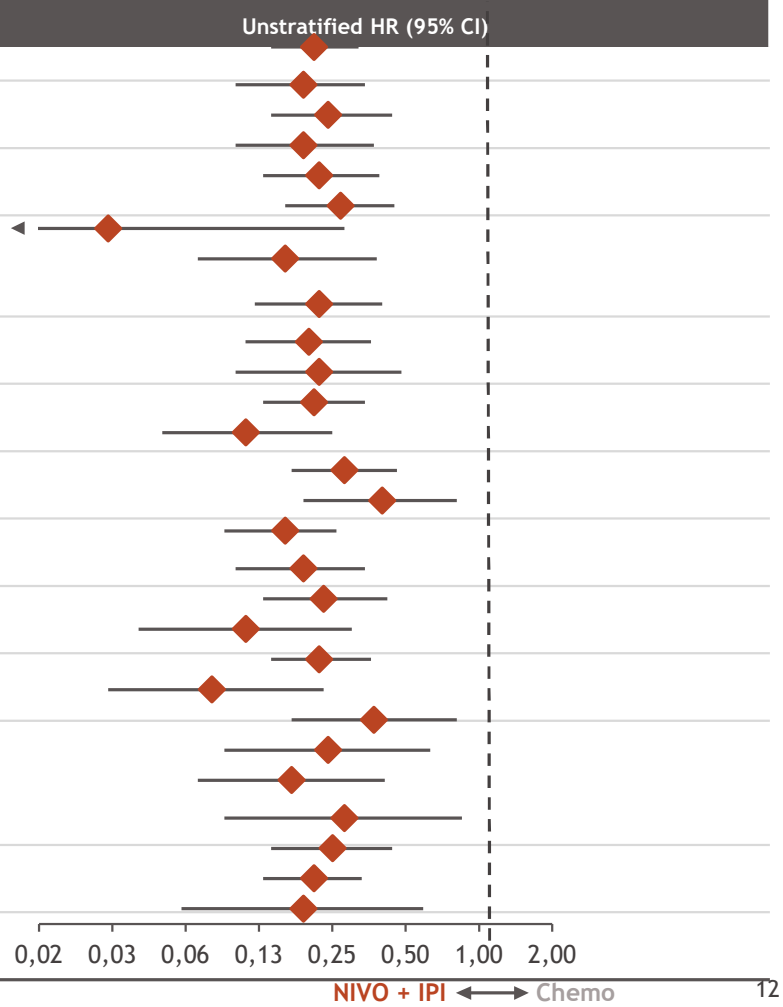


1L all treated patients	NIVO + IPI (n = 200)		Chemo (n = 88)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
TRAEs,[a] n (%)				
Any TRAEs	160 (80)	46 (23)	83 (94)	42 (48)
Serious TRAEs	38 (19)	32 (16)	17 (19)	14 (16)
TRAEs leading to discontinuation	33 (17)	23 (12)	28 (32)	9 (10)
Treatment-related deaths, n (%)	2 (1)		0 (0)[b]	
IMAEs,[c] 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

Andre T, ASCO GI 2024, NEJM 2024

Progression-free survival subgroup analysis

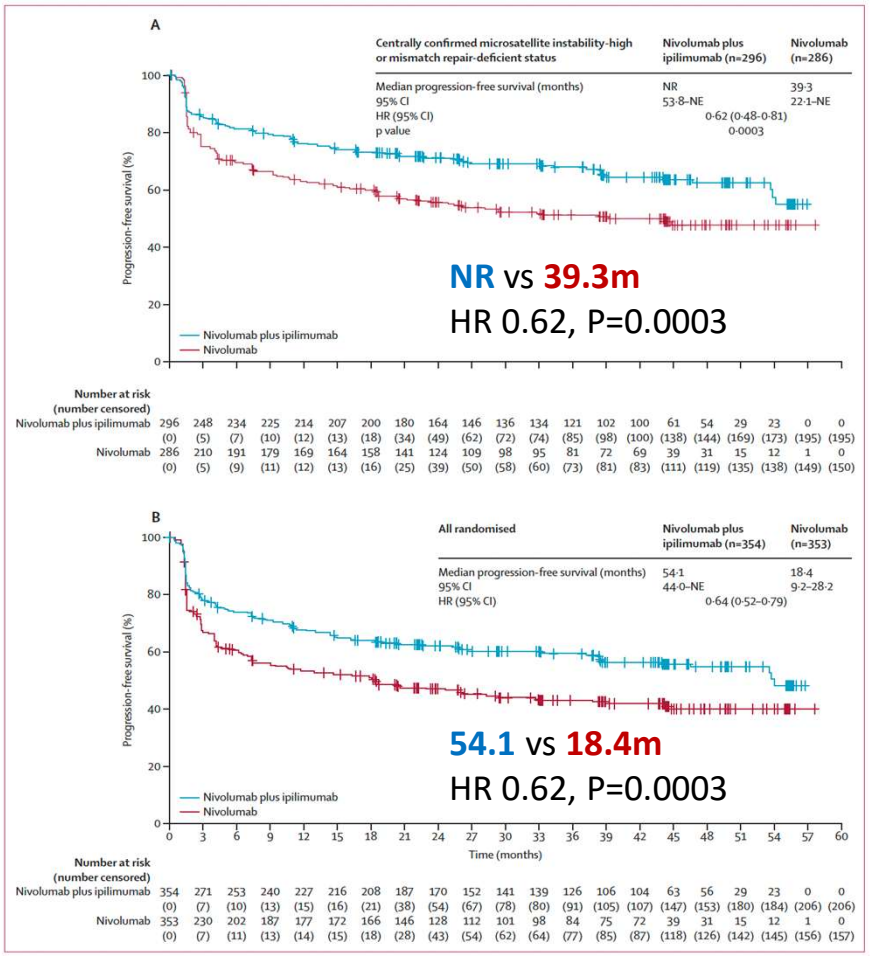
Category (1L centrally-confirmed MSI-H/dMMR)	Subgroup	Median PFS,[a] months		Unstratified HR
		NIVO + IPI	Chemo	
Overall (N = 255)		NR	5.9	0.21
Age, years	< 65 (n = 138)	NR	5.7	0.19
	≥ 65 (n = 117)	NR	5.9	0.24
Sex	Male (n = 117)	NR	5.9	0.19
	Female (n = 138)	NR	6.2	0.22
Region	US/Canada/Europe (n = 167)	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
Prior surgery	Yes (n = 222)	NR	7.1	0.21
	No (n = 33)	NR	3.0	0.19

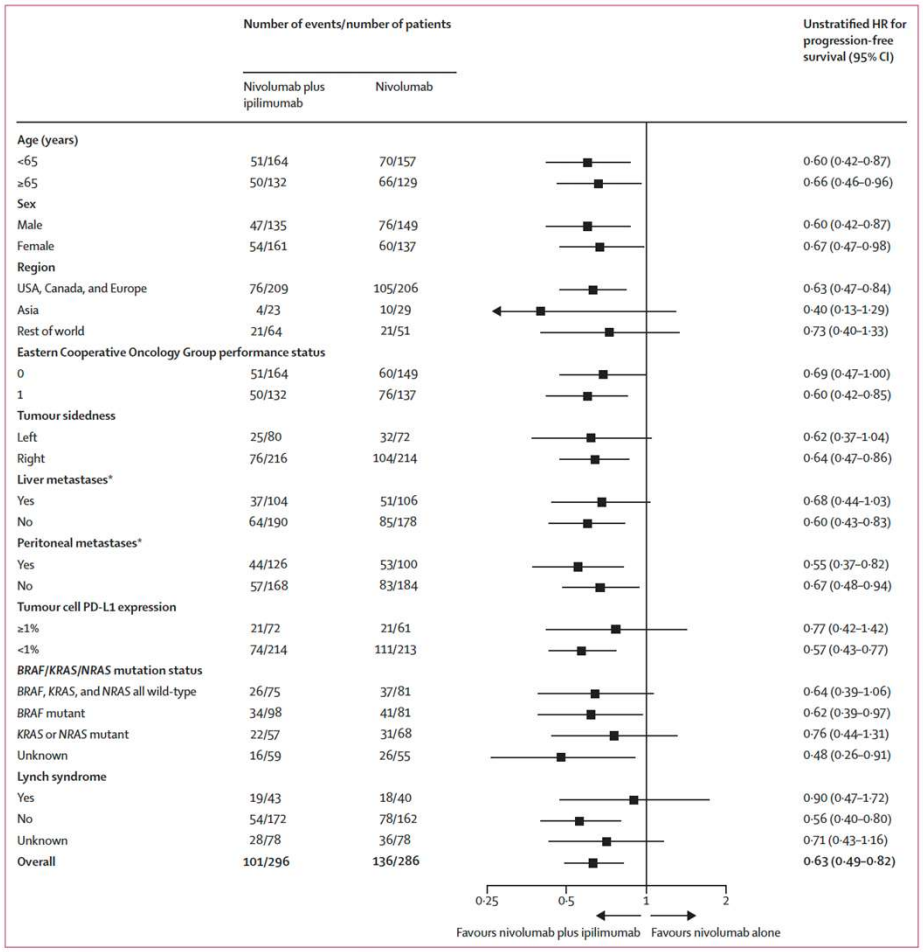


HRs not computed for subgroups with less than 10 patients per treatment arm. [a]Per BICR.

Primary Endpoint: NIVO + IPI vs Nivolumab across all lines

PFS by BICR in centrally confirmed dMMR/MSI mCRC

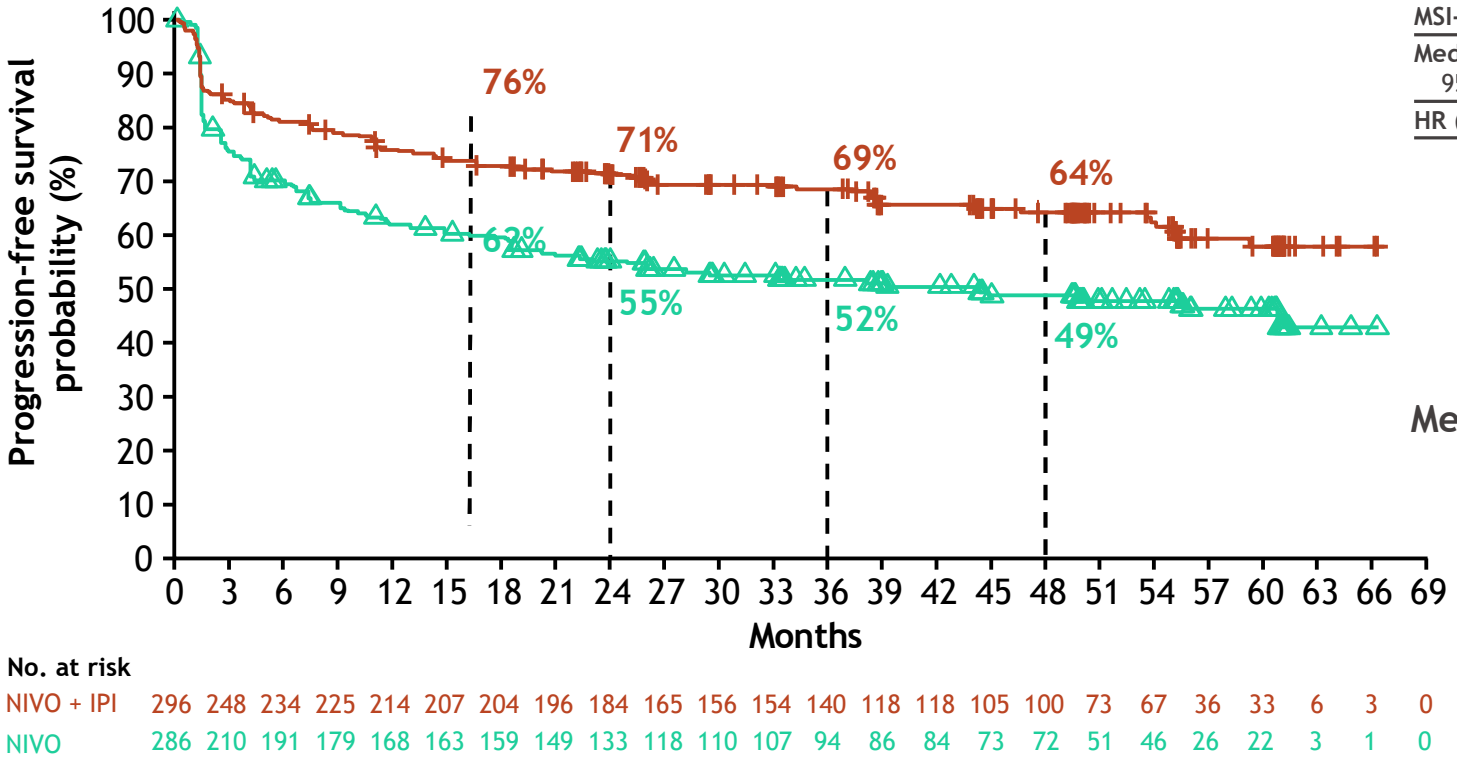




Andre T, ASCO GI 2025, Lancet 2025

At data cutoff (Aug 2024), median follow-up was 47 months

Updated PFS (BICR): NIVO + IPI vs NIVO across all lines in centrally confirmed dMMR/MSI patients



Centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 296)	NIVO (n = 286)
Median PFS[a], mo	NR	44.3
95% CI	NE-NE	22.1-NE
HR (95% CI)	0.62 (0.48-0.80)	

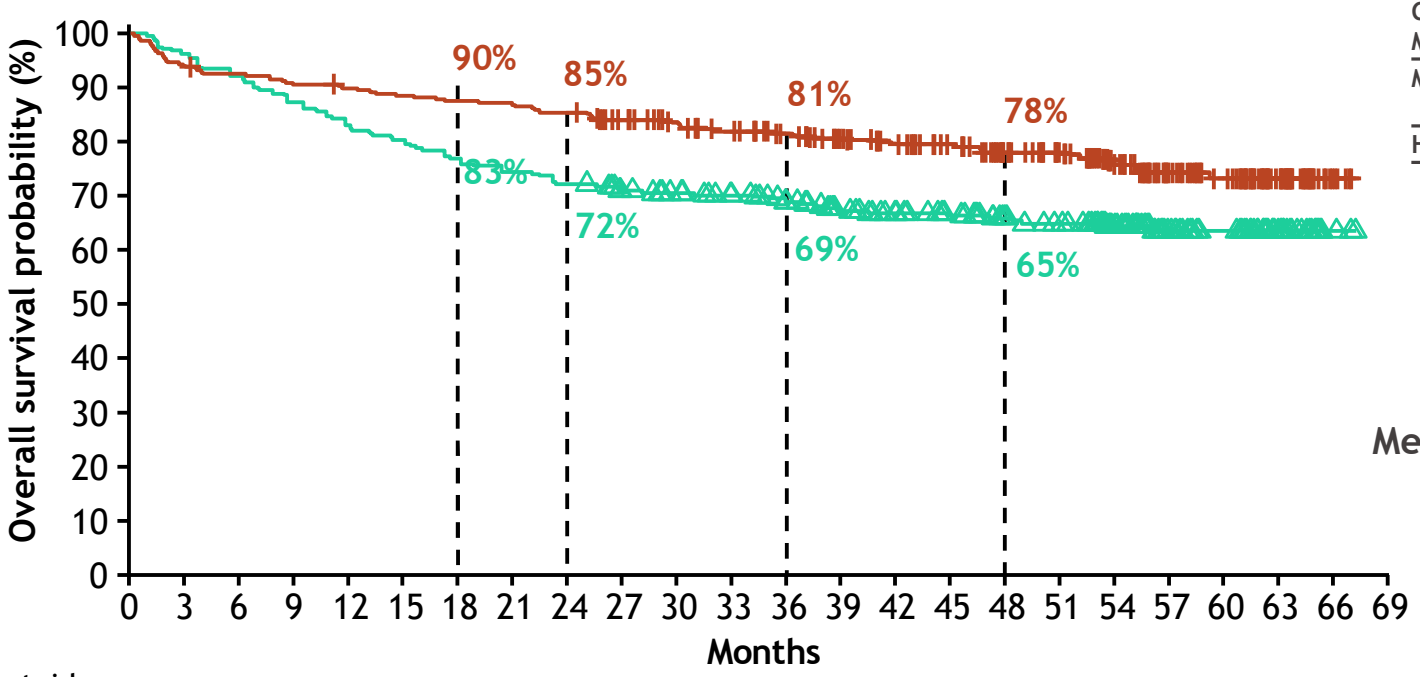
ORR: 73% vs 61%

Median follow-up: 55.1 months

- In patients with centrally confirmed MSI-H/dMMR mCRC, NIVO + IPI continued to demonstrated clinically meaningful improvements in PFS vs NIVO across all lines (HR 0.62, [95% CI 0.48-0.80])
  - These data are consistent with those observed in the all randomized population by local testing (HR 0.63, [95% CI 0.51-0.78])

Lonardi S, ESMO 2025

OS: NIVO + IPI vs NIVO across all lines in centrally confirmed patients



Centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 296)	NIVO (n = 286)
Median OS, mo	NR	NR
95% CI	NE-NE	NE-NE
HR (95% CI)	0.61 (0.45-0.83)	

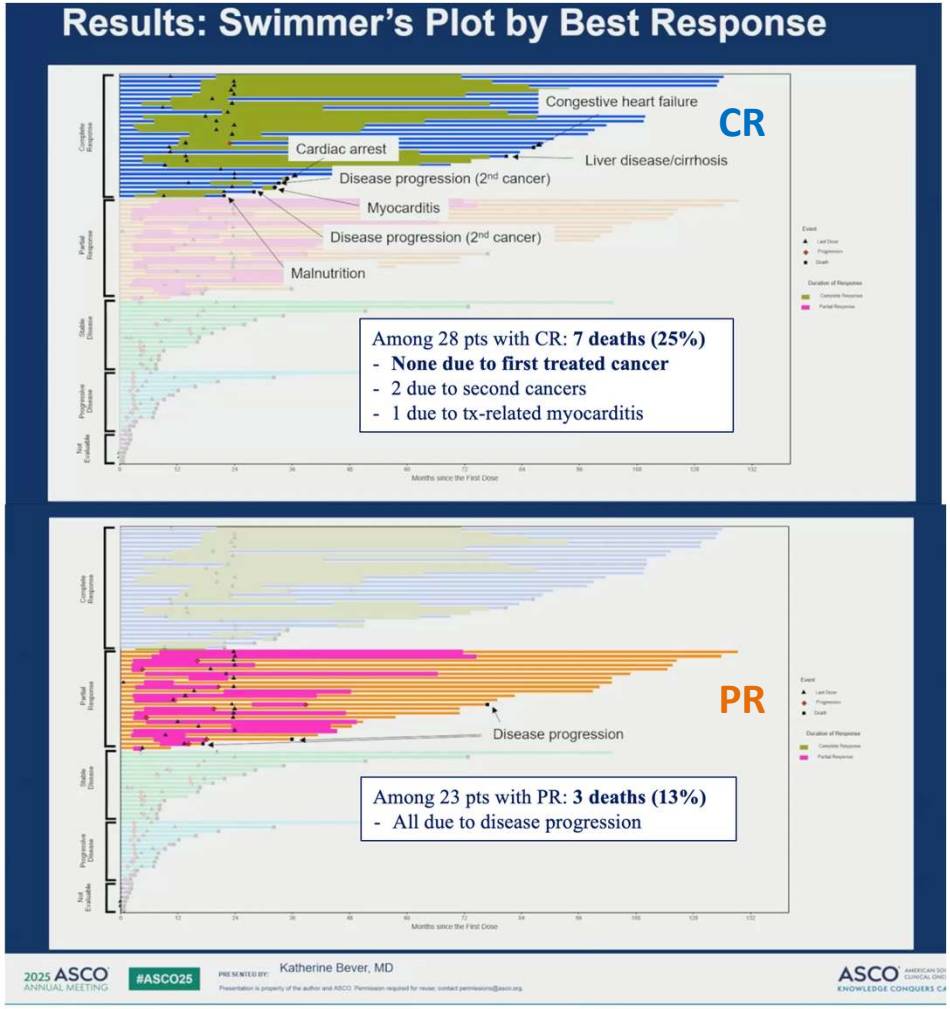
Median follow-up: 55.1 months

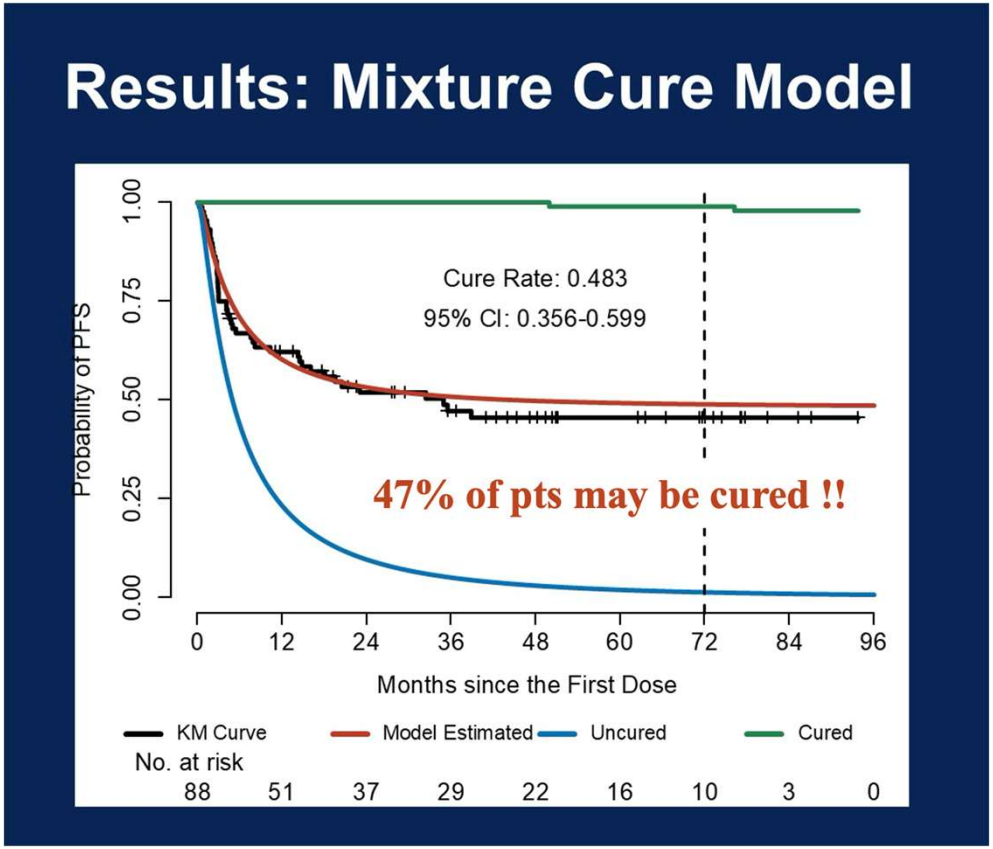
- In patients with centrally confirmed MSI-H/dMMR mCRC, descriptive analyses indicated that OS favored NIVO + IPI vs NIVO across all lines (HR 0.61, [95% CI 0.45-0.83])
  - With ~69% of expected events observed (168 of ~243 expected deaths), OS data remain immature

At this interim analysis, only a small alpha was allocated to this endpoint and the threshold was very high (statistical boundary for significance, 0.0007).

Lonardi S, ESMO 2025

Pembrolizumab in dMMR/MSI tumors: 10-Years of Follow-Up





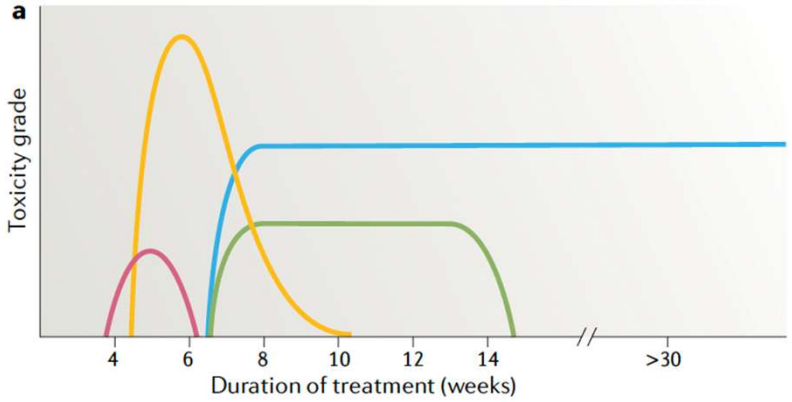
- ✓ PD after 2 years was rare (2/88 pts (2.3%))
- ✓ 4 trAEs occurred after 2 years (one G5 – myocarditis)

Bever K et al, ASCO 2025

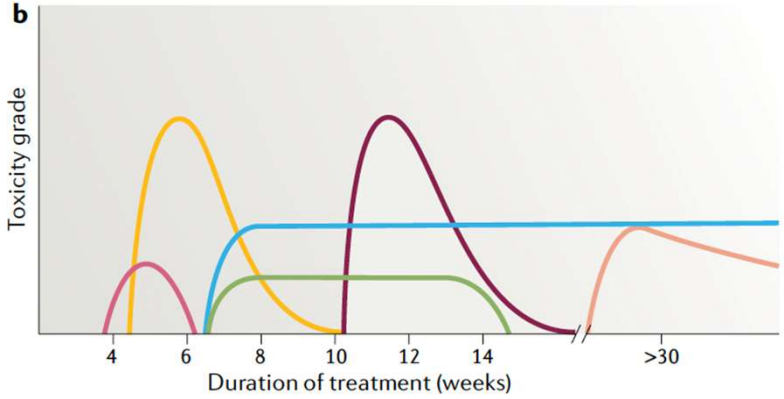

BENEFIT
RISK

Kinetics of main immune-related AEs

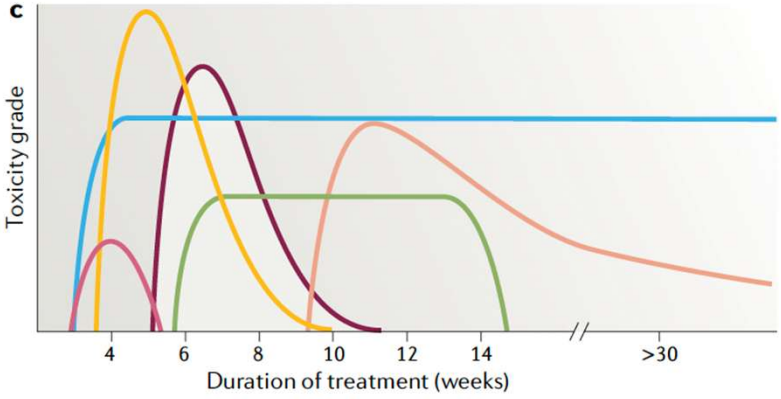
Ipilimumab

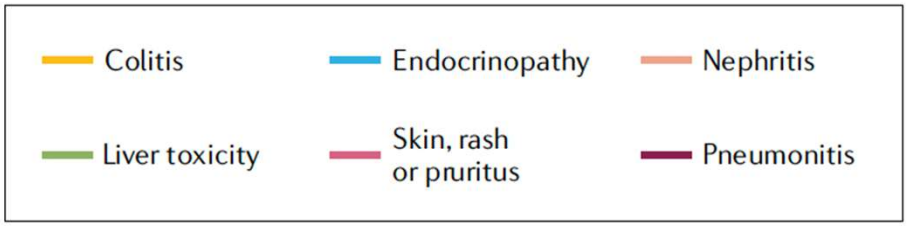


Anti-PD1/PDL1



Anti-PD1/PDL1 + Ipilimumab





Martis F, Nature Rev Clin Oncol 2019

Safety of NIVO + IPI vs NIVO (all lines)

All treated patients, n (%)	NIVO + IPI (n = 352)		NIVO (n = 351)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
TRAEs[a]				
Any TRAEs	285 (81)	**78 (22)**	249 (71)	**50 (14)**
Serious TRAEs	65 (18)	55 (16)	29 (8)	24 (7)
TRAEs leading to discontinuation[b]	48 (14)	**33 (9)**	21 (6)	**14 (4)**
Treatment-related deaths[c]	2 (< 1)[d]		1 (< 1)[e]	
TRAEs[a] reported in ≥ 10% of patients				
Pruritus	**91 (26)**	0	**63 (18)**	0
Diarrhea	71 (20)	3 (< 1)	59 (17)	2 (< 1)
Hypothyroidism	**61 (17)**	2 (< 1)	**31 (9)**	0
Asthenia	58 (16)	2 (< 1)	44 (13)	2 (< 1)
Fatigue	42 (12)	1 (< 1)	35 (10)	1 (< 1)
Hyperthyroidism	**40 (11)**	0	**16 (5)**	0
Arthralgia	**38 (11)**	1 (< 1)	**23 (7)**	0
Rash	34 (10)	3 (< 1)	29 (8)	1 (< 1)
Adrenal insufficiency	**34 (10)**	8 (2)	**12 (3)**	3 (< 1)

[a]Includes events reported between first dose and 30 days after last dose of study therapy. [b]Discontinuation of any component of the combination regimen was counted as a drug discontinuation event. [c]Treatment-related deaths were reported regardless of timeframe. [d]Includes 1 event each of myocarditis and pneumonitis. No new treatment-related deaths were reported since the previous interim analysis. [e]One event of pneumonitis.

André T et al . Presented at ASCO-GI 2025


happiness
employment
quality of life
quality
health
lifestyle
success
family
environment
well-being
healthcare
satisfaction
leisure
life
education
society
finance
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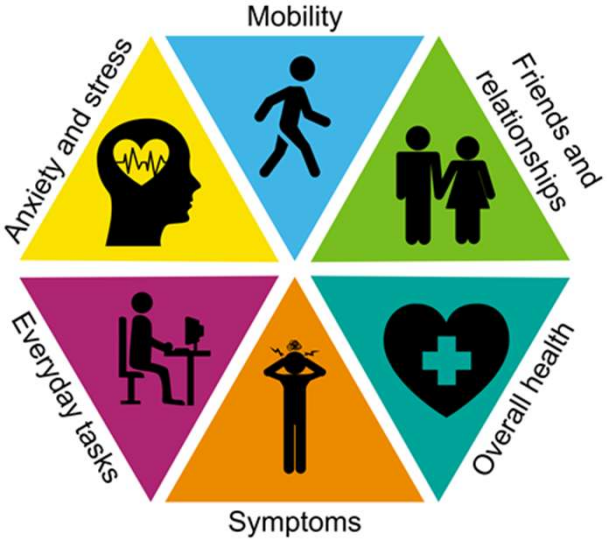
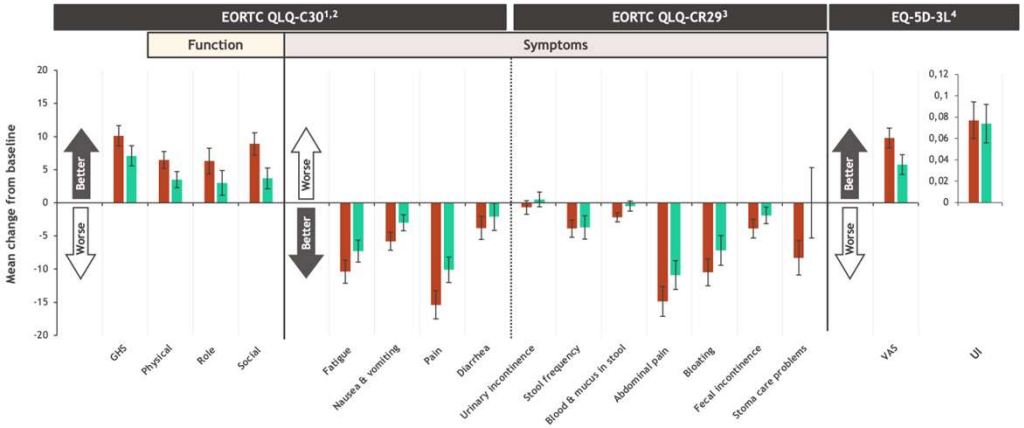
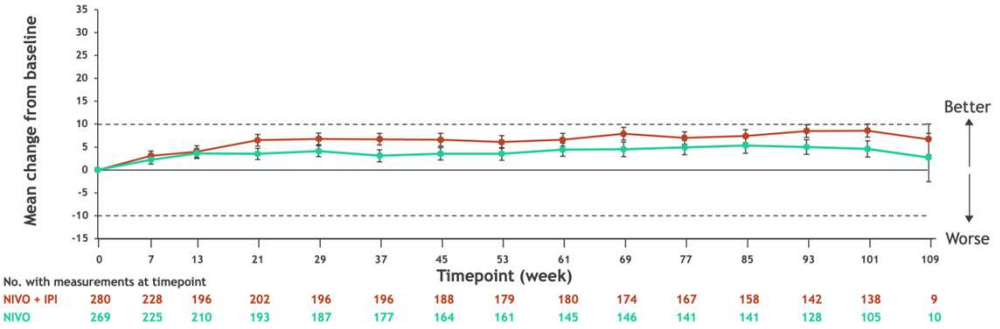

Mobility
Anxiety and stress
Friends and relationships
Everyday tasks
Overall health
Symptoms

CM8HW HR-QoL of NIVO-IPI vs NIVO across all lines

Summary of mean changes from baseline at week 21



Mean change from baseline in QLQ-C30: Physical functioning

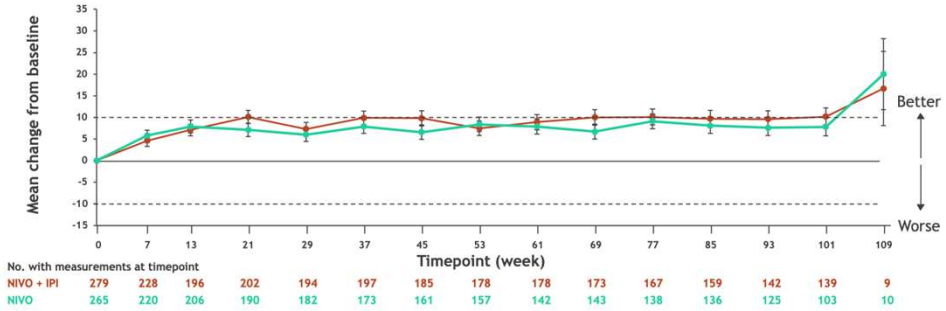


No. with measurements at timepoint

NIVO + IPI	280	228	196	202	196	196	188	179	180	174	167	158	142	138	9
NIVO	269	225	210	193	187	177	164	161	145	146	141	141	128	105	10

- In both treatment arms, physical functioning scores showed a trend for improvement starting week 7

Mean change from baseline in QLQ-C30: Global Health Status

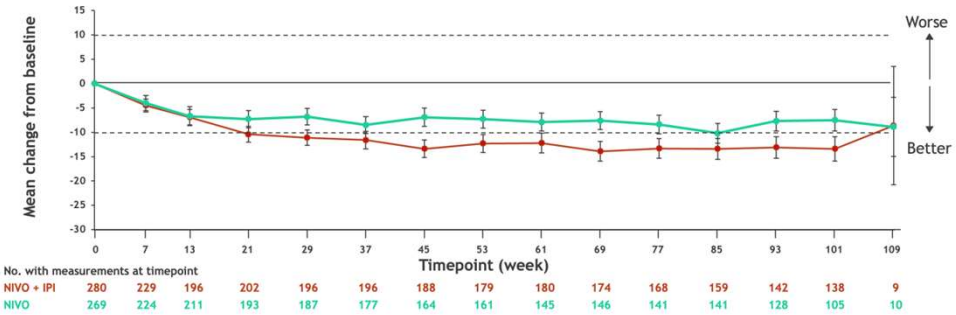


No. with measurements at timepoint

NIVO + IPI	279	228	196	202	194	197	185	178	178	173	167	159	142	139	9
NIVO	265	220	206	190	182	173	161	157	142	143	138	136	125	103	10

- In both treatment arms, GHS scores showed a trend for improvement starting week 7
  - Patients in the NIVO + IPI arm exceeded the minimally important change from baseline starting at week 21

Mean change from baseline in QLQ-C30: Fatigue



No. with measurements at timepoint

NIVO + IPI	280	229	196	202	196	196	188	179	180	174	168	159	142	138	9
NIVO	269	224	211	193	187	177	164	161	145	146	141	141	128	105	10

- In both treatment arms, fatigue scores showed a trend for improvement starting week 7
  - Patients in the NIVO + IPI arm exceeded the minimally important change from baseline starting at week 21
  - Patients in the NIVO arm exceeded the minimally important change from baseline starting at week 85

■ NIVO + IPI ■ NIVO

Elez E, ESMO GI 2025

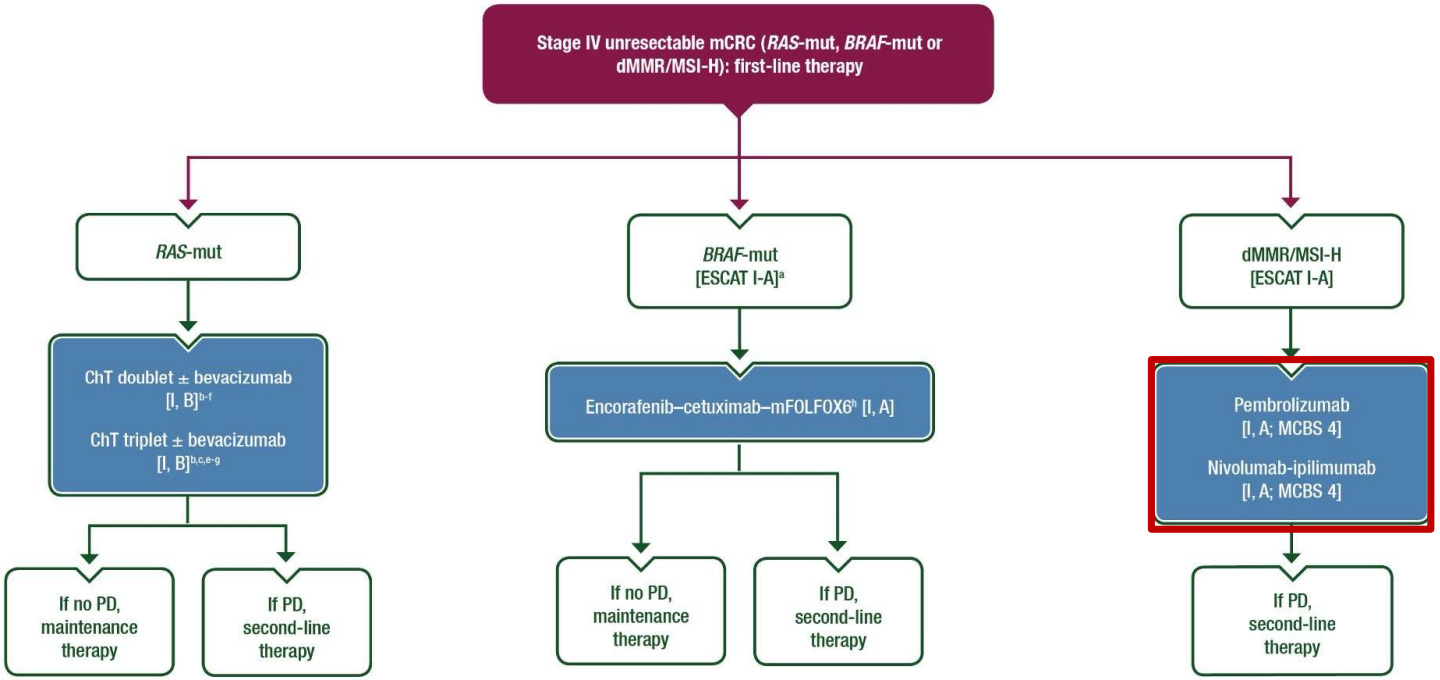
CLINICAL PRACTICE GUIDELINES

ESMO Metastatic Colorectal Cancer Living Guideline
v1.3 July 2025

First-line Therapy

RAS-mut, *BRAF*-mut or dMMR/MSI-H

[a]For patients with *BRAF*-mutated tumours who are also dMMR, first-line immunotherapy is recommended [I, A].
[b]In patients presenting with cardiotoxicity and/or hand-foot syndrome on 5-FU or capecitabine-based ChT, S-1 may be used as an alternative [III, B].
[c]Additional details on treatments and drug combinations can be found under the section 'Management of advanced and metastatic disease without potential conversion' (subsections 'First-line treatment' and 'Second-line treatment').
[d]FOLFIRI–cetuximab ESMO-MCBS v2.0 score: 4; FOLFOX4–panitumumab ESMO-MCBS v2.0 score: 4.
[e]In a very selected population.
[f]CAPOX– or FOLFOX4–bevacizumab ESMO-MCBS v2.0 score: 1.
[g]A triplet with FOLFOXIRI plus bevacizumab is an option for selected patients with good PS and without comorbidities [I, B; ESMO-MCBS v2.0 score: 2].
[h]FDA approved, not EMA approved. If FOLFOX–encorafenib–cetuximab is not possible, FOLFOX–bevacizumab [II, B] or FOLFOXIRI–bevacizumab [II, B] could be recommended.



Predictive markers?

Is there any subgroup that should be treated with anti-PD1 alone?

- Clinical factors:
  - ✓ Pts at higher risk of irAEs (past history of autoimmune disorders)
  - ✓ Elderly, frail, other comorbidities?
  - ✓ Low tumor burden, no tumor-related symptoms?
- dMMR/MSI subtypes
  - ✓ Type of MMR deficiency? (Lynch vs sporadic, mutated protein)
  - ✓ RAS/BRAF mutational profile?
- Immune biomarkers?

Predictive markers - type of MMR defficiency?

- ✓ 3301 dMMR/MSI CRC tumors were profiled by IHC and NGS
- ✓ Real world OS was extracted from insurance claims and calculated from first treatment with ICIs
- ✓ **OS with Ipi/Nivo > Pembro in MLH1/PMS2 co-loss due to hypermethylation (sporadic MSI) and PMS2 loss only**

Figure 2: Median Overall survival (ICI-treatment to last contact) in dMMR CRC patients (Ipilimumab/Nivolumab vs. Pembrolizumab)

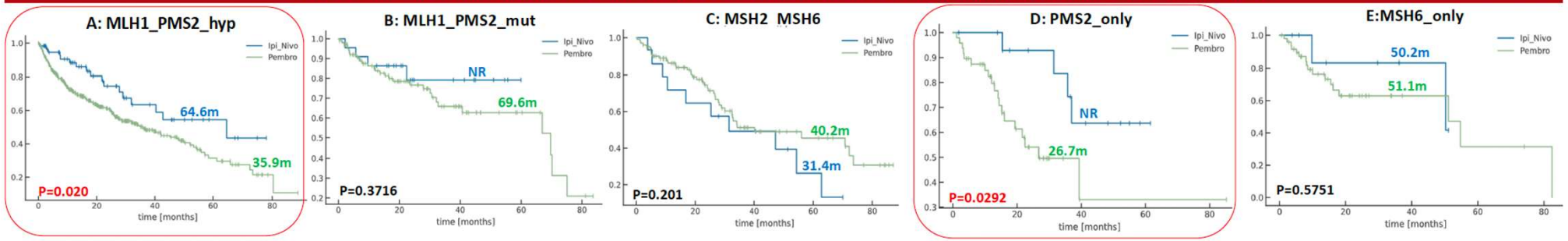


Figure2: The median OS in patients with MLH1_PMS2_hyp **(Fig 2A)**, MLH1_PMS2_mut **(Fig 2B)**, MSH2_MSH6 **(Fig 2C)**, PMS2_only **(Fig 2D)** and MSH6_only **(Fig 2E)** treated with Ipi/Nivo vs. Pembrolizumab was 64.6m vs.35.9m (p=0.020), NR vs. 69.6m (p=0.3716), 40.2m vs. 31.4m (p=0.201), NR vs. 26.7m (p=0.0292) and 50.2m vs. 51.1 (p=0.5751) respectively.

CM 8HW – PFS Nivolumab-Ipilimumab vs Chemotherapy

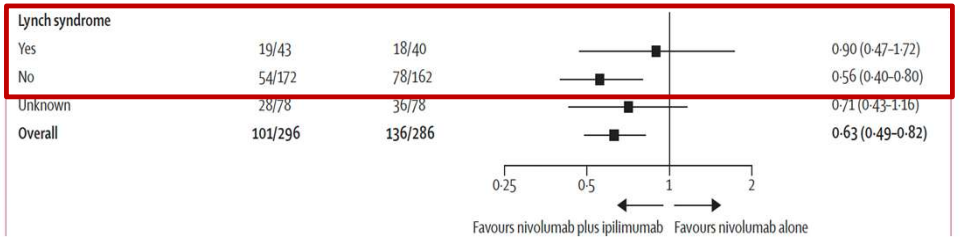
Category (1L centrally-confirmed MSI-H/dMMR)	Subgroup	Median PFS,[a] months NIVO + IPI	Median PFS,[a] months Chemo	Unstratified HR	Unstratified HR (95% CI)
BRAF/*KRAS*/*NRAS* mutation status	*BRAF*/*KRAS*/*NRAS* all wild type (n = 58)	34.3	5.4	0.08	
	BRAF mutant (n = 72)	NR	9.2	0.37	
	KRAS or *NRAS* 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	
Prior surgery	Yes (n = 222)	NR	7.1	0.21	
	No (n = 33)	NR	3.0	0.19	

0,02 0,03 0,06 0,13 0,25 0,50 1,00 2,00

NIVO + IPI ⟷ Chemo

HRs not computed for subgroups with less than 10 patients per treatment arm. [a]Per BICR.

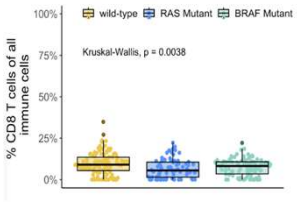
CM 8HW – PFS Nivolumab-Ipilimumab vs Nivolumab



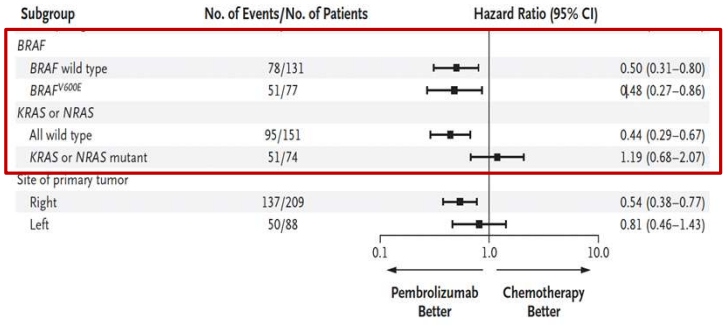
Khushman M, ESMO 2025; Andre T, NEJM 2024, Lancet 2025

Predictive markers – RAS/BRAF mutation profile?

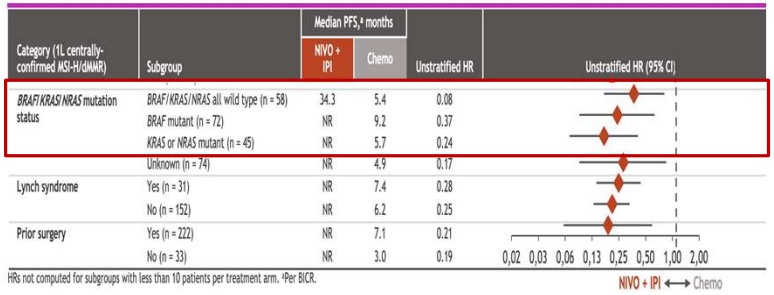
- 448 stage I-IV MSI/dMMR CRC profiled by NGS (Salem M, CCR 2025)
- **RASmut** vs BRAFmut/RAS-BRAFwt:
  - ✓ lower NTB (Neoantigen Tumor Burden) and PD-L1 expression
  - ✓ lower overall inflammation and fewer infiltrating CD8+ T-cells in TiME (Tumor Immune Microenvirenoment)



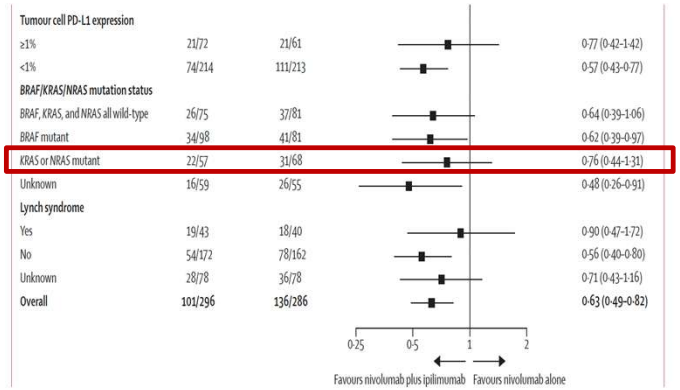
KN-177 – PFS Pembro vs Chemotherapy



CM 8HW – PFS Nivo-Ipi vs Chemotherapy



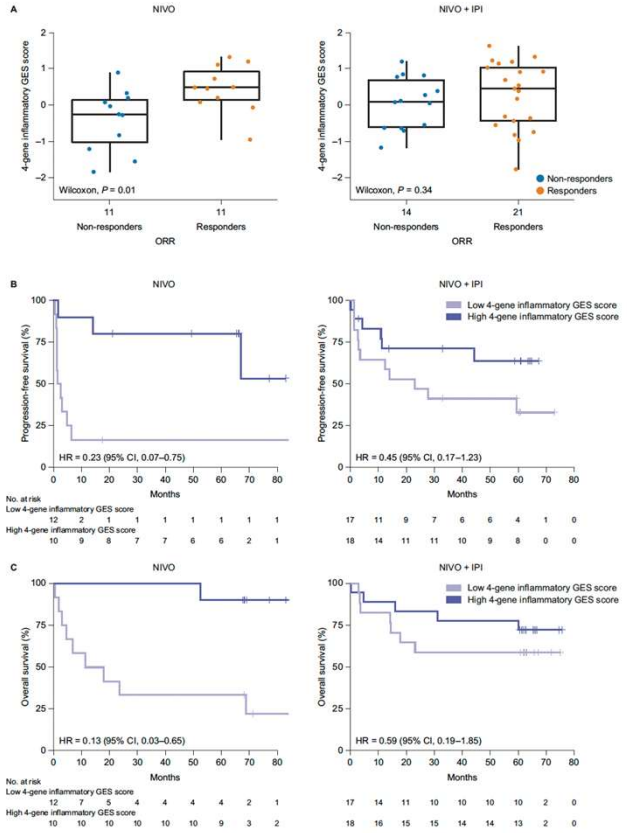
CM 8HW – PFS Nivo-Ipi vs Nivolumab



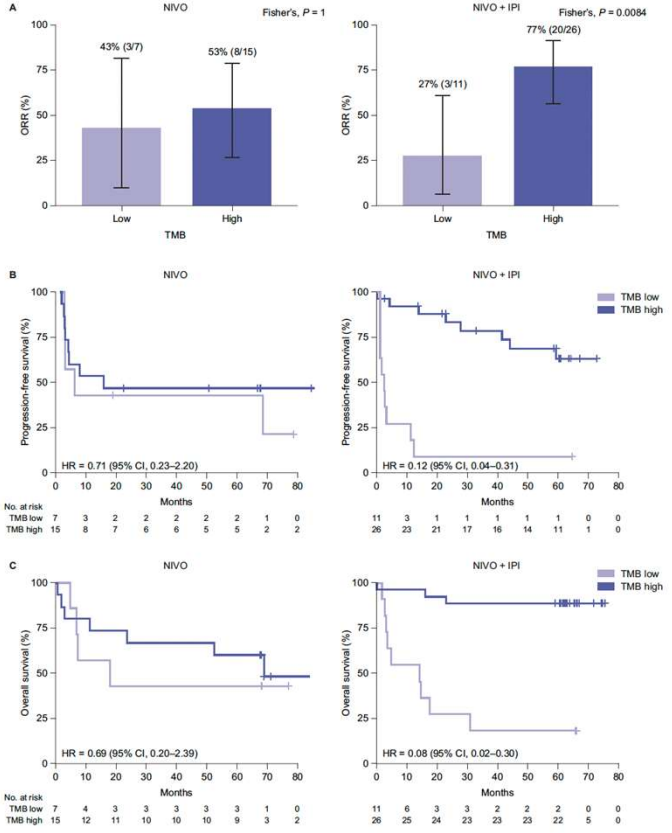
Salem M, CCR 2025; Andre T, NEJM 2020, NEJM 2024, Lancet 2025

CM-142 Exploratory Immune Biomarkers

Higher expression of **inflammation-related GES** associated with improved response to **NIVOLUMAB**



Higher **TMB**, **TIB** and **degree of MSI** associated with improved response to **NIVOLUMAB + IPILIMUMAB**



Lei M, Nature Comm 2025

Other strategies to overcome primary resistance

Strategy: add chemo/bevacizumab
COMMIT (NCT02997228): 1L, phase 3 trial (N = 231)[1]

- Untreated MSI-H/dMMR mCRC
- ECOG PS 0–2
- Measurable disease per RECIST v1.1

R 1:1

- **ATEZOLIZUMAB** 840 mg IV
- **FOLFOX/bevacizumab[a] + ATEZO** 840 mg IV

Primary endpoint: PFS (ITT population)

Adapted with permission from Overman MJ.[1]

Strategy: add encorafenib-cetuximab (*BRAF* mutated)
SEAMARK (NCT05217446): 1L, phase 2 trial (N = 104)[2]

- Previously untreated stage IV mCRC
- Locally confirmed MSI-H/dMMR
- Locally confirmed *BRAF* V600E mutation in tumor tissue or blood
- Measurable disease per RECIST v1.1
- ECOG PS ≤ 1
- Adequate organ function

R 1:1

- **Encorafenib + cetuximab + PEMBROLIZUMAB**
- **PEMBROLIZUMAB**

Primary endpoint: PFS per investigator (RECIST v1.1)

Reproduced with permission from Kopetz S.[1]

[a]Oxaliplatin 85 mg/m^2 IV + leucovorin 400 mg/m^2 IV + bevacizumab 5 mg/kg IV + 5-FU 400 mg/m^2 IV bolus on day 1 followed by 5-FU 2400 mg/m^2 IV over 46 hours. 1L, first line; 5-FU, fluorouracil; ATEZO, atezolizumab; BICR, blinded independent central review; BRAF, B-Raf proto-oncogene; chemo, chemotherapy; dMMR, deficient mismatch repair; ICI, immune checkpoint inhibitor; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; ORR, objective response rate; PEMBRO, pembrolizumab; PFS, progression-free survival; PS, performance status; R, randomization. 1. Overman MJ, et al. Poster presentation at the American Society for Clinical Oncology (ASCO) Annual Meeting; June 4–8, 2021; Virtual. Abstract TPS3618. 2. Kopetz S, et al. Poster presentation at the American Society of Clinical Oncology Gastrointestinal Cancers Symposium (ASCO GI); January 19–21, 2023; San Francisco, CA. Abstract TPS3634. 3. Andre T, et al. Presentation at the American Society of Clinical Oncology Gastrointestinal Cancers Symposium (ASCO GI); January 20–22, 2022; San Francisco, CA. Abstract TPS3639.

Conclusions

- **Pembrolizumab vs CT** improves ORR, PFS and QoL, and has a more favorable toxicity profile and a strong trend towards improved OS despite > 60% crossover as 1L tx of metastatic dMMR/MSI CRC
- **Nivolumab and Ipilimumab vs CT** improves ORR, PFS and QoL, and has a more favorable toxicity profile as 1L tx of metastatic dMMR/MSI CRC. OS data are immature.
- **Nivolumab and Ipilimumab vs Nivolumab** improves ORR and PFS with a strong trend towards improved OS as 1L or any line of treatment for metastatic dMMR/MSI CRC
- **Nivo-Ipi vs Nivo** is associated with higher rates of irAEs, G3-4 TRAEs (24% vs 17%) and treatment interruption due to TRAEs (12% vs 4%)
- Dual PD1-CTLA4 vs single PD1 blockade offers clinically meaningful improvements in efficacy with somewhat increased toxicity with no detrimental effect on QoL
- Optimal candidates for single PD1 blockade ? (higher risk of irAEs, Lynch Sd??)
- Larger follow-up and validated predictive markers needed for more solid conclusions

Open issues & Future perspectives

- Dual PD1/CTLA4 blockade:
  - ✓ Optimal dose and schedule
  - ✓ Optimal duration of therapy
  - ✓ Despite success, 35% PD at 5 years – still some room for improvement?
  - ✓ Can we reduce toxicity ?
  - ✓ Long-term follow-up
- Role of rechallenge and treatment options at PD
- As we move to earlier lines of therapy, how will we manage metastatic disease?
- How can we overcome primary and secondary resistance

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