大腸癌免疫治療時代來臨:從實證到實務

三軍總醫院 血液腫瘤科

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Date:20260328 1450-1530

OPDIVO (nivolumab) + YERVOY (ipilimumab)

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TSCPM 台灣癌症安寧緩和醫學會 Taiwan Society of Cancer Palliative Medicine

outline

treatment guidelines for stage IV mCRC first-line treatment

dMMR/MSI-H

CheckMate 8HW

Keynote 177

Case sharing

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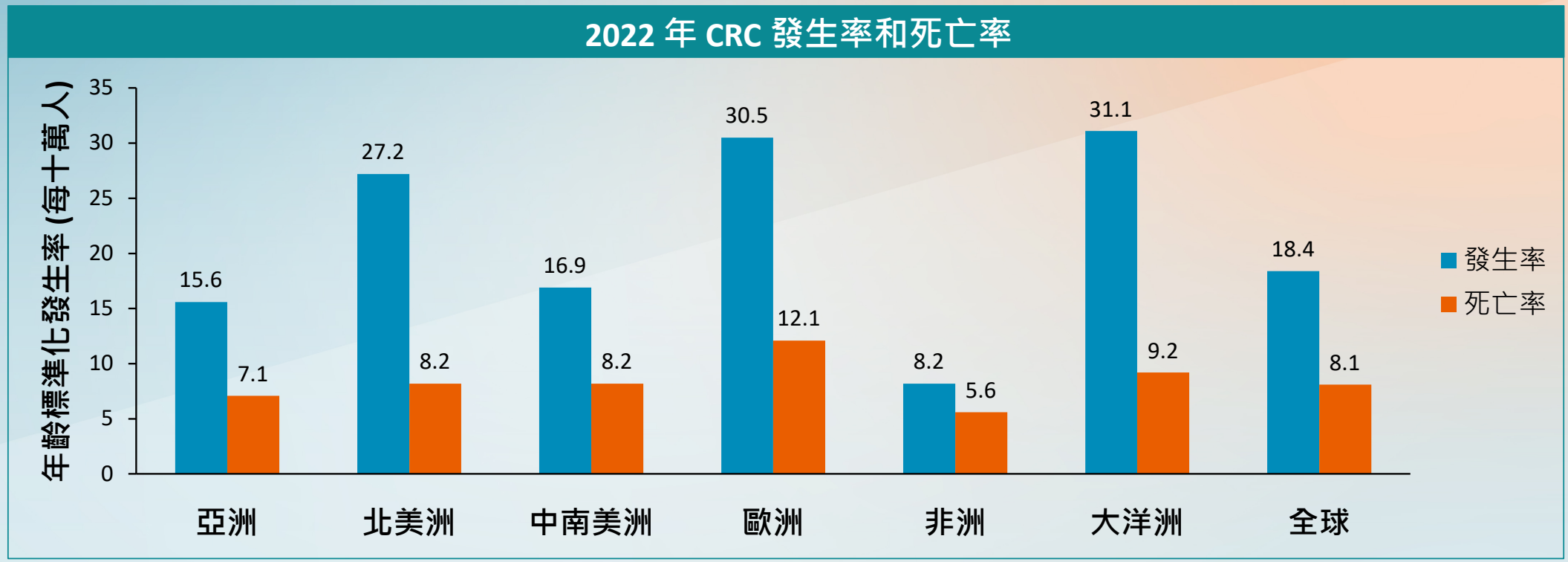
CRC is the third most common cancer globally and the second leading cause of cancer-related mortality



高發生率地區多集中於已開發國家，死亡率差異受早期篩檢與治療可近性影響

CRC, colorectal cancer.

Globocan. 2022. Global cancer data. Available at https://gco.iarc.fr/today/en/dataviz/tables?mode=cancer&group_populations=1&multiple_populations=1&populations=903_904_905_908_909_935

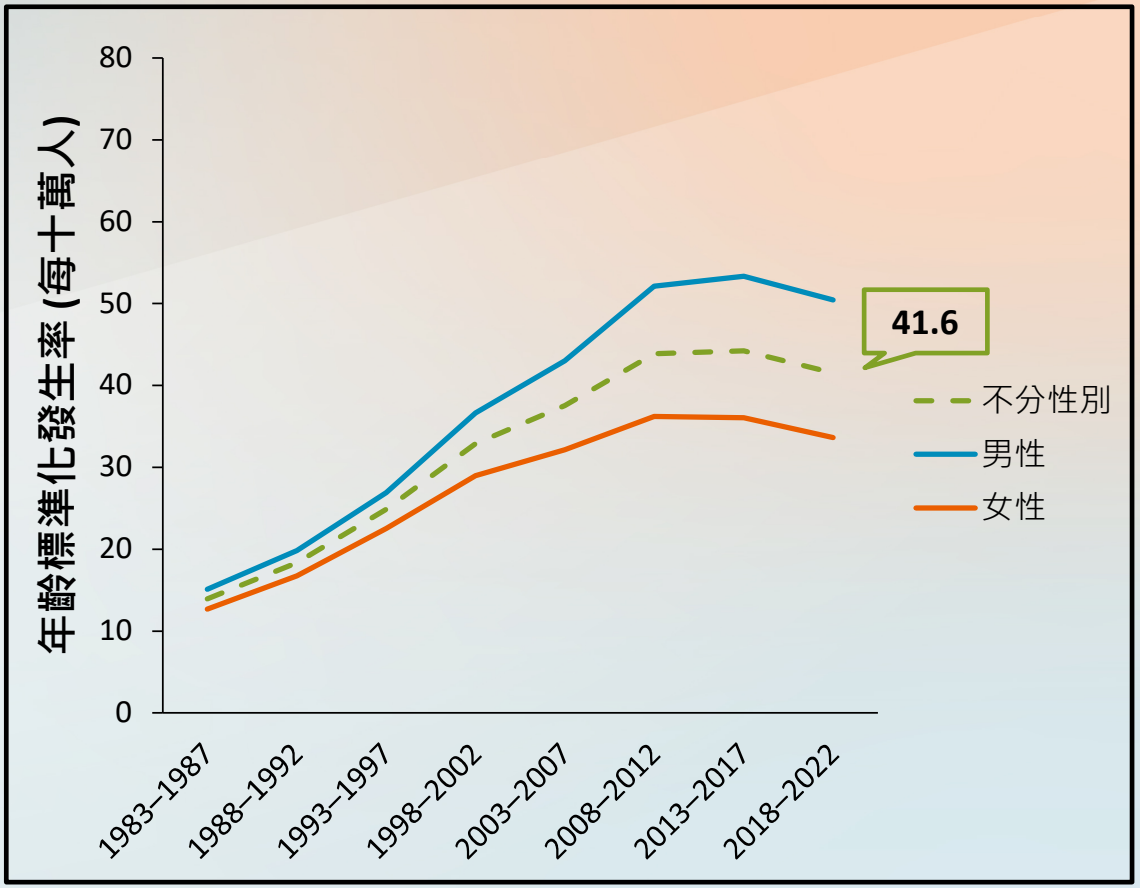
CRC in Taiwan: A high ASIR (41.6 per 100,000; twice the global average) and leading rankings in cancer incidence and mortality

10 大癌症發生率

順位	原發部位
1	女性乳房
2	肺、支氣管及氣管
3	攝護腺
4	結腸、直腸、乙狀結腸連結部及肛門
5	肝及肝內膽管
6	口腔、口咽及下咽
7	子宮體
8	甲狀腺
9	卵巢、輸卵管及寬韌帶
10	胃

10 大癌症死亡率

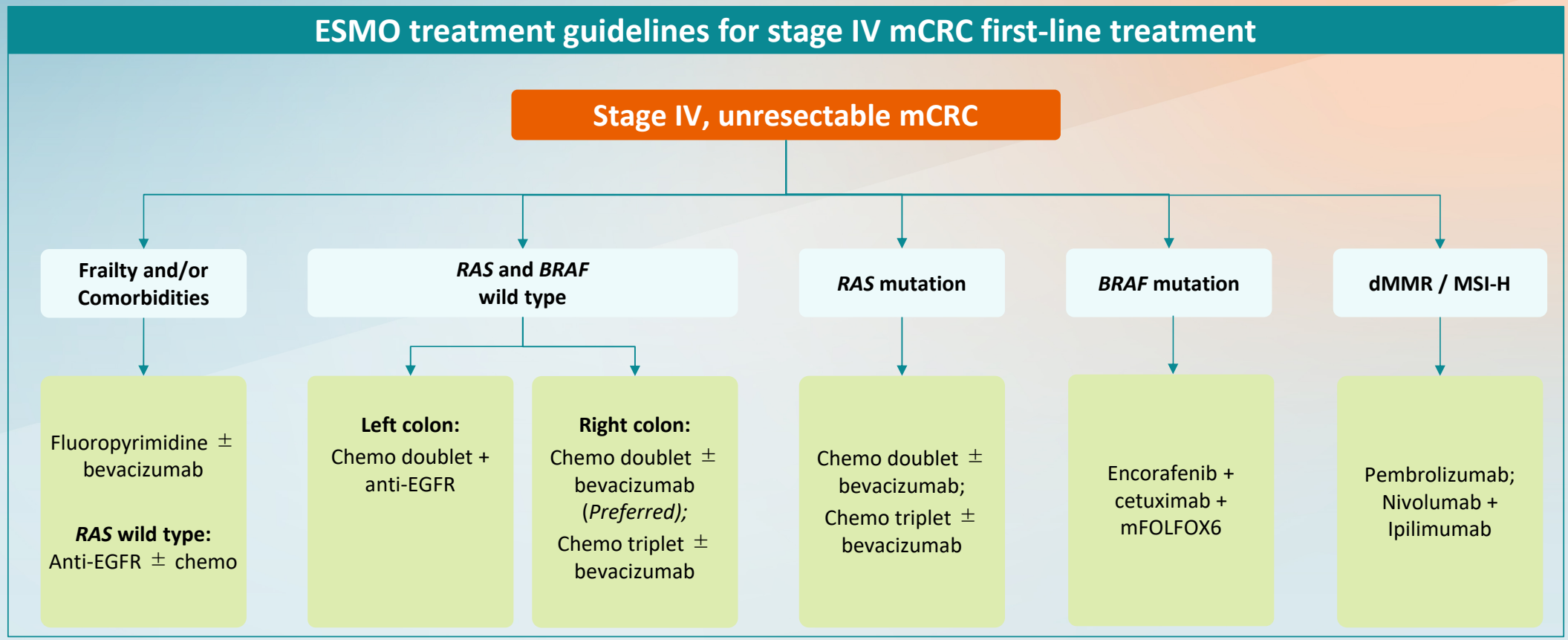
順位	原發部位
1	肺、支氣管及氣管
2	肝及肝內膽管
3	結腸、直腸、乙狀結腸連結部及肛門
4	女性乳房
5	口腔、口咽及下咽
6	攝護腺
7	胰
8	胃
9	食道
10	卵巢、輸卵管及寬韌帶



ASIR, age-standardized incidence rate; CRC, colorectal cancer.
Taiwan Cancer Registry Report 2022.

Biomarker and genomic testing is required for treatment decisions in all patients diagnosed with mCRC

ESMO treatment guidelines for stage IV mCRC first-line treatment



dMMR, deficient mismatch repair; EGFR, epidermal growth factor receptor; ESMO, European Society for Medical Oncology; mCRC, metastatic colorectal cancer; mFOLFOX6, modified FOLFOX6 (leucovorin calcium + fluorouracil + oxaliplatin); MSI-H, microsatellite instability–high.

Cervantes A, et al. *Ann Oncol*. 2023;34(1):10-32.

Common Systemic Treatments for CRC (Colon NCCN Guideline 2025 v.5)

Chemotherapy

	5-FU	Leucovorin	Oxaliplatin	Capecitabine	Irinotecan
FOLFOX	✓	✓	✓		
CAPEOX			✓	✓	
FOLFIRI	✓	✓			✓
FOLFIRINOX	✓	✓	✓		✓
5-FU/LV	✓	✓			

Targeted therapy

- **Anti-VEGF (and VEGF pathway):** bevacizumab, ramucirumab, aflibercept, fruquintinib, regorafenib
- **Anti-EGFR:** cetuximab, panitumumab
- **Anti-HER2:** trastuzumab ± (pertuzumab or lapatinib or tucatinib)
- **Others:** sotorasib, adagrasib, encorafenib, entrectinib, Larotrectinib, repotrectinib, selpercatinib, etc.

Immunotherapy

- **Immune checkpoint inhibitors:** nivolumab ± ipilimumab, pembrolizumab, dostarlimab, cemiplimab, retifanlimab, toripalimab, or tislelizumab.

5-FU, 5-fluorouridine; 5-FU/LV fluoracil + leucovorin calcium; CAPEOX, capecitabine + oxaliplatin; CRC, colorectal cancer; FOLFIRI, leucovorin calcium + flououracil + irinotecan hydrochloride; FOLFIRINOX, leucovorin calcium + fluorouracil + irinotecan hydrochloride + oxaliplatin; FOLFOX, leucovorin calcium + fluorouracil + oxaliplatin.

1. Cervantes A, et al. *Ann Oncol*. 2023;34:10-32. 2. NCCN. Clinical Practice Guidelines in Oncology: Colon Cancer. Version 5.2025.

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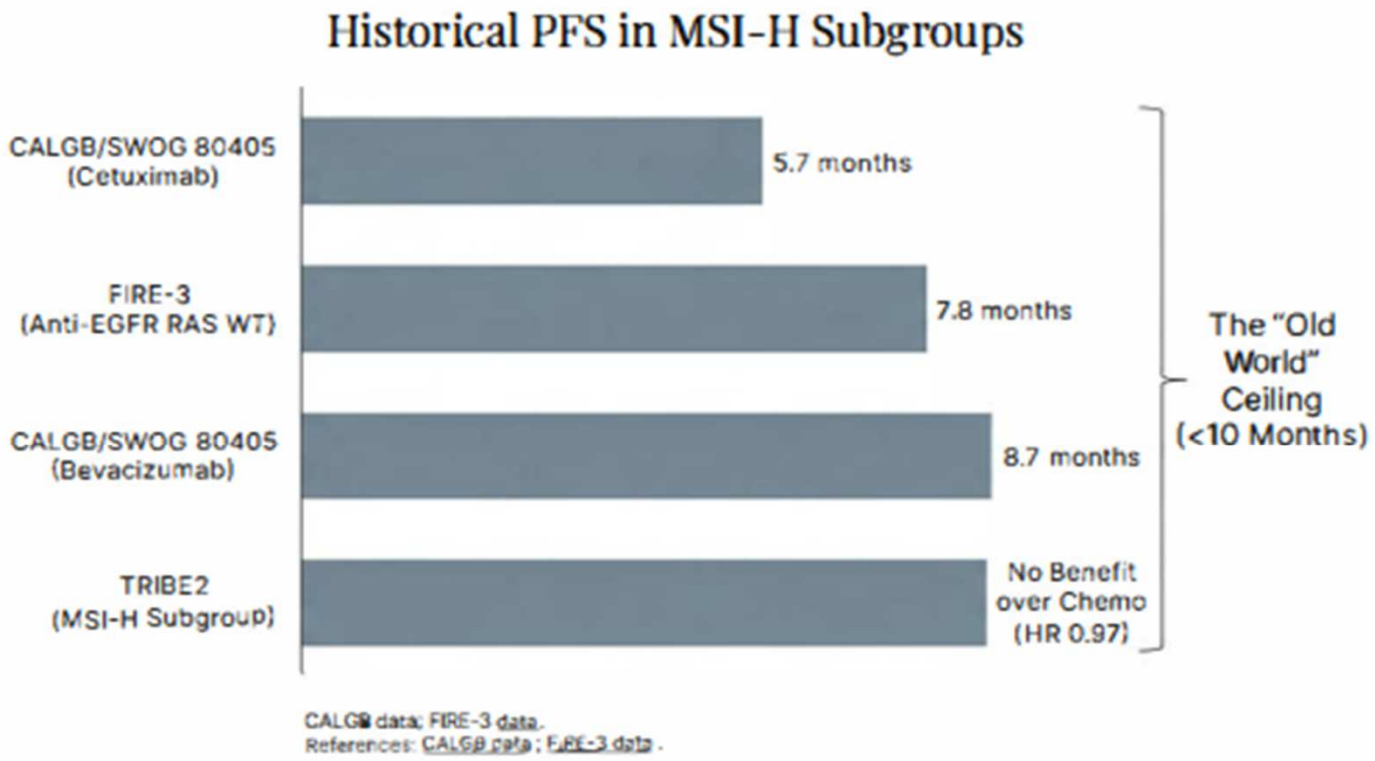
CheckMate 8HW

Keynote 177

Case sharing

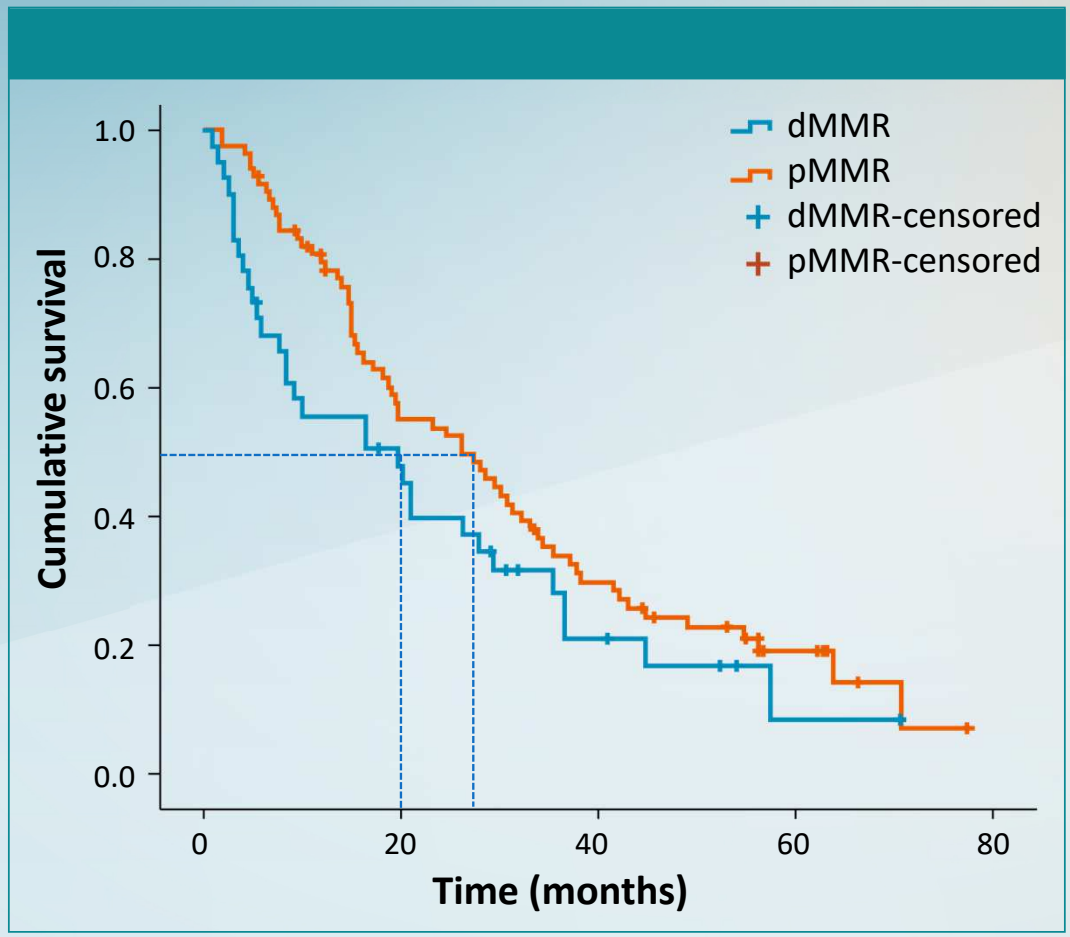
Historical Context: Targeted Therapies Failed to Improve Outcomes in MSI-H Subgroups

Prior to immunotherapy, adding targeted agents (Cetuximab or Bevacizumab) to chemotherapy yielded poor Progression-Free Survival (PFS) in MSI-H patients across major trials.
Historical 5-year survival was <15%.



CALGB data; FIRE-3 data.
References: CALGB data ; FIRE-3 data .

dMMR mCRC before immunotherapy: poor prognosis



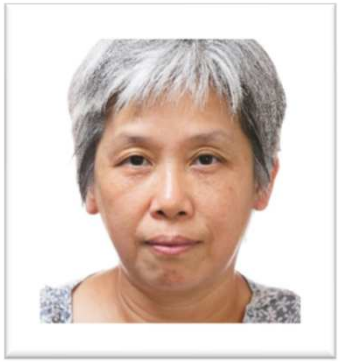
- Retrospective, case–control (41 dMMR *vs* 84 pMMR, oxaliplatin-based 1L chemo)
- Poor response: dMMR RR 11.7% *vs* pMMR 28.6%
- Survival disadvantage:
  - dMMR: 20.1 mo *vs* pMMR: 26.6 mo
  - Sporadic dMMR: 5.9 mo *vs* Lynch-related dMMR: 29.8 mo
- Associated with *BRAF* mutations, poor differentiation, right-sided tumors

chemo, chemotherapy; dMMR, deficient mismatch repair; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability–high; pMMR, proficient mismatch repair.

Alex AK, et al. *Clin Colorectal Cancer.* 2017;16(3):228-239.

Different Types of Cancer but the Same Unique Molecular Biomarker[a]

Jack
Stage IV
Colorectal Cancer



Helen
Unresectable
Stage III Gastric Cancer

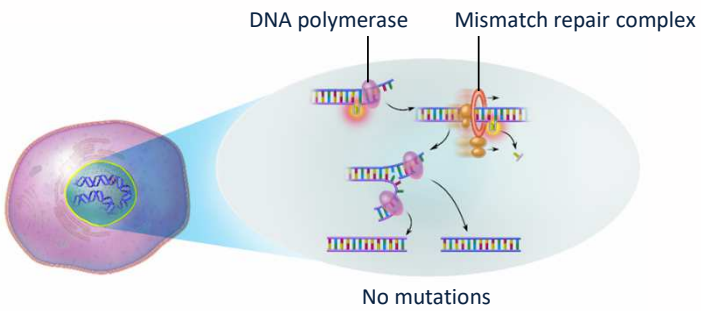
Susan
Stage IV
Endometrial Cancer

Tumor biomarker testing in advanced cancer revealed the presence of **MSI-H/dMMR**

[a]These are hypothetical patient cases.
dMMR = mismatch repair deficient; MSI-H = microsatellite instability-high.

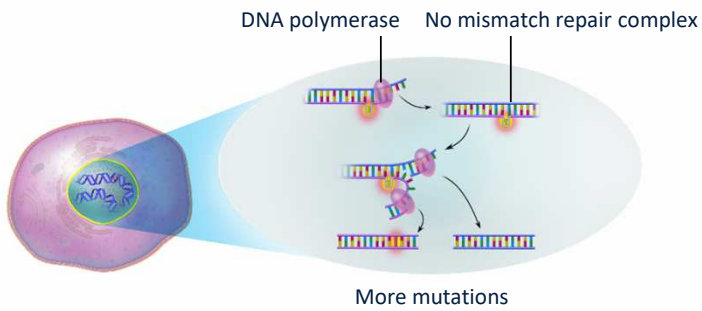
What Are DNA Mismatch Repair and Microsatellite Instability?

Proficient MMR (pMMR) Cell



- In normal cells, DNA mismatch repair (MMR) system recognizes and repairs genetic mismatches generated during DNA replication.[1,2]

Deficient MMR (dMMR) Cell



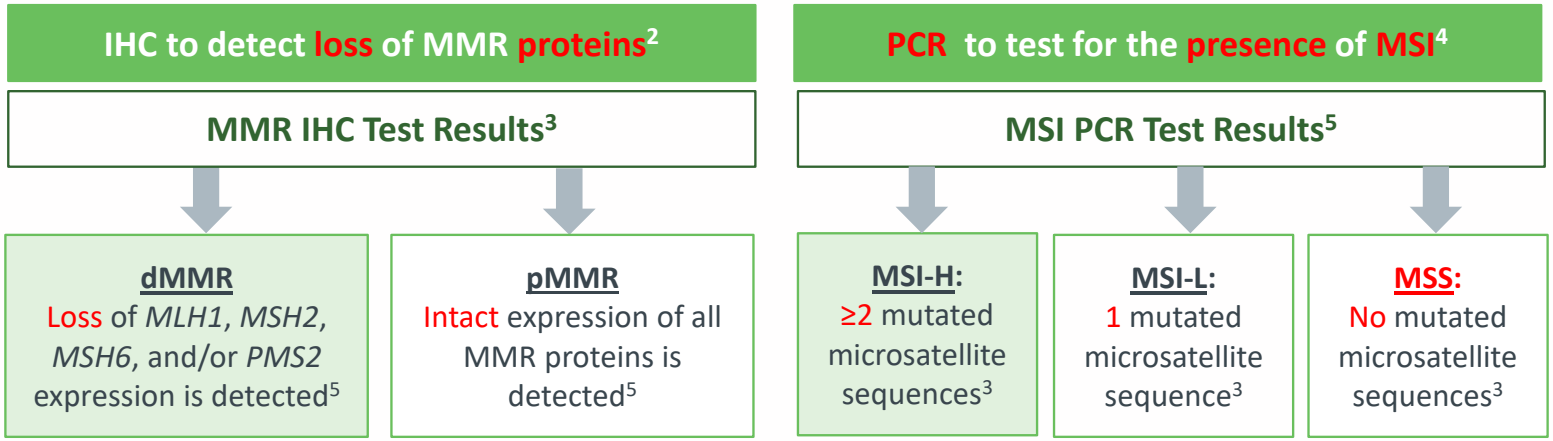
- A dMMR system results in the persistence of DNA mismatches in microsatellites that may then be incorporated into the genetic code as mutations.[1,2]
  - A dMMR system can be hereditary or sporadic in nature.[2]
- Tumors that have a **dMMR system** can develop **microsatellite instability (MSI)**, which is the expansion or reduction in the length of repetitive sequences in tumor DNA compared with normal DNA.[2]
- Tumors that have MSI due to a dMMR system can exhibit the MSI-high (MSI-H) phenotype.[1,2]

Images adapted from Li SKH, Martin A. *Trends Mol Med.* 2016;22(4):274–289.

1. Li SKH, Martin A. *Trends Mol Med.* 2016;22(4):274–289.
2. Boland CR, Goel A. *Gastroenterology*. 2010;138(6):2073–2087.

How to Test for MSI and MMR

- IHC for MMR and DNA analysis for MSI are different assays that measure the same biological effect.[1]

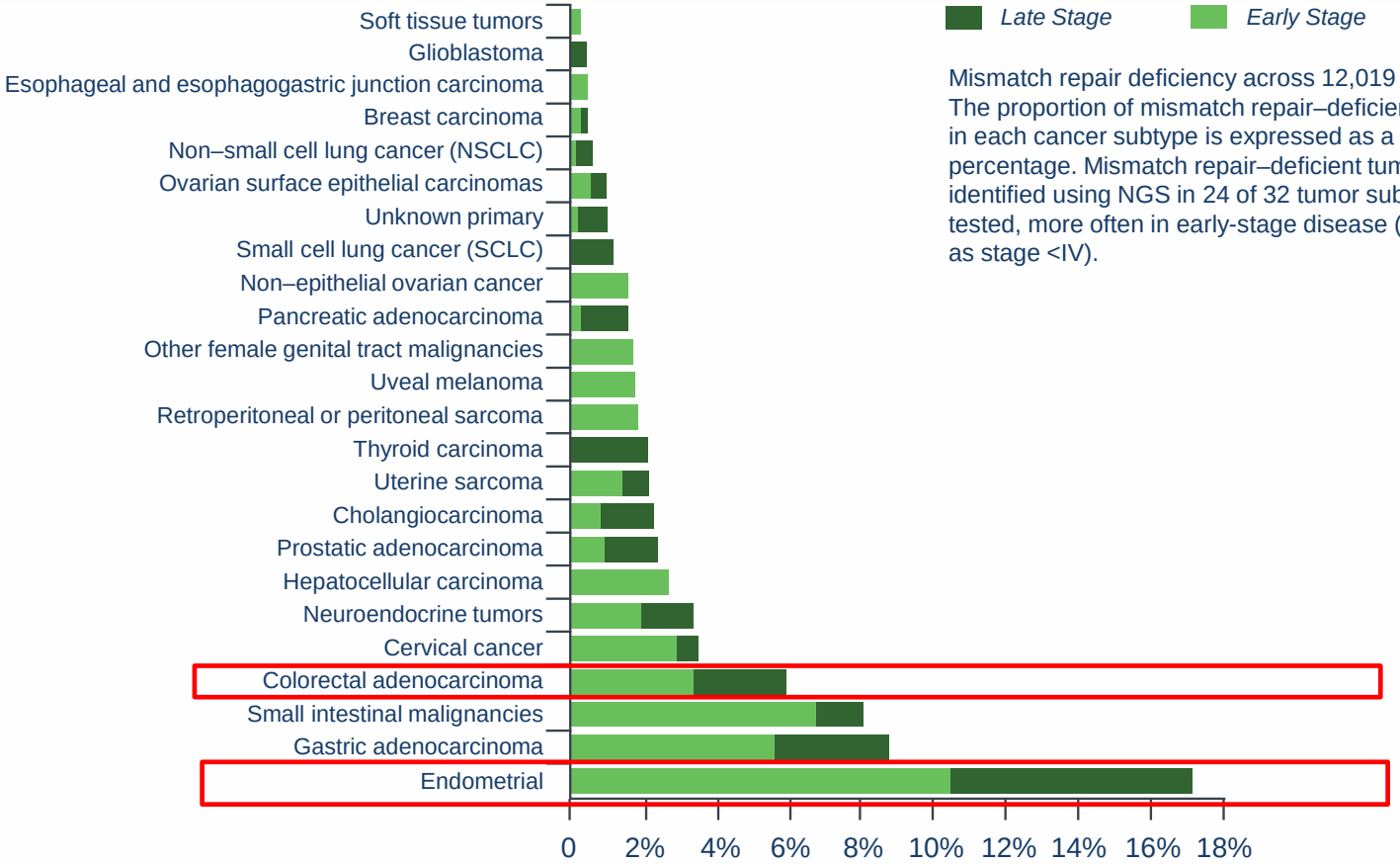


- MSI status can also be evaluated by next-generation sequencing (NGS).[4]

dMMR = mismatch repair deficient; IHC = immunohistochemistry; MLH = MutL homologue; MMR = mismatch repair; MSH = MutS homologue; MSI = microsatellite instability; MSI-H = microsatellite instability-high; MSI-L = microsatellite instability-low; MSS = microsatellite stable; PCR = polymerase chain reaction; pMMR = proficient mismatch repair; PMS = postmeiotic segregation.

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Colon Cancer V.2.2018. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed June 1, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org.
2. Kheirelseid EAH et al. *J Gastrointest Oncol*. 2013;4(4):397–408.
3. Vilar E, Gruber SB. *Nat Rev Clin Oncol*. 2010;7(3):153–162.
4. Salipante SJ et al. *Clin Chem*. 2014;60(9):1192–1199.
5. Boland CR et al. *Cancer Res*. 1998;58(22):5248–5257.

MSI-H or dMMR Occurs in a Variety of Cancers[1]



Mismatch repair deficiency across 12,019 tumors. The proportion of mismatch repair–deficient tumors in each cancer subtype is expressed as a percentage. Mismatch repair–deficient tumors were identified using NGS in 24 of 32 tumor subtypes tested, more often in early-stage disease (defined as stage <IV).

dMMR = mismatch repair deficient; MSI-H = microsatellite instability-high; NGS = next-generation sequencing.

1. Adapted from Le DT et al. *Science*. 2017;357(6349):409–413.

MSI/MMR Testing in Colorectal Cancer

MSI/MMR status is widely maintained as a prognostic and predictive marker in stage II CRC[1–5]

- stage II and/or III MSI-H/dMMR CRC have a more **favorable prognosis** than those with proficient mismatch repair (pMMR) tumors[2,3]
- CRC exhibiting MSI-H have longer survival than stage-matched MSS cancers[4]

- stage II CRC disease, MSI-H/dMMR is a predictor of **decreased benefit** (and possibly detrimental impact) **with 5-FU**–based adjuvant C/T[4,5]

CRC = colorectal cancer; dMMR = mismatch repair deficient; MMR = mismatch repair; MSI = microsatellite instability; MSI-H = microsatellite instability-high. MSS = microsatellite stable.

1. Moreira L et al. *JAMA*. 2012;308(15):1555–1565. **2.** Kawakami H et al. *Curr Treat Options Oncol.* 2015;16(7):1–15. **3.** Richman S. *Int J Oncol.* 2015;47(4):1189–1202. **4.** Ribic CM et al. *N Engl J Med*. 2003;349(3):247–257. **5.** Sargent DJ et al. *J Clin Oncol*. 2010;28(20):3219–3226.

outline

treatment guidelines for stage IV mCRC first-line treatment

dMMR/MSI-H

CheckMate 8HW

Keynote 177

Case sharing

CheckMate 8HW is a randomized phase 3 study comparing NIVO + IPI with NIVO or chemo in patients with MSI-H/dMMR mCRC

Study design

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)

R 2:2:1

- *n* = 353 → NIVO 240 mg Q2W for 6 doses, followed by NIVO 480 mg Q4W[b]
- *n* = 354 → NIVO 240 mg + IPI 1 mg/kg Q3W for 4 doses, followed by NIVO 480 mg Q4W[b]
- *n* = 132 → Investigator's choice chemo[c] (mFOLFOX6 or FOLFIRI ± bevacizumab or cetuximab)

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; PFS2 by investigator[e]; ORR by BICR[e]; PROs

[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.

BICR, blinded independent central review; chemo, chemotherapy; CRC, colorectal cancer; dMMR, deficient mismatch repair; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IPI, ipilimumab; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability–high; NIVO, nivolumab; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival 2; PROs, patient-reported outcomes; R, randomization.

ASCO 2025, Abstract 3501.

Baseline patient demographics and disease characteristics were well balanced among 3 groups

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)

Dara 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, *n* = 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.

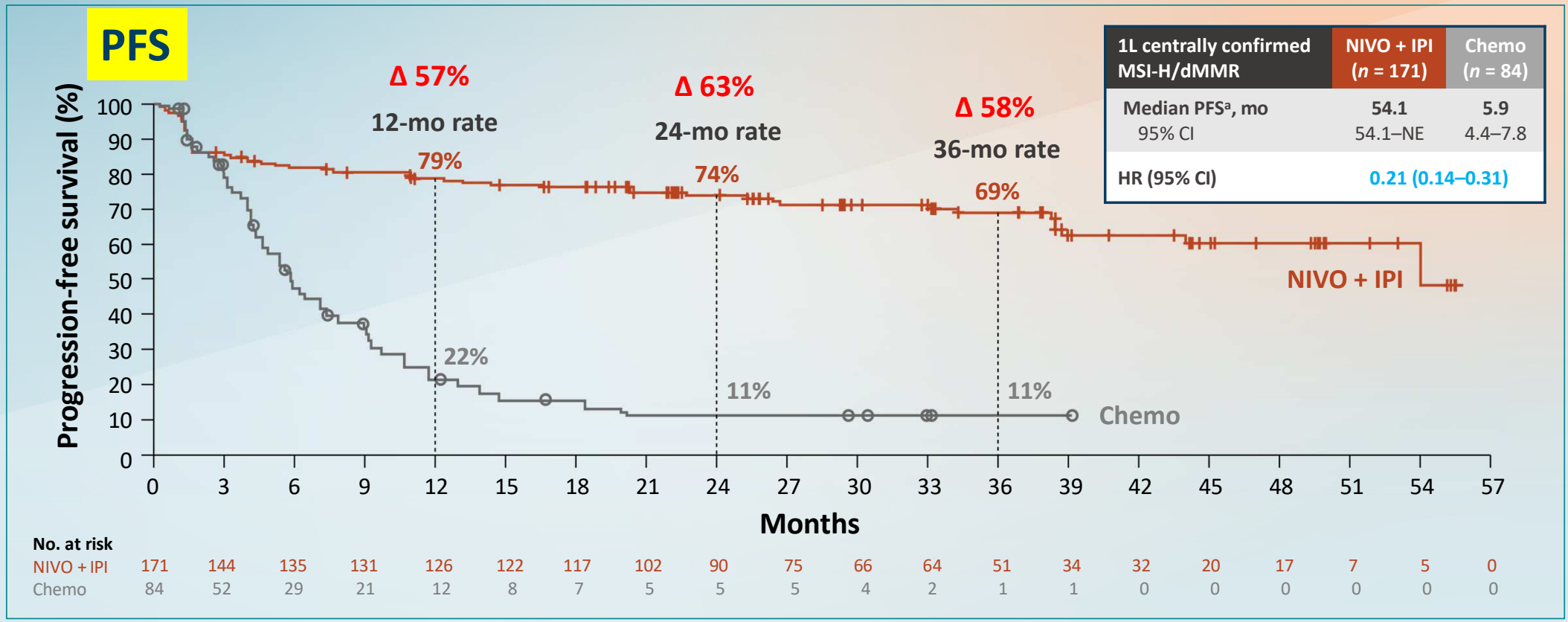
chemo, chemotherapy; dMMR, deficient mismatch repair; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IPI, ipilimumab; IRT, Interactive Response Technology; MSI-H, microsatellite instability–high; MSS, microsatellite stable; NIVO, nivolumab; pMMR, proficient mismatch repair.

ASCO 2025, Abstract 3501.

Primary endpoint: PFS in

NIVO + IPI *vs* Chemo as 1L Therapy

NIVO + IPI delivering durable disease control: 79% reduction in the risk of death or disease progression and nearly 70% of patients remain progression-free at 3 Years



1L centrally confirmed MSI-H/dMMR	NIVO + IPI (*n* = 171)	Chemo (*n* = 84)
Median PFS[a], mo	54.1	5.9
95% CI	54.1–NE	4.4–7.8
HR (95% CI)	0.21 (0.14–0.31)	

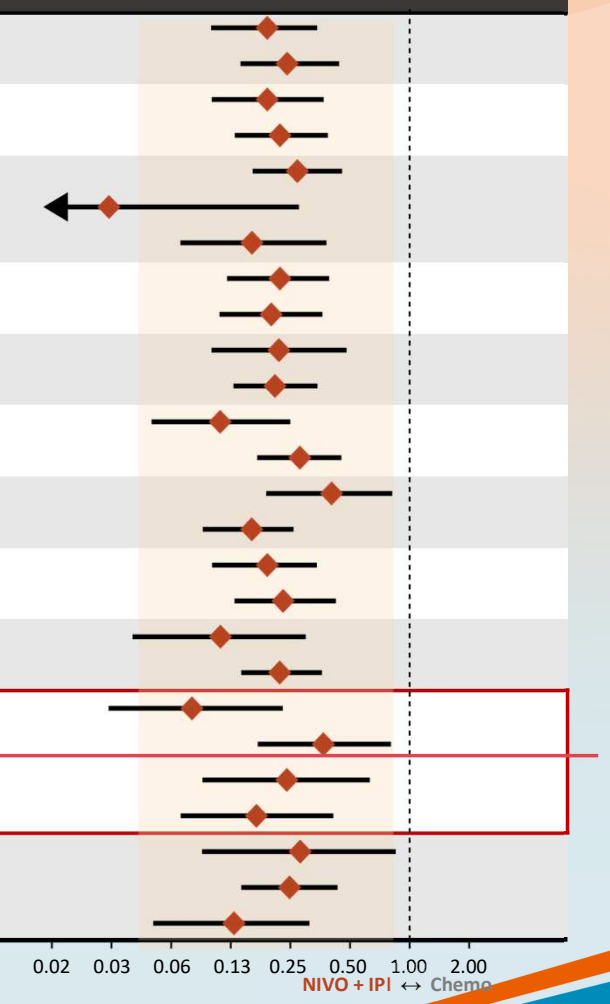
[a] Per BICR. Median follow-up, 47.0 mo.

chemo, chemotherapy; CI, confidence interval; dMMR, deficient mismatch repair; HR, hazard ratio; IPI, ipilimumab; MSI-H, microsatellite instability–high; NE, not evaluable; NIVO, nivolumab; PFS, progression-free survival.

ASCO 2025, Abstract 3501.

NIVO + IPI delivers superior PFS across all subgroups, including *RAS/BRAF* mutations and liver/lung metastases

Category (1L centrally confirmed MSI-H/dMMR)	Subgroup	Median PFS[a], mo		Unstratified HR
		NIVO + IPI	Chemo	
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* 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



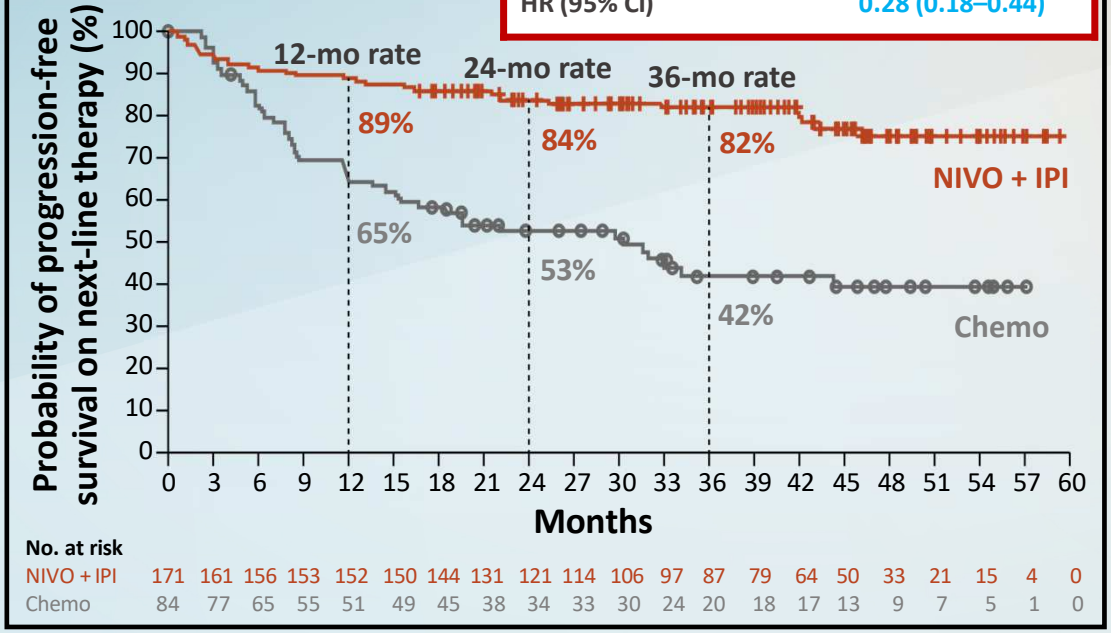
chemo, chemotherapy; CI, confidence interval; dMMR, deficient mismatch repair; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; IPI, ipilimumab; MSI-H, microsatellite instability–high; NIVO, nivolumab; NR, not reported; PFS, progression-free survival.

ASCO 2024, Abstract 3503.

NIVO + IPI demonstrates superior PFS2 with a 72% risk reduction, despite high subsequent IO use in the chemotherapy arm (71%)

PFS2

1L centrally confirmed MSI-H/dMMR	NIVO + IPI (*n* = 171)	Chemo (*n* = 84)
Median PFS2[a], mo	NR	30.3
95% CI	NE–NE	15.2–NE
HR (95% CI)	0.28 (0.18–0.44)	



Subsequent therapy[b] (1L centrally confirmed MSI-H/dMMR)	NIVO + IPI (*n* = 171)	Chemo (*n* = 84)
Radiotherapy, *n* (%)	3 (2)	1 (1)
Surgery, *n* (%)	7 (4)	5 (6)
Systemic therapy[c], *n* (%)	27 (16)	61 (73)
Immunotherapy	10 (6)	60 (71)
On-study crossover to NIVO + IPI	0	39 (46)
Non-study immunotherapy	10 (6)	21 (25)
EGFR inhibitors	5 (3)	1 (1)
Platinum compounds	11 (6)	3 (4)
VEGFR targeted therapy	8 (5)	4 (5)
MEK, NRAS, and BRAF inhibitors	2 (1)	1 (1)
Other systemic anticancer therapy	17 (10)	5 (6)

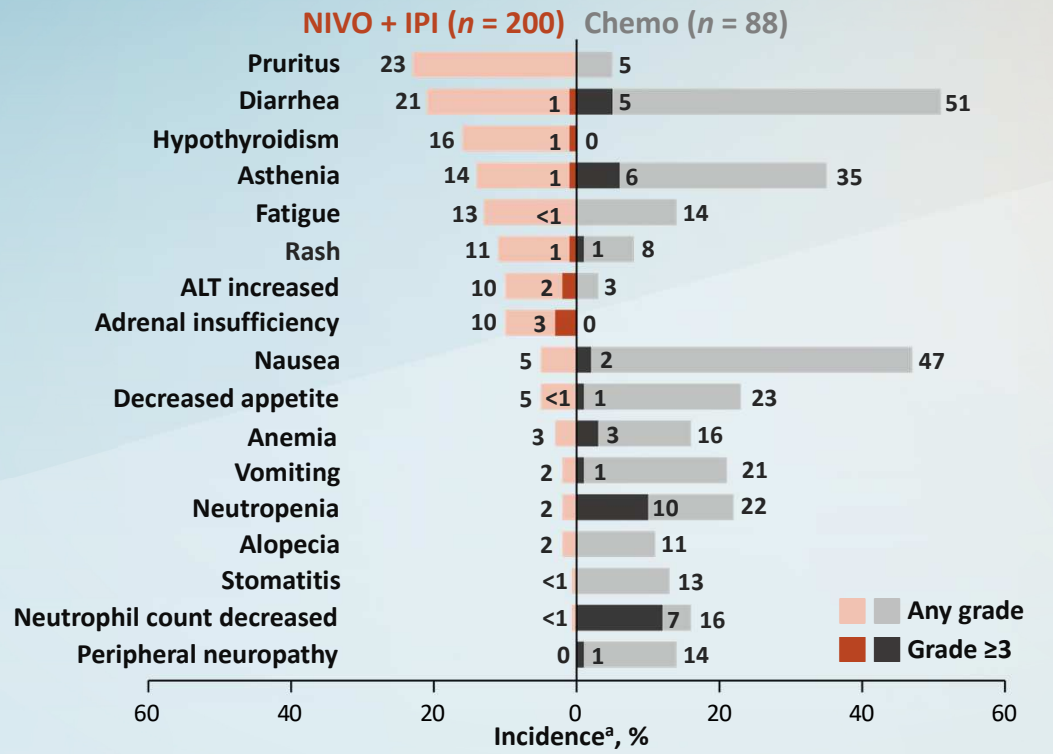
PFS2, time from randomization to progression after subsequent systemic therapy, initiation of second subsequent systemic therapy, or death. [a] Per INV. [b] Patients may have received more than 1 type of subsequent therapy. [c] Patients may have received multiple subsequent systemic therapies.

chemo, chemotherapy; CI, confidence interval; dMMR, deficient mismatch repair; HR, hazard ratio; IO, immunotherapy; IPI, ipilimumab; MSI-H, microsatellite instability–high; NE, not evaluable; NIVO, nivolumab; PFS2, progression-free survival 2.

ASCO 2025, Abstract 3501.

Any-grade and grade 3/4 TRAEs were less frequent in the NIVO + IPI arm than in chemo arm

TRAEs occurring in ≥ 10% of patients



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]	

[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.
chemo, chemotherapy; IPI, ipilimumab; NIVO, nivolumab; TRAEs, treatment-related adverse events.
ASCO2024, Abstract 3503

The majority of IMAEs were grade 1 or 2, with all grade 3/4 IMAEs occurring in ≤ 5% of patients

IMAEs[a] (1L all treated patients), *n* (%)	NIVO + IPI (*n* = 200)		Chemo (*n* = 88)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Hypothyroidism	33 (17)	2 (1)	1 (1)	0
Adrenal insufficiency	21 (11)	7 (4)	0	0
Hyperthyroidism	18 (9)	0	1 (1)	0
Diarrhea/colitis	13 (7)	9 (5)	1 (1)	0
Hepatitis	11 (6)	6 (3)	0	0
Rash	11 (6)	3 (2)	0	0
Hypophysitis	10 (5)	5 (3)	0	0
Pneumonitis	4 (2)	3 (2)	0	0
Thyroiditis	3 (2)	1 (< 1)	0	0
Diabetes mellitus	2 (1)	0	0	0
Nephritis and renal dysfunction	1 (< 1)	1 (< 1)	0	0
Hypersensitivity	0	0	1 (1)	1 (1)

[a] IMAEs are specific events considered as potential immune-mediated events by investigator, occurring within 100 days after the last dose of study treatment, regardless of causality, and, with the exception of endocrine events, are treated with immune-modulating medication.

chemo, chemotherapy; **IMAEs, immune-mediated adverse events;** IPI, ipilimumab; NIVO, nivolumab.

ASCO2024, Abstract 3503

Median duration of treatment were 20.5 months, 16.4 month, and 5.1 months in NIVO + IPI, NIVO, and chemo arm, respectively

Disposition	NIVO + IPI	NIVO	Chemo
All randomized patients, *n*	354	353	132
All treated patients, *n*	352	351	115
Ongoing treatment[a], *n* (%)	20 (6)	13 (4)	0
Completed treatment[a,b], *n* (%)	159 (45)	137 (39)	0
Discontinued treatment[a], *n* (%)	173 (49)	201 (57)	115 (100)
Median duration of treatment (range)[c], mo	20.5 (0–35.9)[d]	16.4 (0–36.0)	5.1 (0.1–32.8)
Median number of doses (range)[c]	NIVO: 23 (1–41) IPI: 4 (1–4)	NIVO: 21 (1–43)	-
Received all 4 doses of IPI, *n* (%)	288 (82)	-	-
Death[a], *n* (%)	103 (29)	149 (42)	54 (47)
Disease progression	74 (21)	122 (35)	37 (32)
Other[e]	29 (8)	27 (8)	17 (15)

Among patients treated with chemo,
66 patients (75%) received a biologic agent (bevacizumab, *n* = 56; cetuximab, *n* = 10)

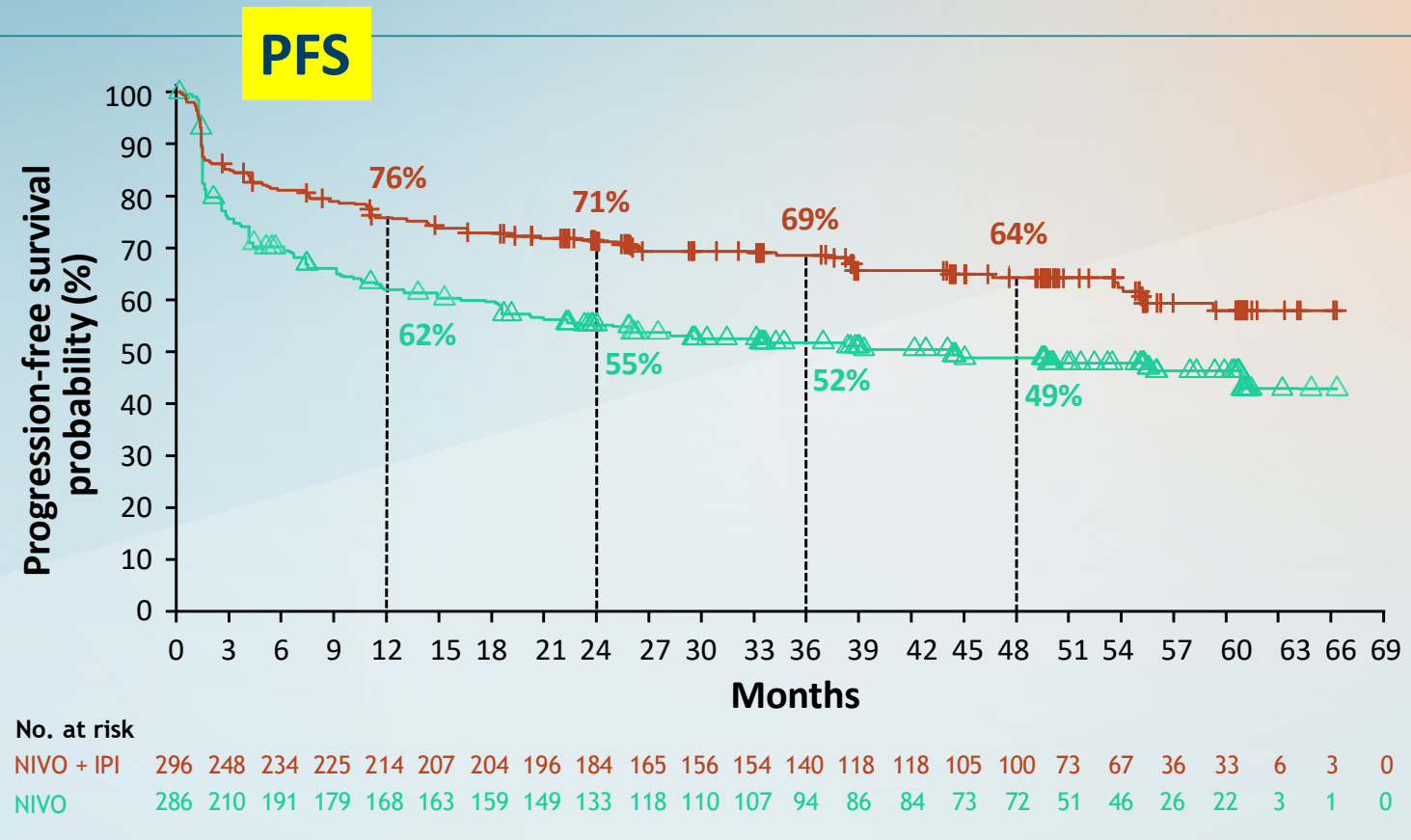
[a] Percentages shown are based on all treated patients. [b] For NIVO + IPI and NIVO arms: completed 2 years of treatment. [c] Other reasons for discontinuation included death (*n* = 6), withdrawal of consent (*n* = 2), pregnancy (*n* = 1), patient no longer met study criteria (*n* = 1), maximum clinical benefit (*n* = 1), and other reasons (*n* = 18). [c] Patients can continue NIVO treatment upon early IPI discontinuation. [d] Median duration of treatment was 20.5 (range, 0–35.9) mo for NIVO and 2.1 (range, 0–3.7) mo for IPI. [e] Other reasons for death included treatment-related toxicity (*n* = 3), other reasons (*n* = 48), and unknown (*n* = 22).
chemo, chemotherapy; IPI, ipilimumab; NIVO, nivolumab.
ASCO 2025, Abstract 3501.

Primary endpoint: PFS in

NIVO + IPI *vs* NIVO mono across all lines

CheckMate 8HW

Across all lines of therapy, NIVO + IPI continues to outperform NIVO monotherapy, with mPFS not reached *vs* 44.3 months



	NIVO + IPI (*n* = 296)	NIVO (*n* = 286)
Median PFS[a], mo 95% CI	NR NE–NE	44.3 22.1–NE
HR (95% CI)	0.62 (0.48–0.80)	

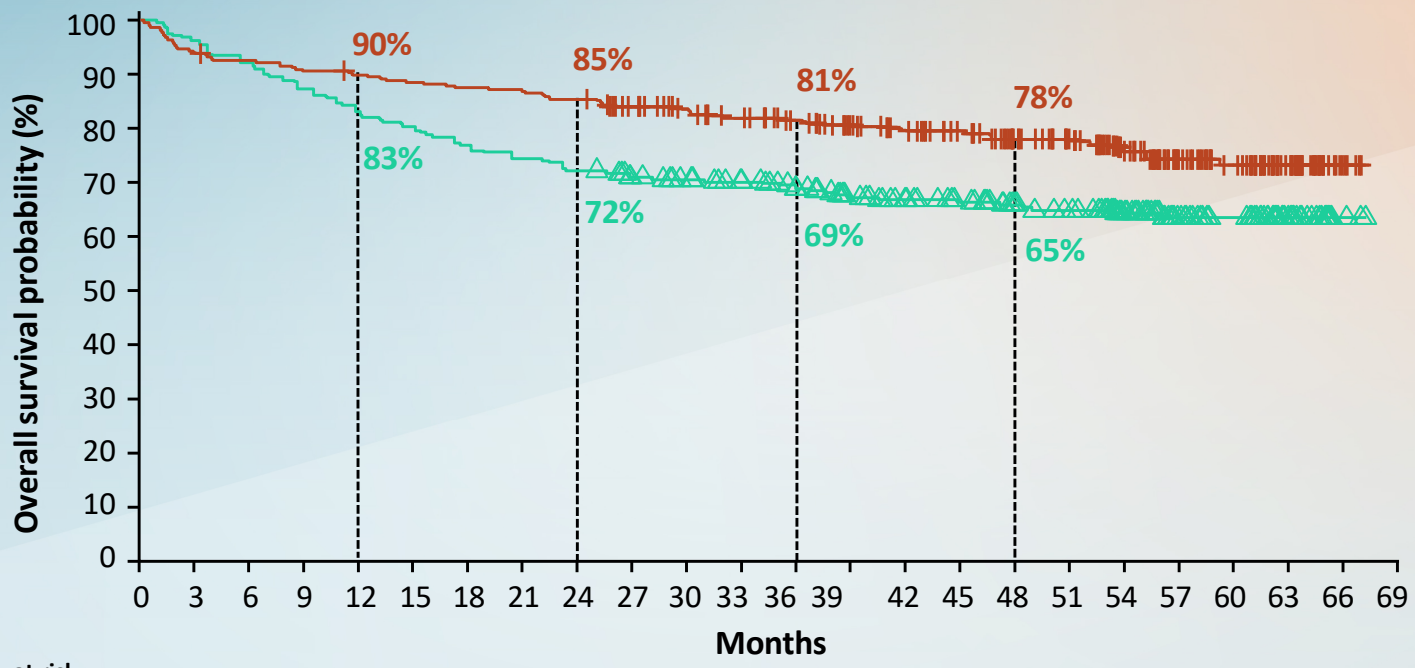
In patients with centrally confirmed MSI-H/dMMR mCRC, NIVO + IPI continued to demonstrated clinically meaningful improvements in PFS *vs* NIVO across all lines (HR 0.62, [95% CI 0.48–0.99])

- These data are consistent with those observed in the all randomized population by local testing (HR 0.63, [95% CI 0.51–0.78])

NIVO monotherapy is approved in 2L+ dMMR/MSI-H mCRC by TFDA. Median follow-up for all randomized patients was 55.1 (range 24.7-68.5) months. [a] As assessed by BICR.
CI, confidence interval; dMMR, deficient mismatch repair; HR, hazard ratio; IPI, ipilimumab; mCRC, metastatic colorectal cancer; mPFS, median progression-free survival; MSI-H, microsatellite instability–high; NE, not evaluable; NIVO, nivolumab; PFS, progression-free survival.
ESMO 2025, Presentation LBA29.

CheckMate 8HW

OS favored NIVO + IPI *vs* NIVO across all lines



No. at risk

NIVO + IPI	296	279	273	267	264	260	257	255	251	240	229	219	209	196	186	175	160	149	118	83	65	35	5	0
NIVO	286	275	263	252	238	228	220	213	207	195	189	182	172	157	148	139	127	122	102	63	50	23	3	0

	NIVO + IPI (*n* = 296)	NIVO (*n* = 286)
Median OS[a], mo 95% CI	NR NE–NE	NR NE–NE
HR (95% CI)	0.61 (0.45–0.83)	

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

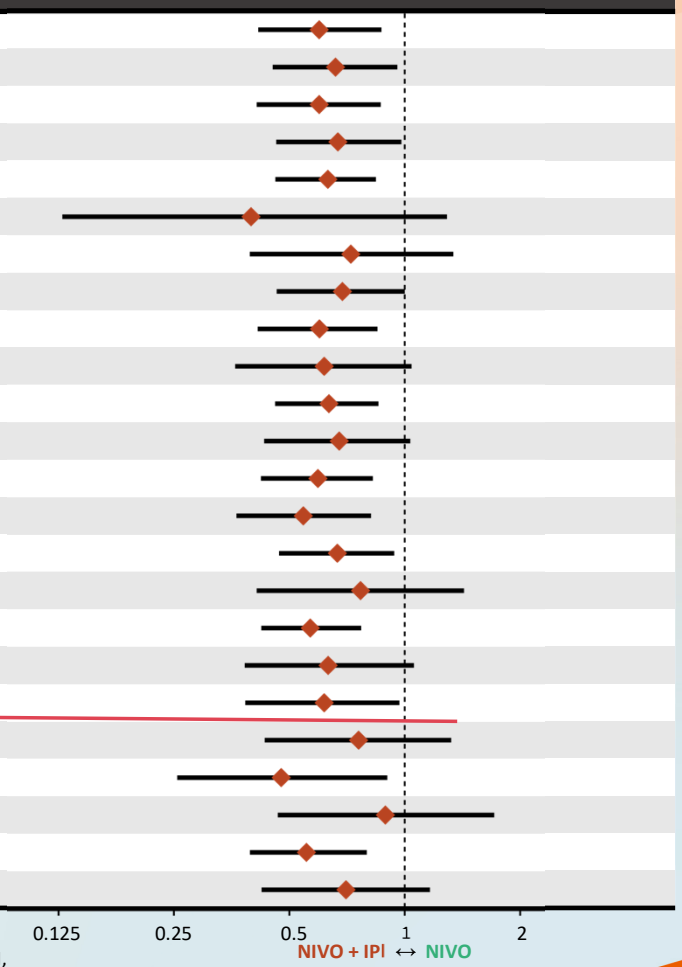
NIVO monotherapy is approved in 2L+ dMMR/MSI-H mCRC by TFDA. NIVO monotherapy is approved in 2L+ dMMR/MSI-H mCRC by TFDA. Median follow-up for all randomized patients was 55.1 (range 24.7–68.5) months. At this interim analysis, only a small alpha was allocated to this endpoint and the threshold was very high (statistical boundary for significance, 0.0007).

CI, confidence interval; dMMR, deficient mismatch repair; HR, hazard ratio; IPI, ipilimumab; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability–high; NE, not evaluable; NIVO, nivolumab; NR, not reported; OS, overall survival.

ESMO 2025, Presentation LBA29.

PFS consistently favored NIVO + IPI in prespecified subgroups across all lines of therapy

Category (centrally confirmed MSI-H/dMMR)	Subgroup	Median PFS[a], mo		Unstratified HR
		NIVO + IPI	NIVO	
Age, years	< 65 (*n* = 321)	NR	NR	0.60
	≥ 65 (*n* = 261)	NR	29.4	0.66
Sex	Male (*n* = 284)	NR	28.2	0.60
	Female (*n* = 298)	NR	NR	0.67
Region	US/Canada/Europe (*n*= 415)	NR	29.4	0.63
	Asia (*n* = 52)	NR	NR	0.40
	Rest of world (*n* = 115)	NR	NR	0.73
ECOG PS	0 (*n* = 313)	54.1	NR	0.69
	1 (*n* = 269)	NR	18.2	0.60
Tumor sidedness	Left (*n* = 152)	NR	NR	0.62
	Right (*n* = 430)	NR	33.2	0.64
Liver metastases[a,b]	Yes (*n* = 210)	NR	NR	0.68
	No (*n* = 368)	NR	33.2	0.60
Peritoneal metastases[a,b]	Yes (*n* = 226)	54.1	24.8	0.55
	No (*n* = 352)	NR	NR	0.67
Tumor cell PD-L1 expression	≥1% (*n* = 133)	NR	NR	0.77
	< 1% (*n* = 427)	NR	24.8	0.57
***BRAF/KRAS/NRAS* mutation status**	*BRAF/KRAS/NRAS* all wild type (*n* = 156)	NR	44.3	0.64
	BRAF mutant (*n* = 179)	NR	25.9	0.62
	KRAS or *NRAS* mutant (*n* = 125)	NR	NR	0.76
	Unknown (*n* = 114)	54.1	38.1	0.48
Clinical history of Lynch syndrome	Yes (*n* = 83)	53.8	38.1	0.90
	No (*n* = 334)	NR	44.3	0.56
	Unknown (*n* = 156)	NR	33.2	0.71

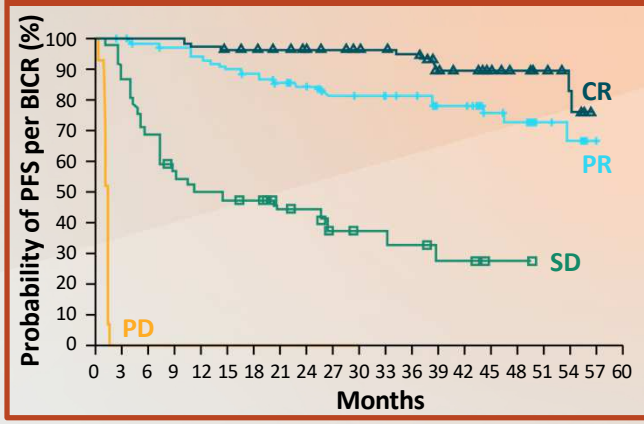


NIVO monotherapy is approved in 2L+ dMMR/MSI-H mCRC by TFDA. [a] Per BICR. [b] Patients may have had more than one site of metastasis.
CI, confidence interval; dMMR, deficient mismatch repair; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; IPI, ipilimumab; MSI-H, microsatellite instability–high; NIVO, nivolumab; NR, not reported; PFS, progression-free survival.
ASCO GI 2025, Abstract LBA143.

NIVO + IPI demonstrates clinically meaningful ORR improvement, higher CR, and lower PD *vs* NIVO monotherapy across all line

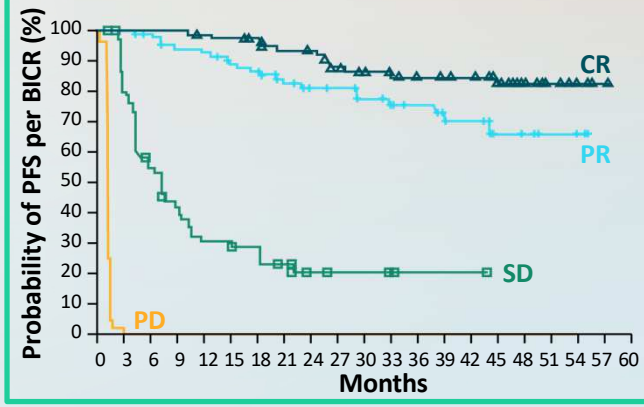
Centrally confirmed MSI-H/dMMR	NIVO + IPI (*n* = 296)	NIVO (*n* = 286)
ORR[a], % (95% CI)	**71 (65–76)**	58 (52–64)
Difference in ORR[b], % (95% CI)	13 (5–21)	
p value[c]	0.0011	
Best overall response[a,d], %		
Complete response	**30**	28
Partial response	**40**	30
Stable disease	14	19
Progressive disease	10	19
Median TTR (range)[a,e], mo	2.8 (1.2–44.5)	2.8 (1.2–29.5)
Median DOR (95% CI)[a,e], mo	NR (NE)	NR (NE)

NIVO + IPI



Centrally confirmed MSI-H/dMMR	Median PFS[b], mo (95% CI)
CR (*n* = 90)	NR (NE–NE)
PR (*n* = 119)	NR (53.6–NE)
SD (*n* = 44)	11.3 (7.3–33.1)
PD (*n* = 30)	1.4 (1.3–1.5)

NIVO



Centrally confirmed MSI-H/dMMR	Median PFS[b], mo (95% CI)
CR (*n* = 80)	NR (NE–NE)
PR (*n* = 85)	NR (NE–NE)
SD (*n* = 59)	7.3 (4.2–10.2)
PD (*n* = 54)	1.4 (1.4–1.5)

NIVO monotherapy is approved in 2L+ dMMR/MSI-H mCRC by TFDA. [a] Per BICR. [b] Strata-adjusted difference in ORR (NIVO + IPI arm - NIVO arm) based on Cochran-Mantel-Haenszel method of weighting. [c] Two-sided *p* value from stratified Cochran-Mantel -Haenszel test. Boundary for statistical significance: $p < 0.006$. [d] Not evaluable: NIVO + IPI, *n* = 17; NIVO, *n* = 14. [e] In responders only (NIVO + IPI, *n* = 209; NIVO, *n* = 165).

BICR, blinded independent central review; CI, confidence interval; CR, complete response; dMMR, deficient mismatch repair; DOR, duration of response; IPI, ipilimumab; MSI-H, microsatellite instability–high; NE, not evaluable; NIVO, nivolumab; NR, not reported; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TTR, time to response.

ASCO 2025, Abstract 3501; ASCO GI 2025 Abstract LBA143.

Grade 3/4 TRAEs: 22% with NIVO + IPI *vs* 14% with NIVO; safety profile consistent with previous reports

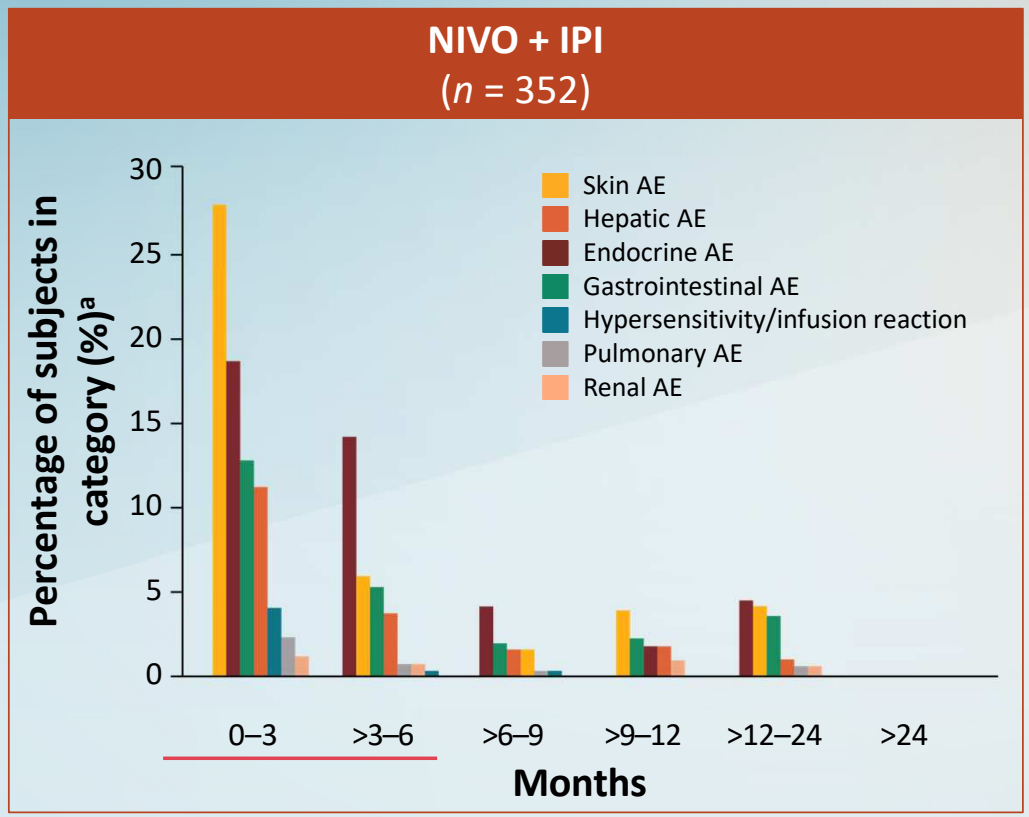
All treated patients, *n* (%)	NIVO + IPI (*n* = 352)		NIVO (*n* = 351)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
TRAEs[a]				
Any TRAEs	285 (81)	78 (22)	249 (71)	50 (14)
Serious TRAEs	65 (18)	55 (16)	29 (8)	24 (7)
TRAEs leading to discontinuation[b]	48 (14)	33 (9)	21 (6)	14 (4)
Treatment-related deaths[c]	2 (<1)[d]		1 (< 1)[e]	
TRAEs[a] reported in ≥10% of patients				
Pruritus (搔癢)	91 (26)	0	63 (18)	0
Diarrhea	71 (20)	3 (< 1)	59 (17)	2 (<1)
Hypothyroidism	61 (17)	2 (<1)	31 (9)	0
Asthenia (衰弱,無力)	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)

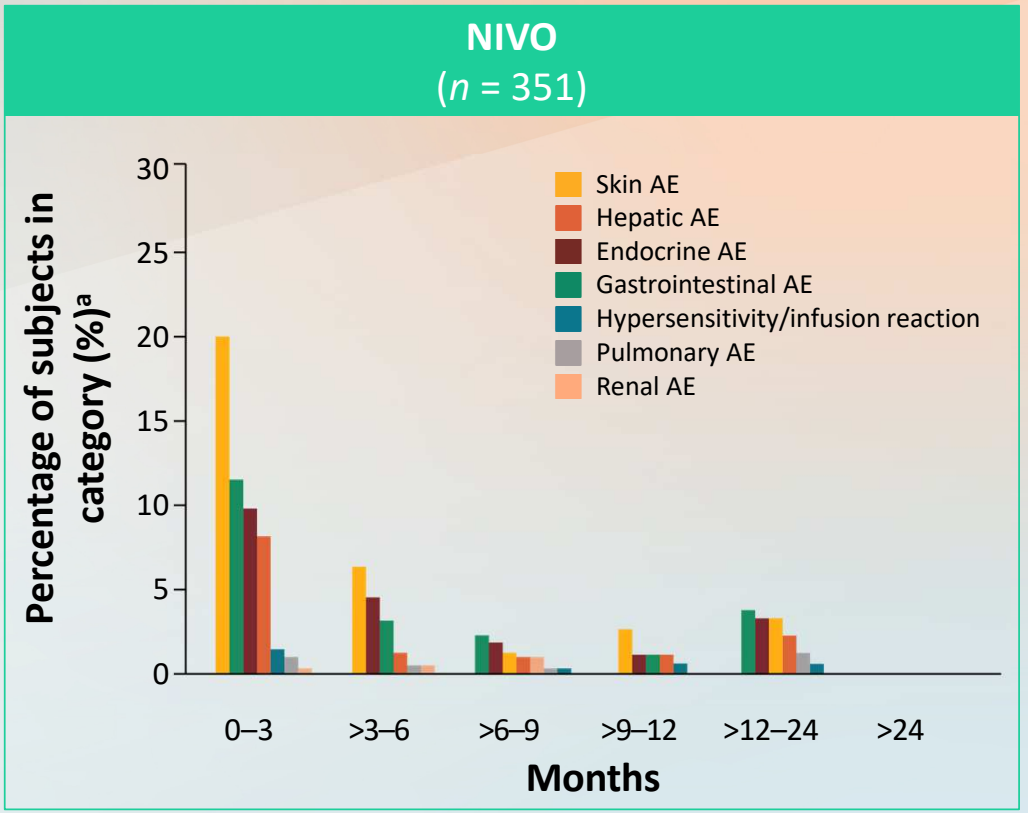
NIVO monotherapy is approved in 2L+ dMMR/MSI-H mCRC by TFDA. [a] Includes events reported between first dose and and 30 days after last dose of study therapy. [b] Discontinuation of any component of the combination regimen was counted as a drug discontinuation event. [c] Treatment-related deaths were 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.

IPI, ipilimumab; NIVO, nivolumab; TRAEs, treatment-related adverse events.

ASCO 2025, Abstract 3501.

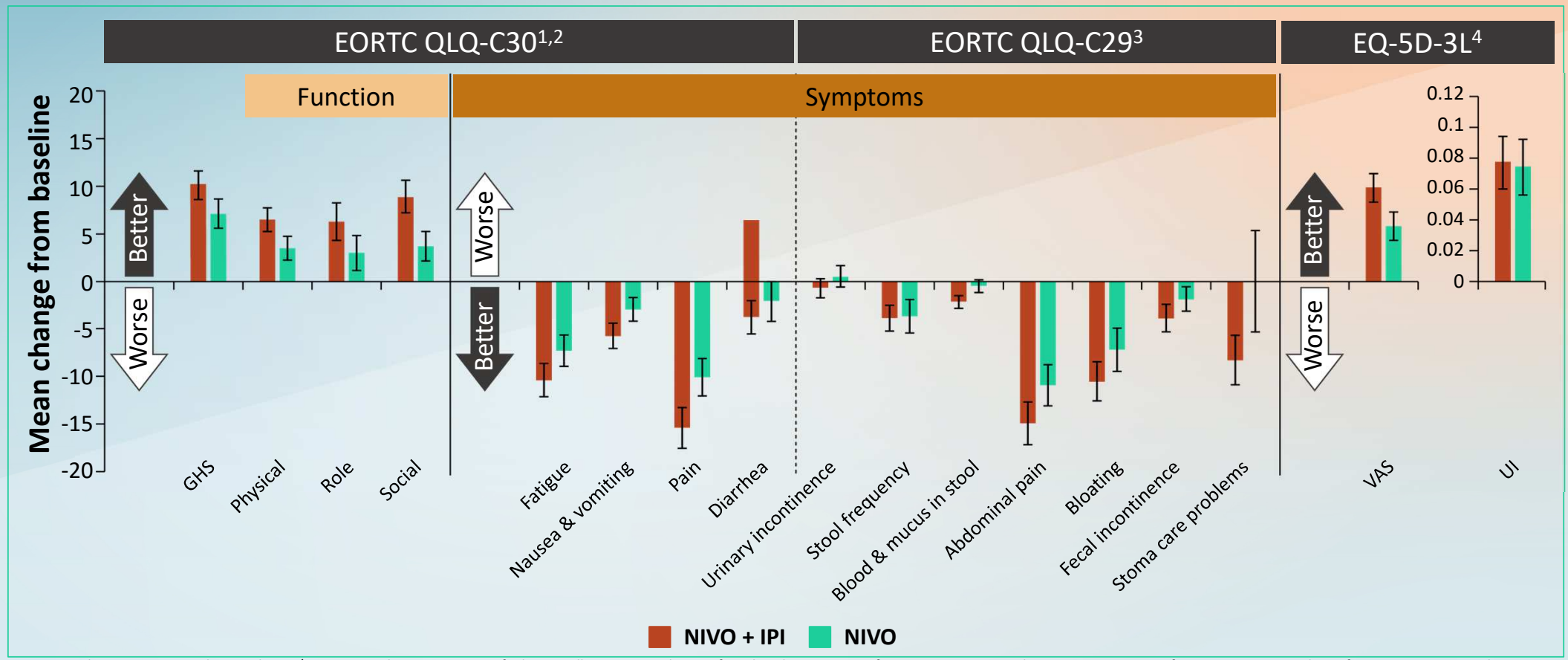
The majority of any-grade irAE in the NIVO + IPI and NIVO arms emerged within the first 6 months of the treatment





NIVO monotherapy is approved in 2L+ dMMR/MSI-H mCRC by TFDA. [a] Includes events reported between first dose and 30 days after last dose of study treatment. Patients with ≥ 1 any grade event in a given category were counted only once in the time interval corresponding to the first event. Patients with multiple events from different categories within the same time interval were counted once in each category. Proportion of patients in each category is based on the patients still on treatment for the respective time interval. [b] Number of patients still receiving treatment is identified at the beginning of each respective time interval. [c] TRAEs with potential immunologic etiology that require frequent monitoring/intervention.
AE, adverse event; IPI, ipilimumab; irAE, immune related adverse event; NIVO, nivolumab.
ASCO 2025, Abstract 3501.

The addition of IPI to NIVO significantly improved PFS *vs* NIVO alone while maintaining HRQoL



NIVO monotherapy is approved in 2L+ dMMR/MSI-H mCRC by TFDA. Prespecified minimally important changes from baseline were 10.0 for EORTC QLO-C30 and EORTC QLQ-CR29, 7.0 for EQ-5D-3L VAS, and 0.08 for EQ-5D-3L UI. Error bars represent standard error for the mean.

EORTC QLQ-C29, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Colorectal Cancer Module (29 items); EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; EQ-5D-3L, EuroQol 5-Dimension 3-Level questionnaire; GHS, global health status; HRQoL, health-related quality of life; IPI, ipilimumab; NIVO, nivolumab; PFS, progression-free survival; UI, utility index; VAS, visual analogue scale.

ESMO GI 2025, Abstract 246.

Secondary endpoint: PFS & ORR in

NIVO + IPI *vs* NIVO mono as 1L Therapy

CheckMate 8HW

Baseline characteristics in 1L patients

Characteristic	Category	1L, all randomized		1L, centrally confirmed	
		NIVO + IPI (*n* = 202)	NIVO (*n* = 201)	NIVO + IPI (*n* = 171)	NIVO (*n* = 170)
Age, years	Median (range)	62 (21–86)	63 (20–87)	62 (21–86)	63 (20–87)
Sex, *n* (%)	Female	107 (53)	99 (49)	79 (46)	83 (49)
	Male	95 (47)	102 (51)	92 (54)	87 (51)
Region, *n* (%)	US/Canada/Europe	133 (66)	134 (67)	109 (64)	115 (68)
	Asia	19 (9)	23 (11)	17 (10)	22 (13)
	Rest of world	50 (25)	44 (22)	45 (26)	33 (19)
ECOG PS, *n* (%)	0	111 (55)	105 (52)	97 (57)	92 (54)
Disease stage at initial diagnosis[a], *n* (%)	Stage IV	85 (42)	88 (44)	74 (43)	70 (41)
Tumor sidedness per IRT, *n* (%)	Right	137 (68)	136 (68)	123 (72)	124 (73)
Sites of metastases by BICR[b,c], *n* (%)	Liver	75 (37)	82 (41)	54 (32)	63 (37)
	Lung	44 (22)	52 (26)	37 (22)	42 (25)
	Peritoneum	84 (42)	80 (40)	76 (44)	66 (39)
Tumor cell PD-L1[d], *n* (%)	< 1%	145 (72)	148 (74)	122 (71)	124 (73)
	≥ 1%	43 (21)	38 (19)	43 (25)	37 (22)
***BRAF*, *KRAS*, *NRAS* mutation status[e], *n* (%)**	*BRAF*/*KRAS*/*NRAS* all wild type	49 (24)	55 (27)	43 (25)	46 (27)
	BRAF mutant	53 (26)	43 (21)	51 (30)	41 (24)
	KRAS or *NRAS* mutant	43 (21)	47 (23)	29 (17)	41 (24)
	Unknown	50 (25)	54 (27)	42 (25)	41 (24)
Clinical history of Lynch syndrome[f], *n* (%)	Yes	22 (11)	28 (14)	18 (11)	25 (15)
	No	135 (67)	125 (62)	113 (66)	101 (59)
	Reported as unknown	44 (22)	45 (22)	39 (23)	41 (24)

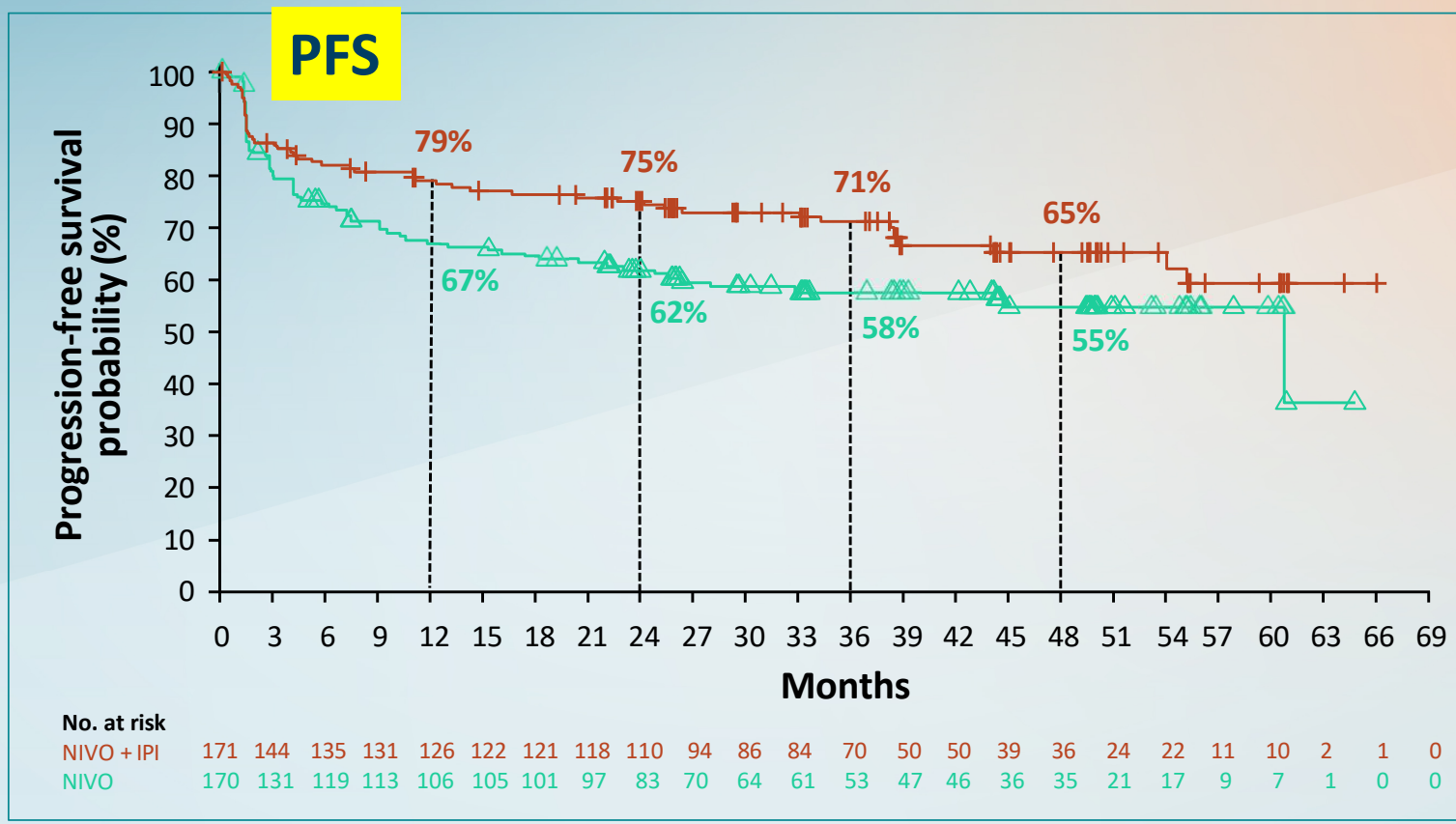
NIVO monotherapy is approved in 2L+ dMMR/MSI-H mCRC by TFDA. [a] Disease stage not reported across all lines: NIVO + IPI, *n* = 2; NIVO, *n* = 1. [b] Patients may have had more than 1 site of metastasis. [c] Sites of metastases not reported across all lines: NIVO + IPI, *n* = 3; NIVO, *n* = 2. [d] Tumor cell PD-L1 expression indeterminate, not evaluable, or not available across all lines: NIVO + IPI, *n* = 25; NIVO, *n* = 26. [e] *BRAF* and *KRAS*/*NRAS* mutant across all lines: NIVO + IPI, *n* = 9; NIVO, *n* = 2. [f] Patients with Lynch syndrome not reported across all lines: NIVO + IPI, *n* = 3; NIVO, *n* = 6.

chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IPI, ipilimumab; IRT, Interactive Response Technology; NIVO, nivolumab.

ESMO 2025, Presentation LBA29.

CheckMate 8HW

NIVO + IPI demonstrates clinically meaningful PFS improvement in 1L MSI-H/dMMR mCRC



	NIVO + IPI (*n* = 171)	NIVO (*n* = 170)
Median PFS[a], mo 95% CI	NR 55.2–NE	60.8 32.8–NE
HR (95% CI) *p* value	0.69 (0.48–0.99) 0.0413	

In patients with centrally confirmed MSI-H/dMMR mCRC, 1L NIVO + IPI demonstrated clinically meaningful improvement in PFS *vs* NIVO (HR 0.69, [95% CI 0.48–0.99])

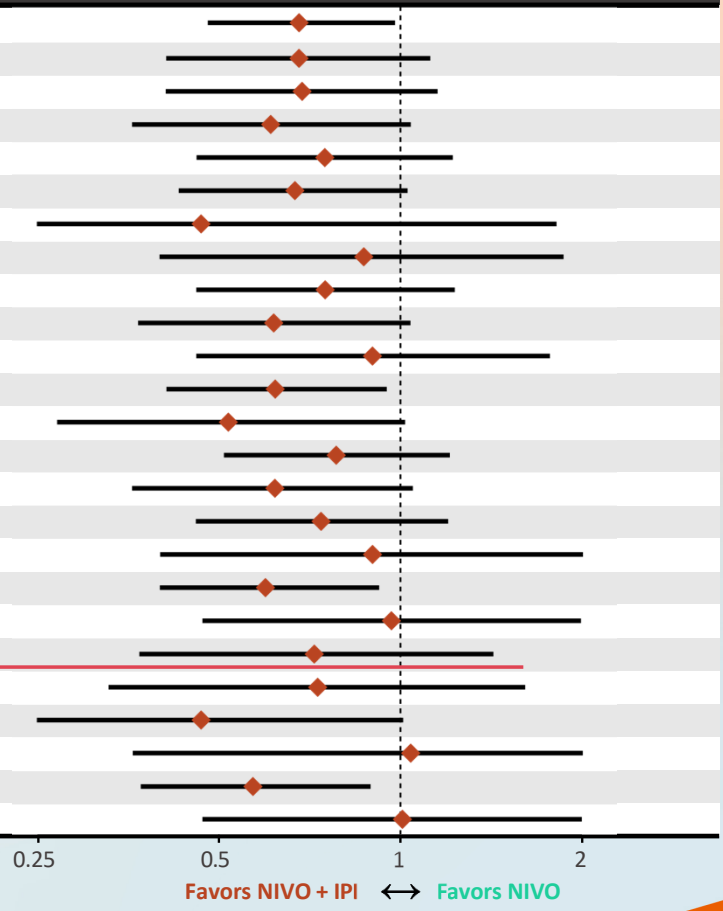
- The prespecified threshold for statistical significance was not met ($p < 0.0383$)
- These data are consistent with those observed in the 1L all randomized population by local testing (HR 0.75, [95% CI 0.56–1.01])

NIVO monotherapy is approved in 2L+ dMMR/MSI-H mCRC by TFDA. Median follow-up for all randomized 1L patients was 50.1 (range 24.7–67.3) months. [a] As assessed by BICR.
chemo, chemotherapy; CI, confidence interval; dMMR, deficient mismatch repair; HR, hazard ratio; IPI, ipilimumab; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability–high; NE, not evaluable; NIVO, nivolumab; PFS, progression-free survival.
ESMO 2025, Presentation LBA29.

CheckMate 8HW

PFS favors NIVO + IPI over NIVO monotherapy across all Subgroups, including *RAS*/*BRAF* mutations and liver/lung metastases

Category (centrally confirmed MSI-H/dMMR)	Subgroup	Median PFS[a], mo		Unstratified HR
		NIVO + IPI	NIVO	
Overall (*N* = 341)		NR	60.8	0.68
Age, years	< 65 (*n* = 191)	NR	NR	0.68
	≥ 65 (*n* = 150)	NR	60.8	0.69
Sex	Male (*n* = 162)	NR	NR	0.61
	Female (*n* = 179)	NR	60.8	0.75
Region	US/Canada/Europe (*n* = 224)	NR	60.8	0.67
	Asia (*n* = 39)	NR	NR	0.47
	Rest of world (*n* = 78)	55.2	NR	0.87
ECOG PS	0 (*n* = 189)	NR	60.8	0.75
	1 (*n* = 152)	NR	44.9	0.62
Tumor sidedness[b]	Left (*n* = 94)	54.1	60.8	0.90
	Right (*n* = 247)	NR	NR	0.62
Liver metastases[a,c]	Yes (*n* = 117)	NR	60.8	0.52
	No (*n* = 221)	NR	NR	0.78
Peritoneal metastases[a,c]	Yes (*n* = 142)	NR	44.9	0.62
	No (*n* = 196)	NR	NR	0.74
Tumor cell PD-L1 expression	≥ 1% (*n* = 80)	NR	60.8	0.90
	< 1% (*n* = 246)	NR	NR	0.60
***BRAF*/*KRAS*/*NRAS* mutation status**	*BRAF*/*KRAS*/*NRAS* all wild type (*n* = 89)	NR	NR	0.97
	BRAF mutant (*n* = 92)	NR	60.8	0.72
	KRAS or *NRAS* mutant (*n* = 70)	NR	NR	0.73
	Unknown (*n* = 83)	NR	NR	0.47
Clinical history of Lynch syndrome	Yes (*n* = 43)	NR	NR	1.04
	No (*n* = 214)	NR	44.9	0.57
	Unknown (*n* = 80)	NR	NR	1.01



NIVO monotherapy is approved in 2L+ dMMR/MSI-H mCRC by TFDA. [a] Per BICR. [b] Per IRT. [c] Patients may have had more than one site of metastasis.
CI, confidence interval; dMMR, deficient mismatch repair; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; IPI, ipilimumab; MSI-H, microsatellite instability–high; NIVO, nivolumab; NR, not reported; PFS, progression-free survival.
ESMO 2025, Presentation LBA29.

CheckMate 8HW

NIVO + IPI demonstrates clinically meaningful ORR improvement, higher CR, and lower PD *vs* NIVO monotherapy in 1L CRC

	NIVO + IPI (*n* = 171)	NIVO (*n* = 170)
ORR,[a,b] %	**73**	61
95% CI	65–79	53–79
Best overall response,[b,c] %		
CR	**35**	31
PR	**37**	31
SD	12	19
PD	11	16
Median time to response (range),[d] months	2.8 (1.2–38.6)	2.7 (1.2–29.5)
Median duration of response (95% CI),[d,e] months	NR (NE)	NR (59.4–NE)

These data are consistent with those observed in the 1L all randomized population by local testing (ORR [95% CI], 66% [59–72] *vs* 54% [47–61])

NIVO monotherapy is approved in 2L+ dMMR/MSI-H mCRC by TFDA. Median follow-up for all randomized 1L patients was 50.1 (range 24.7-67.3) months. [a] The proportion of patients with a CR or PR, with confirmation of response ≥ 4 weeks later (due to rounding, the ORR may not equal the sum of the CR and PR rates). [b] As assessed by BICR using RECIST v1.1. [c] Not evaluable/not reported: NIVO + IPI, *n* = 8 NIVO, *n* = 6. [d] Calculated only for patients with a confirmed objective response (NIVO + IPI, *n* = 124; NIVO, *n* = 104). [e] Median estimated using the Kaplan-Meier method.

CI, confidence interval; CR, complete response; IPI, ipilimumab; NE, not evaulable; NR, not reported; NIVO, nivolumab; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

ESMO 2025, Presentation LBA29.

CheckMate 8HW

Grade 3/4 TRAEs: 24% with NIVO + IPI *vs* 17% with NIVO; safety profile consistent with previous reports

All treated patients, *n* (%)	NIVO + IPI (*n* = 200)		NIVO (*n* = 199)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
TRAEs[a]				
Any TRAEs	164 (82)	47 (24)	156 (78)	34 (17)
Serious TRAEs	37 (19)	31 (16)	19 (10)	16 (8)
TRAEs leading to discontinuation of any component	33 (17)	24 (12)	15 (8)	8 (4)
Treatment-related deaths[b]	2 (1)[c]		1 (< 1)[d]	
TRAEs reported in ≥10% of patients[a]				
Pruritus	47 (24)	0	38 (19)	0
Diarrhea	41 (21)	1 (< 1)	38 (19)	2 (1)
Hypothyroidism	32 (16)	2 (1)	22 (11)	0
Asthenia	28 (14)	2 (1)	24 (12)	2 (1)
Fatigue	26 (13)	1 (< 1)	18 (9)	1 (< 1)
Rash	24 (12)	3 (2)	20 (10)	1 (< 1)
Adrenal insufficiency	20 (10)	6 (3)	9 (5)	2 (1)
ALT increased	20 (10)	3 (2)	15 (8)	2 (1)
Arthralgia	18 (9)	1 (< 1)	11 (6)	0
Hyperthyroidism	18 (9)	0	11 (6)	0

NIVO monotherapy is approved in 2L+ dMMR/MSI-H mCRC by TFDA. [a] Includes TRAEs reported between first dose and 30 days after last dose of study therapy. [b] Treatment-related deaths were reported regardless of timeframe. [c] Includes 1 treatment-related death due to myocarditis and 1 due to pneumonitis. [d] One treatment-related death due to pneumonitis.

IPI, ipilimumab; NIVO, nivolumab; TRAEs, treatment-related adverse events.

ESMO 2025, Presentation LBA29.

Summary

These new results further support NIVO + IPI as a standard of care option for the 1L treatment of MSI-H/dMMR mCRC

1L NIVO + IPI demonstrated clinically meaningful PFS improvements *vs* chemotherapy or NIVO in patients with centrally confirmed MSI-H/dMMR mCRC, with a 79% and 31% reduction in the risk of progression or death respectively

A clinically meaningful improvement in ORR, higher CR rate, and lower PD rate was also observed with 1L NIVO + IPI *vs* NIVO

NIVO + IPI delivers superior PFS across all subgroups, including *RAS*/*BRAF* mutations and liver/lung metastases
(*vs* Chemotherapy in 1L; *vs* NIVO across all line)

No new safety signals or additional treatment-related deaths were observed with 1L NIVO + IPI or NIVO during longer follow-up

CR, complete response; dMMR, deficient mismatch repair; IPI, ipilimumab; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability–high; NIVO, nivolumab; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival.

outline

treatment guidelines for stage IV mCRC first-line treatment

dMMR/MSI-H

CheckMate 8HW

Keynote 177

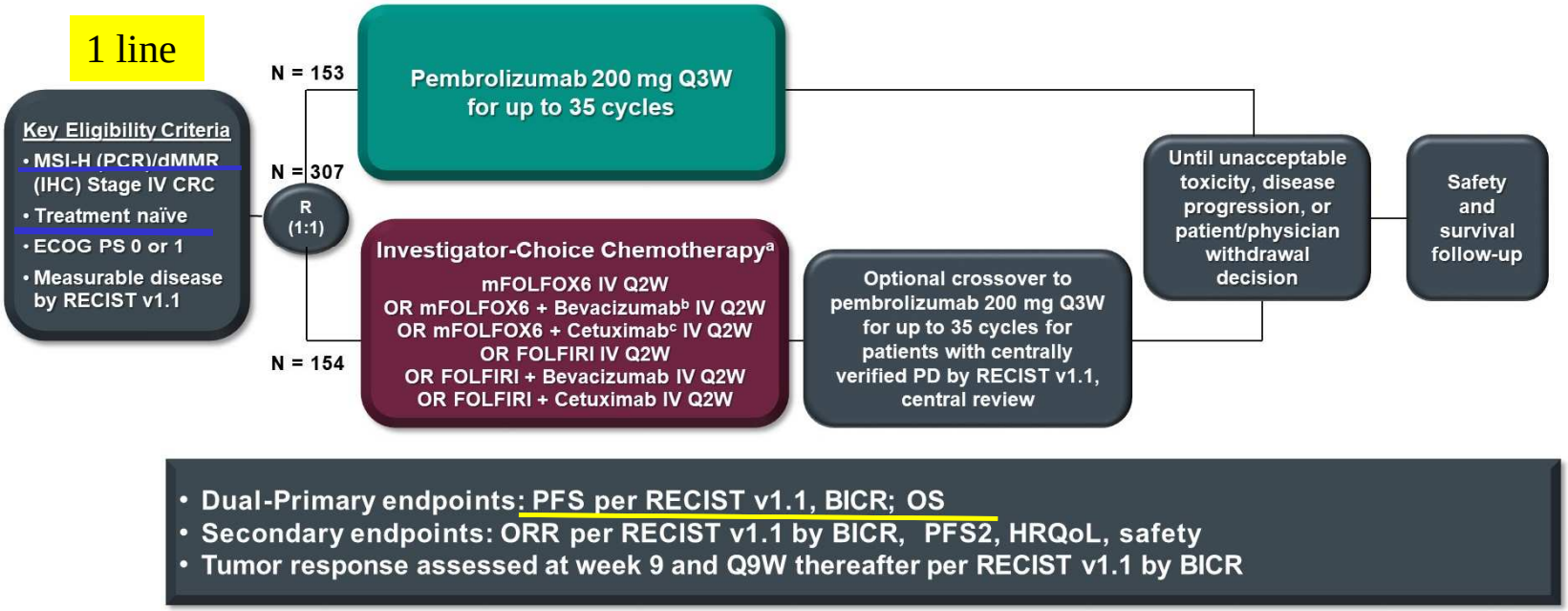
Case sharing

Phase 3

Andre KN177FA ASCO 2021

KEYNOTE-177 Study Design
(NCT02563002)

1 line

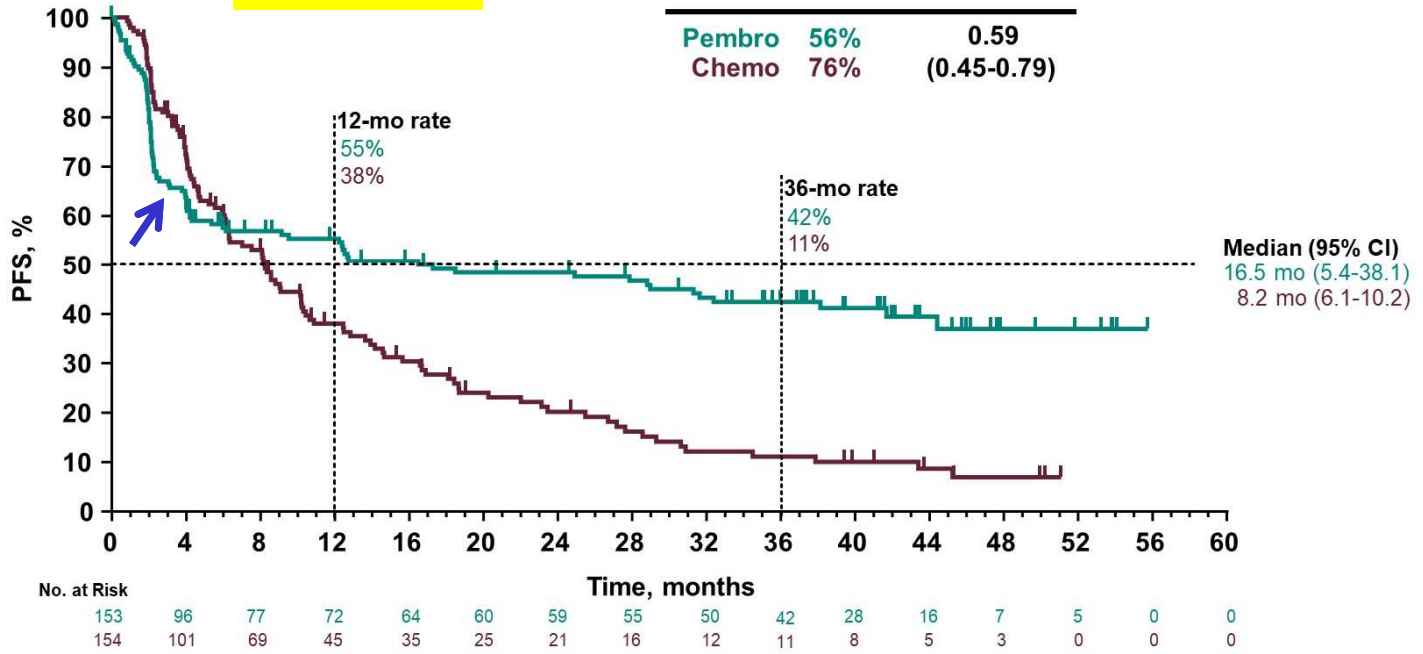


- Dual-Primary endpoints: PFS per RECIST v1.1, BICR; OS
- Secondary endpoints: ORR per RECIST v1.1 by BICR, PFS2, HRQoL, safety
- Tumor response assessed at week 9 and Q9W thereafter per RECIST v1.1 by BICR

[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.

Progression-Free Survival

PFS: 16.5m



Data cut-off: 19Feb2021.

PFS: 16.5m

Table 3 Treatment effects by primary tumour location in *KRAS/RAS* wild-type patients in the main published studies

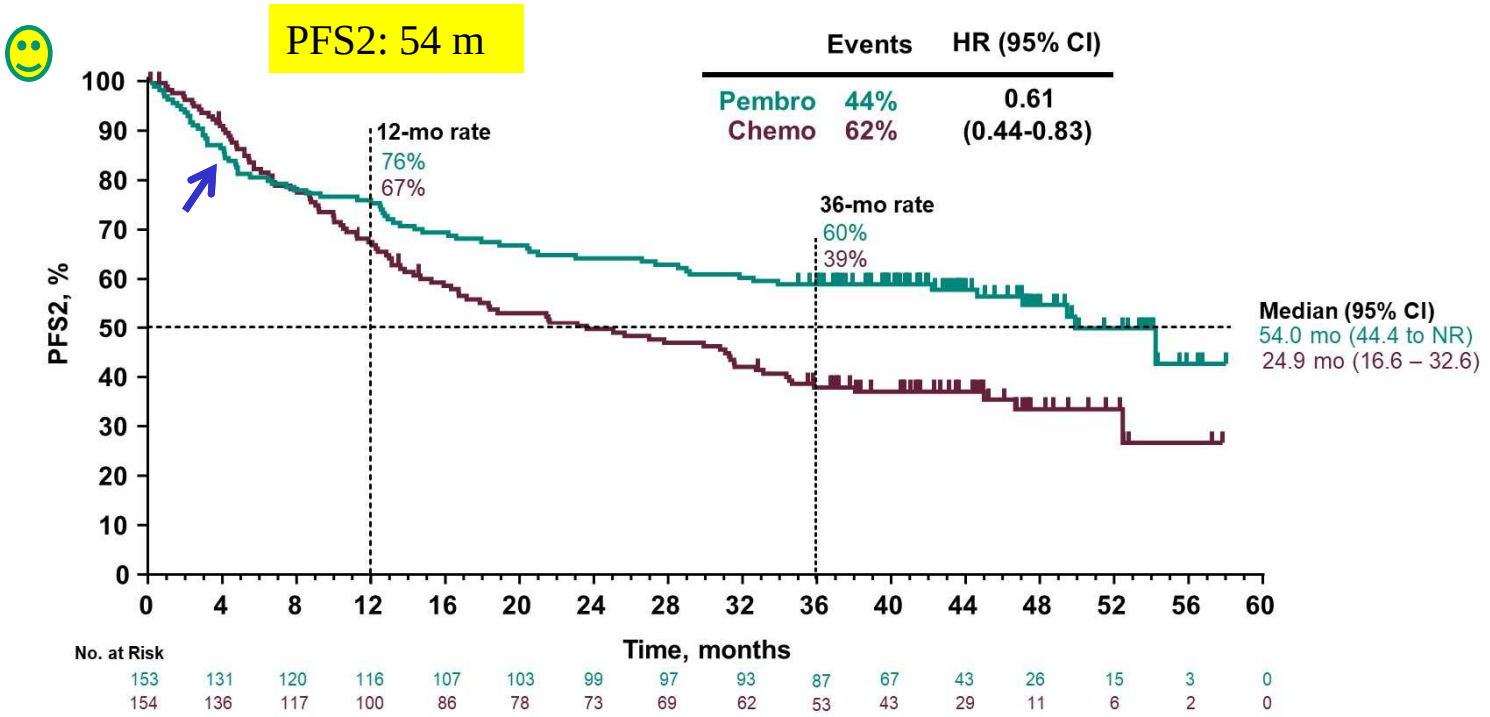
		Median OS (months)		Median PFS (months)	
		Right-sided	Left-sided	Right-sided	Left-sided
CRYSTAL[1]	FOLFIRI	15.0	21.7	7.1	8.9
	FOLFIRI+cetuximab	18.5	28.7*†	8.1	12.0*†
PRIME[7]	FOLFOX	15.4	23.6	7.0	9.2
	FOLFOX+panitumumab	11.1	30.3*†	7.5	12.9*
CALGB/SWOG 80405[6]	FOLFOX or FOLFIRI+bevacizumab	24.5	32.1†	9.5	11.1†
	FOLFOX or FOLFIRI+cetuximab	16.4	37.5†	7.7	12.0†
FIRE-3[1]	FOLFIRI+bevacizumab	23.0	28.0†	9.0	10.7
	FOLFIRI+cetuximab	18.3	38.3*†	7.6	10.7†
PEAK[7]	FOLFOX+panitumumab	17.5	43.4†	8.7	14.6
	FOLFOX+bevacizumab	21.0	32.0†	12.6	11.5
Present study: MACRO-2+PLANET	FOLFOX or FOLFIRI+cetuximab or panitumumab	13.5	32.7†	6.5	10.0†

*P value statistically significant between treatments in the same tumour location.
†P value statistically significant between tumour locations (right vs left)
OS, overall survival; PFS, progression-free survival.

Benavides M, et al. ESMO Open 2019;4:e000599

Progression-Free Survival 2

Time from randomization to progression on next line therapy or any cause death



Data cut-off: 19Feb2021.

Antitumor Response

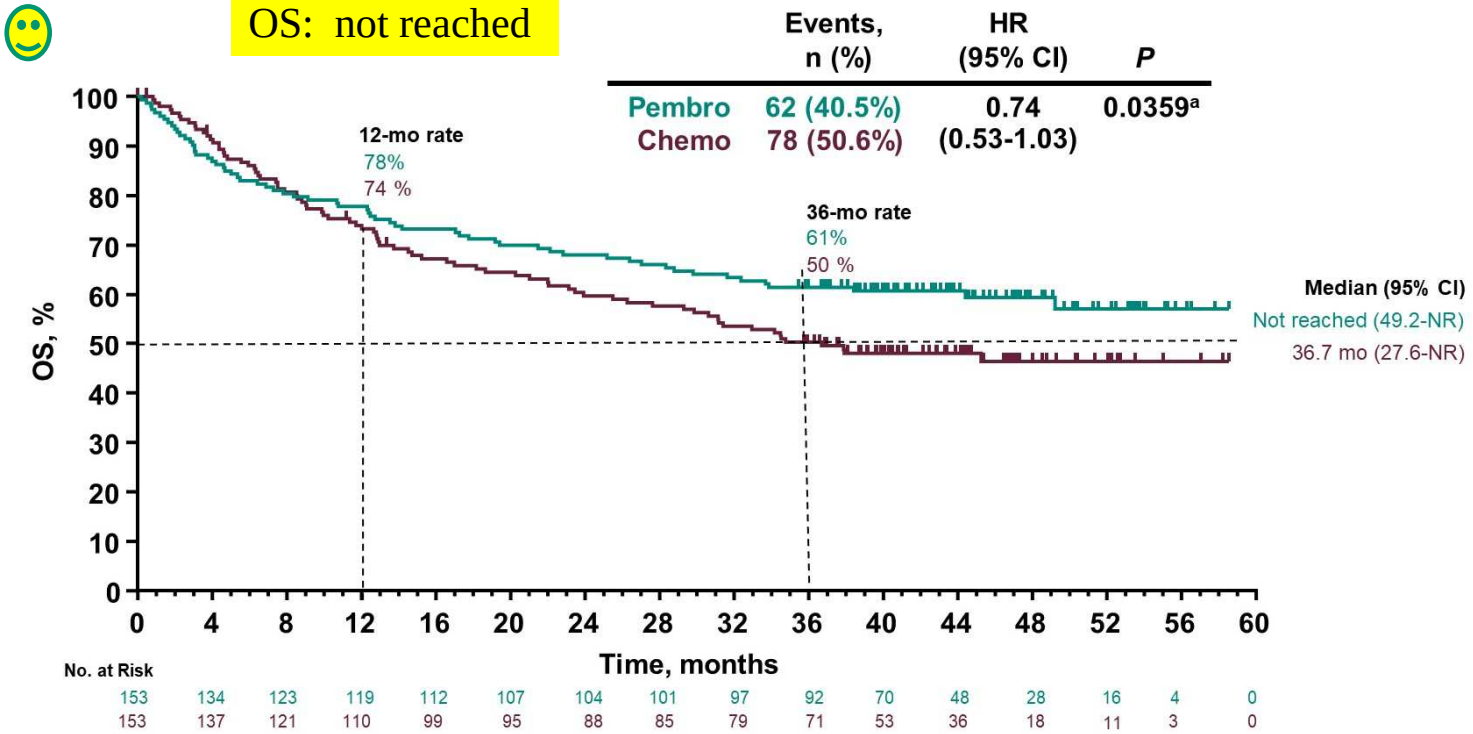
	Pembrolizumab N = 153	Chemotherapy N = 154
ORR, n (%)	**69 (45.1)[a]**	**51 (33.1)**
Best Overall Response, n (%)		
Complete response	20 (13.1)[b]	6 (3.9)
Partial response	49 (32.0)[c]	45 (29.2)
Stable disease	30 (19.6)	65 (42.2)
Disease control rate (CR+PR+SD)	99 (64.7)	116 (75.3)
Progressive disease	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.

Overall Survival

- 56 of 154 (36%) patients in the chemotherapy arm crossed over to receive pembrolizumab after confirmed disease progression

OS: not reached



[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.

outline

treatment guidelines for stage IV mCRC first-line treatment

dMMR/MSI-H

CheckMate 8HW

Kynote 177

Case sharing

Outline

- HNSCC Reimbursement Criteria Update (keynote 048)
- NSCLC Reimbursement Criteria Update (keynote 189)
- MSI-H mCRC Reimbursement Criteria Update (keynote 177)
- Early TNBC Reimbursement Criteria Update (keynote 522, m355)

Outline

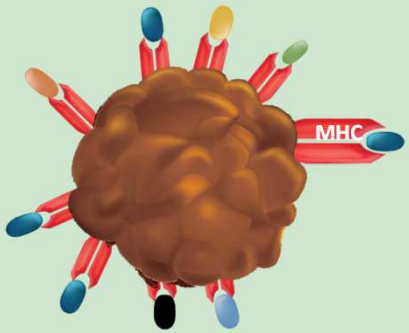
- Frequency of MSI-H/dMMR in cancers and the value of microsatellite instability (MSI) and mismatch repair (MMR) testing.
- Therapeutic rationale for the advanced MSI-H/dMMR cancers.
- Clinical data for a treatment option in advanced MSI-H/dMMR cancers who have failed prior therapy.
  - non-CRC:

    monotherapy KN158/ combination: KN146/ KN775
  - CRC: monotherapy KN164/ KN177
- TMB-H
- Pembrolizumab Q6W

dMMR = mismatch repair deficient; MSI-H = microsatellite instability-high.

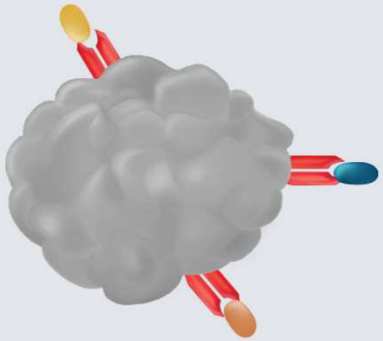
The PD-1 Receptor Can Be a Therapeutic Target in MSI-H/dMMR Tumors

MSI-H/dMMR Tumors Have Higher Mutational Load and Higher Expression of Neoantigens Compared With MSS Tumors[1,2]



MSI-H/dMMR tumor

MSI-H/dMMR tumors are characterized by 10–50 times more tumor-specific neoantigens than MSS tumors[1]



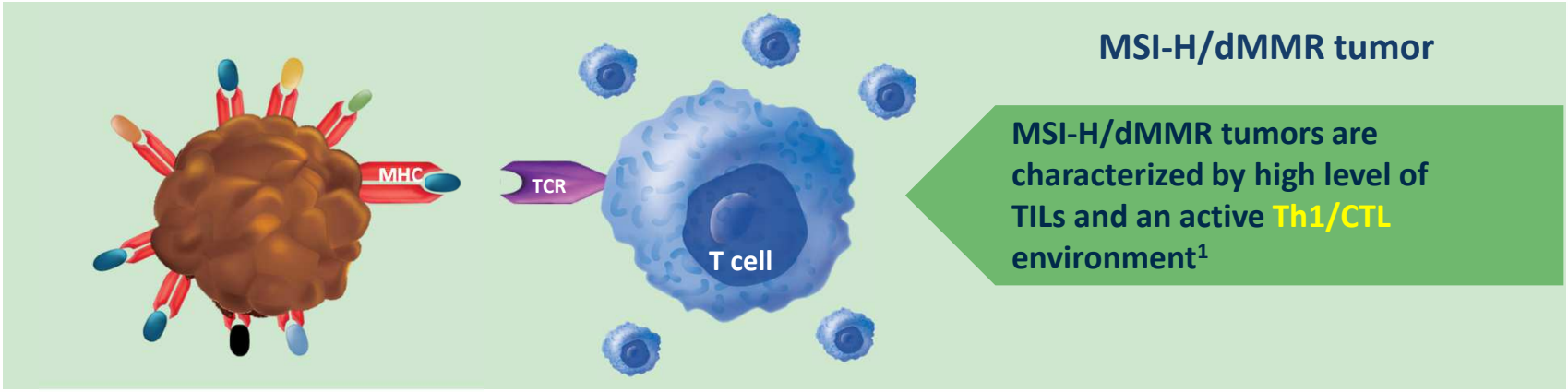
MSS tumor

dMMR = mismatch repair deficient; MHC = major histocompatibility complex; MSI-H = microsatellite instability-high; MSS = microsatellite stable; PD-1 = programmed death receptor-1.

1. Llosa NJ et al. *Cancer Discov.* 2015;5(1):43–51. **2**. Pardoll DM. *Nat Rev Cancer*. 2012;12(4):252–264.

The PD-1 Receptor Can Be a Therapeutic Target in MSI-H/dMMR Tumors

MSI-H/dMMR Tumors Have High Level of TILs[1,2]



CTL = cytotoxic T lymphocyte; dMMR = mismatch repair deficient; MHC = major histocompatibility complex; MSI-H = microsatellite instability-high; MSS = microsatellite stable; PD-1 = programmed death receptor-1; TCR = T-cell receptor; Th1 = T-helper cell 1; TIL = tumor infiltrating-lymphocytes.

1. Llosa NJ et al. *Cancer Discov.* 2015;5(1):43–51. **2.** Pardoll DM. *Nat Rev Cancer*. 2012;12(4):252–264.

The PD-1 Receptor Can Be a Therapeutic Target in MSI-H/dMMR Tumors

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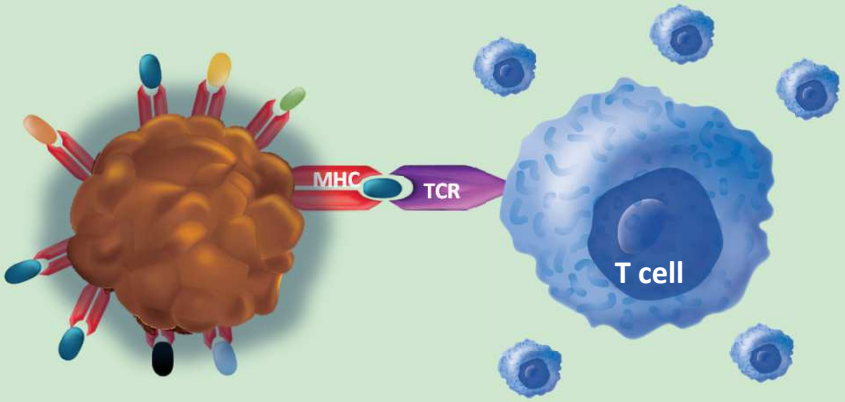
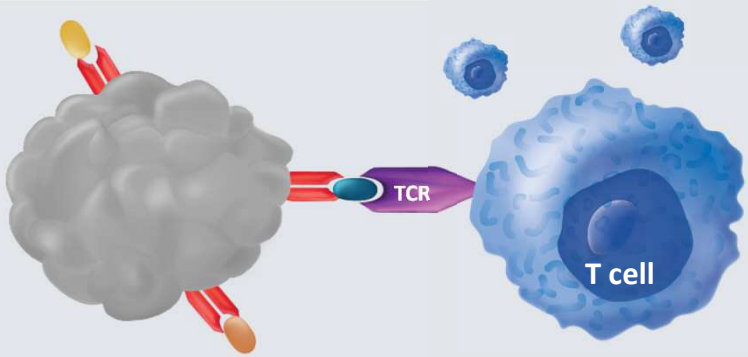


MSI-H/dMMR tumor

MSI-H/dMMR tumors are characterized by high level of TILs and an active Th1/CTL environment[1]



MSS tumor

CTL = cytotoxic T lymphocyte; dMMR = mismatch repair deficient; MHC = major histocompatibility complex; MSI-H = microsatellite instability-high; MSS = microsatellite stable; PD-1 = programmed death receptor-1; TCR = T-cell receptor; Th1 = T-helper cell 1; TIL = tumor infiltrating-lymphocytes.

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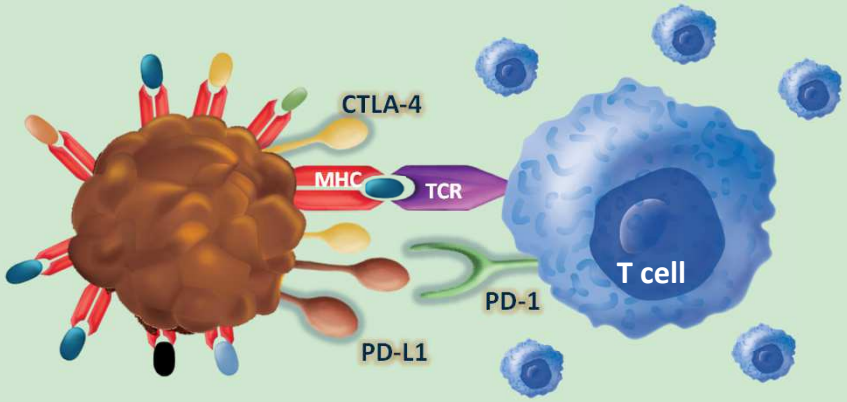
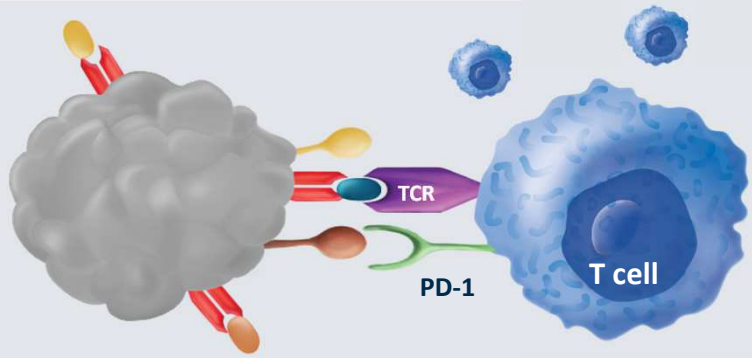
The PD-1 Receptor Can Be a Therapeutic Target in MSI-H/dMMR Tumors

MSI-H/dMMR Tumors Have High Expression of Immune Checkpoint Molecules[1,2]



MSI-H/dMMR tumor

MSI-H/dMMR tumors are characterized by high expression of checkpoint molecules such as PD-1, PD-L1, CTLA-4, LAG-3, and IDO[1]



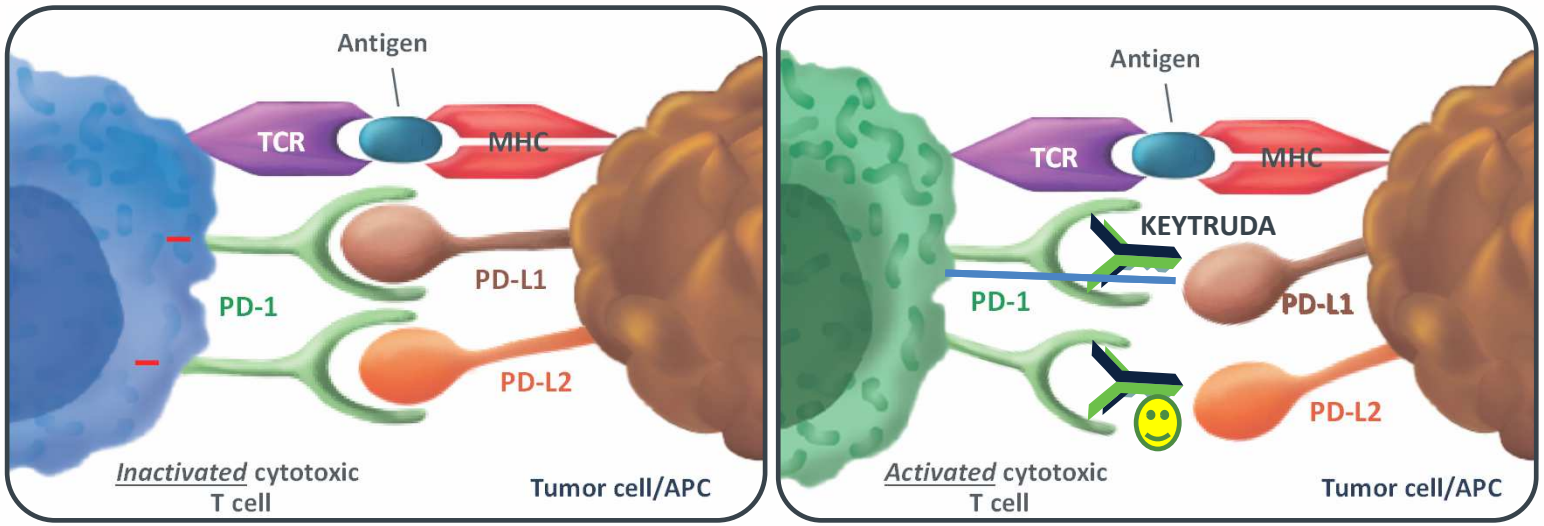
MSS tumor

CTLA-4 = cytotoxic T lymphocyte antigen-4; dMMR = mismatch repair deficient; IDO = indolamine 2'3'-dioxygenase; LAG-3 = lymphocyte-activation gene 3; MHC = major histocompatibility complex; MSI-H = microsatellite instability-high; MSS = microsatellite stable; PD-1 = programmed death receptor-1; PD-L1 = programmed death-ligand-1; TCR = T-cell receptor.

1. Llosa NJ et al. *Cancer Discov.* 2015;5(1):43–51. **2**. Pardoll DM. *Nat Rev Cancer*. 2012;12(4):252–264.

PD-1 Receptor Blockade With KEYTRUDA® (pembrolizumab)

- By inhibiting the PD-1 receptor from binding to its ligands, KEYTRUDA reactivates tumor-specific cytotoxic T lymphocytes in the tumor microenvironment and reactivates antitumor immunity.[1,2]



APC = antigen-presenting cell; MHC = major histocompatibility complex; PD-1 = programmed death receptor-1; PD-L1 = programmed death ligand 1; PD-L2 = programmed death ligand 2; TCR = T-cell receptor.

Image adapted with permission from Pardoll DM. *Nat Rev Cancer.* 2012;12(4):252–264.

1. KEYTRUDA®吉舒達®衛生福利部核准之藥品仿單 **2.** Pardoll DM. *Nat Rev Cancer.* 2012;12(4):252–264.

ESMO guideline