MSD Oncology

Study of pembrolizumab vs standard therapy in participants with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) Stage IV colorectal carcinoma (CRC)

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MSD
Merck Sharp & Dohme (UK) Limited
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Registered in England No. 233687

Slide deck navigation

Click the links below to navigate to the section of interest

Metastatic MSI-H/dMMR overview

KEYNOTE-177 overview

KEYNOTE-177 results

Appendix

- To access the navigation page, click the ‘Home’ icon
- To access the Appendix page, click the ‘Book’ icon
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dMMR, mismatch repair deficient; MSI-H, microsatellite instability-high.

KEYTRUDA® (pembrolizumab) licensed indications

- **Pembrolizumab as monotherapy is indicated for adults with MSI-H or dMMR CRC in the following settings:**
  - First-line treatment of metastatic CRC
  - Treatment of unresectable or metastatic CRC after previous fluoropyrimidine-based combination therapy
- For treatment with pembrolizumab as monotherapy, testing for MSI-H/dMMR tumour status using a validated test is recommended to select patients with CRC
- Patients should be treated with pembrolizumab until disease progression or unacceptable toxicity. Atypical responses (i.e. an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed
- It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.
- No dose reductions of pembrolizumab are recommended. Pembrolizumab should be withheld or discontinued to manage AEs as described within the SmPC

AE, adverse event; CRC, colorectal cancer; dMMR, mismatch repair deficient; IV, intravenous; MSI-H, microsatellite instability-high; Q3W, every 3 weeks; Q6W, every 6 weeks; SmPC, Summary of Product Characteristics.

KEYTRUDA (pembrolizumab) Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/2498/smpc#gref (GB) and https://www.emcmedicines.com/en-gb/northernireland/medicine?id=ce680467-8438-4e60-ab4f-dfab6767ccbe&type=smpc (NI). Accessed November 2023.

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Reimbursements[1–3]

NICE:

- Pembrolizumab is recommended as an option for treating tumours with MSI-H or MMR deficiency in adults with:
  - CRC after fluoropyrimidine combination therapy, only if they cannot have nivolumab with ipilimumab
- Pembrolizumab is recommended as an option for untreated metastatic colorectal cancer with MSI-H or MMR deficiency in adults
- Pembrolizumab is only recommended if:
  - Pembrolizumab is stopped after 2 years and no documented disease progression
  - The company provides pembrolizumab according to the commercial arrangement

SMC:

- Pembrolizumab is accepted for use within NHSScotland as monotherapy for the first-line treatment of metastatic MSI-H or dMMR colorectal cancer in adults
  - Treatment with pembrolizumab is subject to a 2-year clinical stopping rule

CRC, colorectal cancer; dMMR, mismatch repair deficient; IV, intravenous; MSI-H, microsatellite instability-high; SMC, Scottish Medicines Consortium.

1. NICE. Pembrolizumab for previously treated endometrial, biliary, colorectal, gastric or small intestine cancer with high microsatellite instability or mismatch repair deficiency. Available at: https://www.nice.org.uk/guidance/ta914/resources/pembrolizumab-for-previously-treated-endometrial-biliary-colorectal-gastric-or-small-intestine-cancer-with-high-microsatellite-instability-or-mismatch-repair-deficiency-pdf-82615487137477. Access November 2023; 2. NICE. Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency. Available at: https://www.nice.org.uk/guidance/ta709/resources/pembrolizumab-for-untreated-metastatic-colorectal-cancer-with-high-microsatellite-instability-or-mismatch-repair-deficiency-pdf-82611081504709. Accessed November 2023; 3. Scottish Medicines Consortium (SMC). Pembrozliumab (KEYTRUDA). Available at: https://www.scottishmedicines.org.uk/medicines-advice/pembrolizumab-keytruda-cc-full-smc2375/. Accessed November 2023.

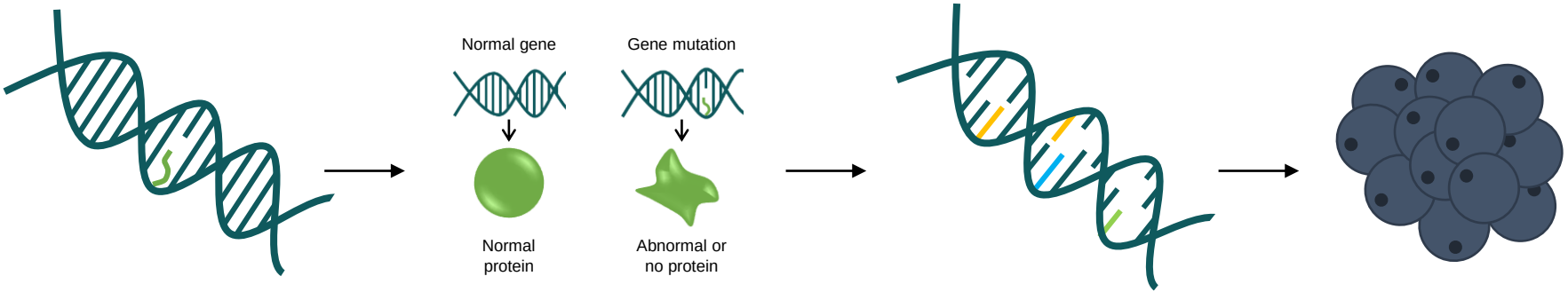
Metastatic MSI-H/dMMR overview

DNA MMR and MSI: An overview

MSI-H/dMMR CRC treatment landscape

CRC, colorectal cancer; dMMR, mismatch repair deficient; MSI, microsatellite instability; MSI-H, microsatellite instability-high.

DNA MMR and MSI: An overview[1,2]



Sporadic or Lynch syndrome-related mutations can occur in MMR genes *MLH1*, *MSH2*, *MSH6* or *PMS2*[1,2]

Mutations in MMR genes lead to the loss of MMR protein activity resulting in DNA mismatches[1,2]

The persistence of DNA mismatches results in MSI, and mutations are incorporated into the genetic code[1]

The accumulation of genetic mutations promotes tumourigenesis[1]

For more information on identifying metastatic MSI-H/dMMR patients suitable for pembrolizumab monotherapy, click here

Figure adapted from Boland CR. *Gastroenterology* 2010 and Kawakami H. *Curr Treat Options Oncol* 2015.
MMR, mismatch repair; MSI, microsatellite instability.
1. Boland CR et al. *Gastroenterology* 2010;138:2073–2087; 2. Kawakami H et al. *Curr Treat Options Oncol* 2015;16:30.

Metastatic MSI-H/dMMR CRC treatment landscape

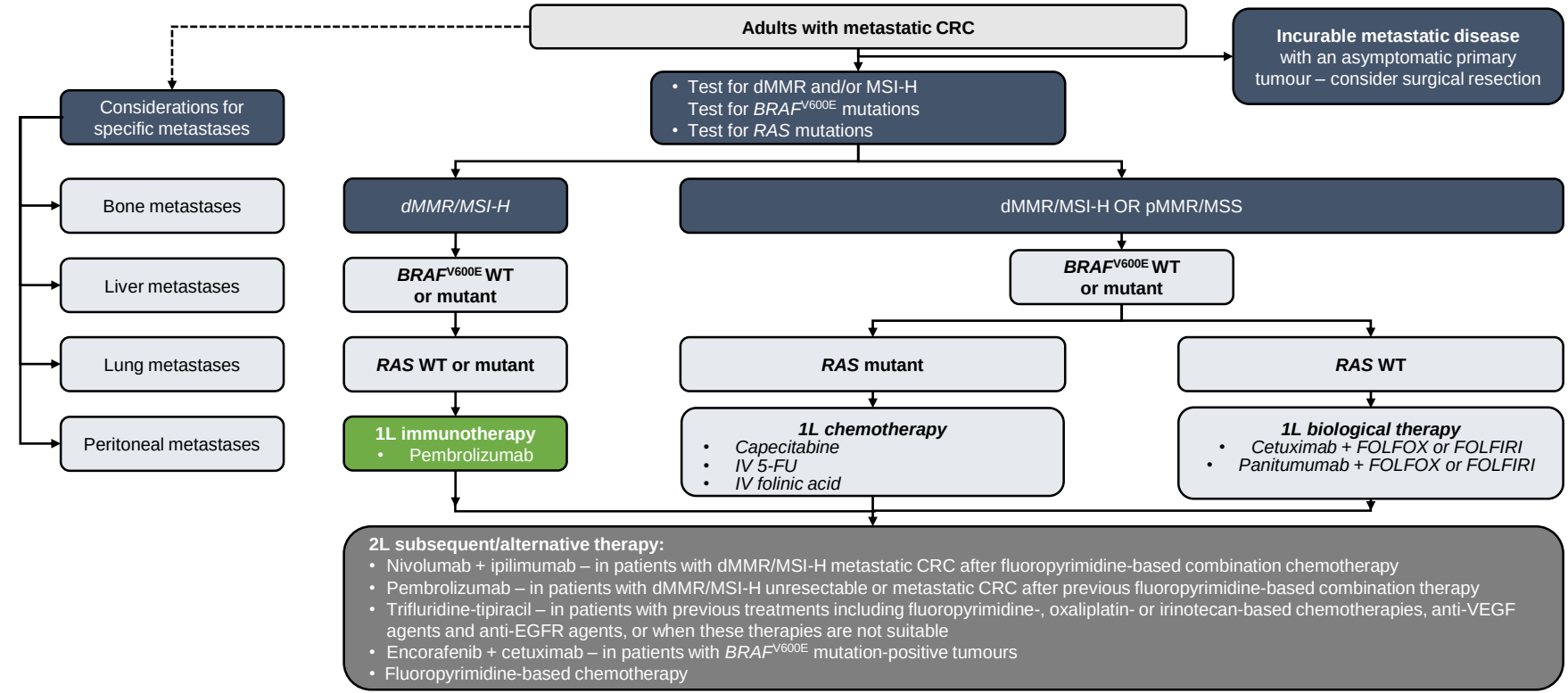


Figure adapted from NICE. Managing metastatic colorectal cancer.
1L, first line; 2L, second line; 5-FU, 5-fluorouracil; CRC, colorectal cancer; dMMR, mismatch repair deficient; EGFR, epidermal growth factor receptor; FOLFIRI, folinic acid, 5-fluorouracil and irinotecan; FOLFOX, folinic acid, 5-fluorouracil and oxaliplatin; IV, intravenous; MSI-H, microsatellite instability-high; MSS, microsatellite stable; pMMR, mismatch repair proficient; VEGF, vascular endothelial growth factor; WT, wild-type.
NICE. Colorectal cancer guidance. Available at: https://www.nice.org.uk/guidance/ng151. Accessed November 2023.

KEYNOTE-177 overview

Study design

Baseline characteristics

KEYNOTE-177: Study design[1,2]

Multicentre, randomised, open-label, active-controlled, crossover, Phase 3 study

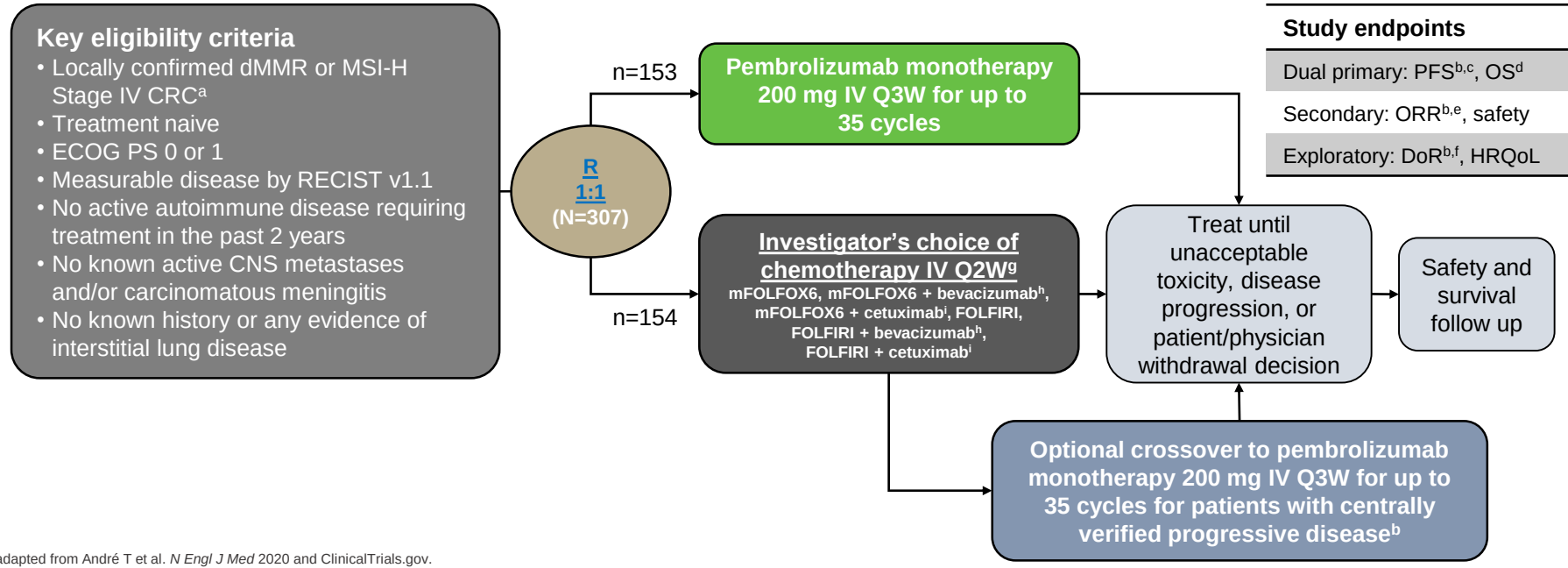


Figure adapted from André T et al. *N Engl J Med* 2020 and ClinicalTrials.gov.

[a]MSI or MMR tumour status was determined locally using PCR or IHC, respectively. [b]Assessed by BICR per RECIST v1.1. [c]Defined as the time from randomisation to first disease progression or death from any cause. [d]Defined as the time from randomisation to death from any cause. [e]Complete or partial response. [f]Defined as the time from first complete or partial response to first disease progression. [g]Chosen before randomisation. [h]Bevacizumab 5 mg/kg. [i]Cetuximab 400 mg/m^2 over 2 hours then 250 mg/m^2 over 1 hour every week.

BICR, blinded independent central review; CNS, central nervous system; CRC, colorectal cancer; DoR, duration of response; dMMR, mismatch repair deficient; ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFIRI, leucovorin, 5-fluorouracil and irinotecan; HRQoL, health-related quality of life; IHC, immunohistochemistry; IV, intravenous; mFOLFOX6, modified leucovorin, 5-fluorouracil and oxaliplatin; MSI-H, microsatellite instability-high; ORR, objective response rate; OS, overall survival; PCR, polymerase chain reaction; PFS, progression-free survival; Q2W, every 2 weeks; Q3W, every 3 weeks; R, randomisation; RECIST v1.1, Response Evaluation Criteria in Solid Tumors Version 1.1.

1. André T et al. *N Engl J Med* 2020;383:2207–2218; 2. NCT02563002. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT02563002. Accessed November 2023.

KEYNOTE-177: Baseline characteristics in the intention-to-treat population[a]

Characteristic	Pembrolizumab (n=153)	Chemotherapy (n=154)
Median age (range), year	63.0 (24–93)	62.5 (26–90)
≥65 years of age, n (%)	73 (48)	71 (46)
Male sex, n (%)	71 (46)	82 (53)
ECOG PS of 0[b], n (%)	75 (49)	84 (55)
MSI-H[c], n (%)	153 (100)	153 (99)
Region, n (%)		
Asia	22 (14)	26 (17)
Western Europe or North America	109 (71)	113 (73)
Rest of the world	22 (14)	15 (10)
Primary tumour location, n (%)		
Right side	102 (67)	107 (69)
Left side	46 (30)	42 (27)
Other site/site missing[d]	5 (3)	5 (3)

Characteristic	Pembrolizumab (n=153)	Chemotherapy (n=154)
Stage, n (%)		
Recurrent metachronous[e]	80 (52)	74 (48)
Newly diagnosed with metastatic disease	73 (48)	80 (52)
Prior systemic therapy, n (%)		
Adjuvant	33 (22)	37 (24)
Neoadjuvant with or without adjuvant systemic therapy	5 (3)	8 (5)
None	115 (75)	109 (71)
Mutation status, n (%)		
BRAF, *KRAS*, *NRAS* all WT	34 (22)	35 (23)
KRAS or *NRAS* mutant	33 (22)	41 (27)[f]
$BRAF^{V600E}$ mutant	34 (22)	43 (28)[f]
Could not be evaluated for *BRAF*, *KRAS* or *NRAS*[g]	52 (34)	38 (25)

Tables adapted from André T et al. *N Engl J Med* 2020.
[a]Percentages may not total 100% because of rounding. [b]An ECOG PS score of 0 indicates fully active. [c]MSI-H status was determined locally by polymerase chain reaction or immunohistochemical test. [d]The tumour site was classified as other if primary tumours were located on both the left and right sides. [e]Recurrence was defined as a secondary colorectal cancer occurring 6 months or more after the index cancer. [f]Three patients who had both a $BRAF^{V600E}$ mutation and a *KRAS* or *NRAS* mutation are included. [g]Patients could not be evaluated for *BRAF*, *KRAS* or *NRAS* if no $BRAF^{V600E}$, *KRAS* or *NRAS* mutation was present and if at least one of the mutation statuses was undetermined or missing or the type of *BRAF* mutation was not $BRAF^{V600E}$.
ECOG PS, Eastern Cooperative Oncology Group performance status; MSI-H, microsatellite instability-high; WT, wild-type.
André T et al. *N Engl J Med* 2020;383:2207–2218.

KEYNOTE-177 results

PFS in the ITT population	PFS in key subgroups	PFS 5-year update	OS in the ITT population
OS in key subgroups	OS 5-year update	Response data	DoR
DoR 5-year update	Summary of AEs (1)	Summary of AEs (2)	Summary of AEOSIs
AEs 5-year update	TRAEs 5-year update	Pembrolizumab MSI-H/dMMR CRC indication	Summary

AE, adverse event; AEOSI, adverse event of special interest; DoR, duration of response; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival.

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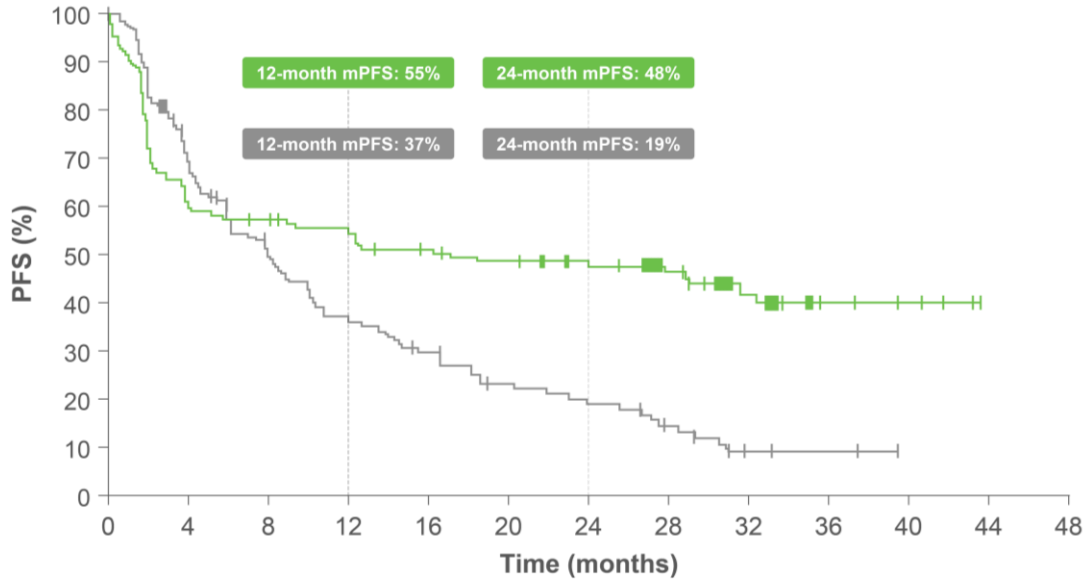
KEYNOTE-177: PFS in the ITT population[a]

Treatment arm	Median (95% CI), months	HR (95% CI)	p value
Pembrolizumab	16.5 (5.4–32.4)	0.60 (0.45–0.80)	0.0002
Chemotherapy	8.2 (6.1–10.2)	—	—



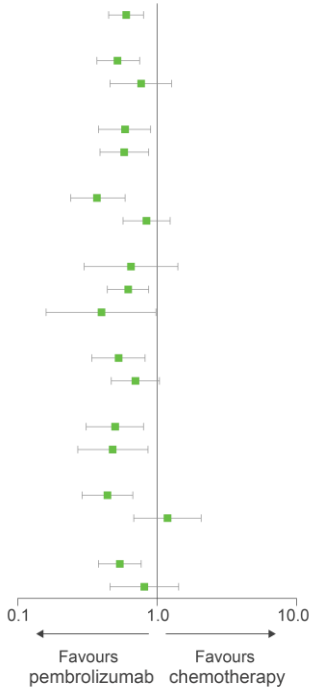
No. at risk													
Pembrolizumab	153	96	77	72	64	60	55	37	20	7	5	0	0
Chemotherapy	154	100	68	43	33	22	18	11	4	3	0	0	0

Double median PFS:
16.5 months (95% CI: 5.4–32.4) with pembrolizumab vs 8.2 months (95% CI: 6.1–10.2) with chemotherapy

Data cut-off: 19 February 2020. Median follow up: 32.4 months.
Figure adapted from André T et al. *N Engl J Med* 2020.
[a]PFS was assessed according to the RECIST v1.1, by independent central reviewers. [b]Based on Cox regression model. [c]Based on log-rank test.
CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; mPFS, median progression-free survival; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors Version 1.1.
André T et al. *N Engl J Med* 2020;383:2207–2218.

KEYNOTE-177: PFS in key subgroups[1,2]

Subgroup	No. of events/No. of patients	Hazard ratio (95% CI)
Overall	195/307	0.60 (0.45–0.80)
Age		
≤70 yr	132/217	0.52 (0.37–0.75)
>70 yr	63/90	0.77 (0.46–1.27)
Gender		
Male	91/153	0.59 (0.38–0.90)
Female	104/154	0.58 (0.39–0.87)
ECOG PS		
0	90/159	0.37 (0.24–0.59)
1	105/148	0.84 (0.57–1.24)
Geographic region		
Asia	28/48	0.65 (0.30–1.41)
Western Europe or North America	146/222	0.62 (0.44–0.87)
Rest of the world	21/37	0.40 (0.16–0.98)
Stage		
Recurrent metachronous	87/154	0.53 (0.34–0.82)
Newly diagnosed	108/153	0.70 (0.47–1.04)
BRAF		
BRAF WT	78/131	0.50 (0.31–0.80)
$BRAF^{V600E}$	51/77	0.48 (0.27–0.86)
KRAS/NRAS		
KRAS/NRAS all WT	95/151	0.44 (0.29–0.67)
KRAS or *NRAS* mutant	51/74	1.19 (0.68–2.07)
Site of primary tumour		
Right	137/209	0.54 (0.38–0.77)
Left	50/88	0.81 (0.46–1.43)



Endpoint was not powered for statistical comparison in subgroups[2]

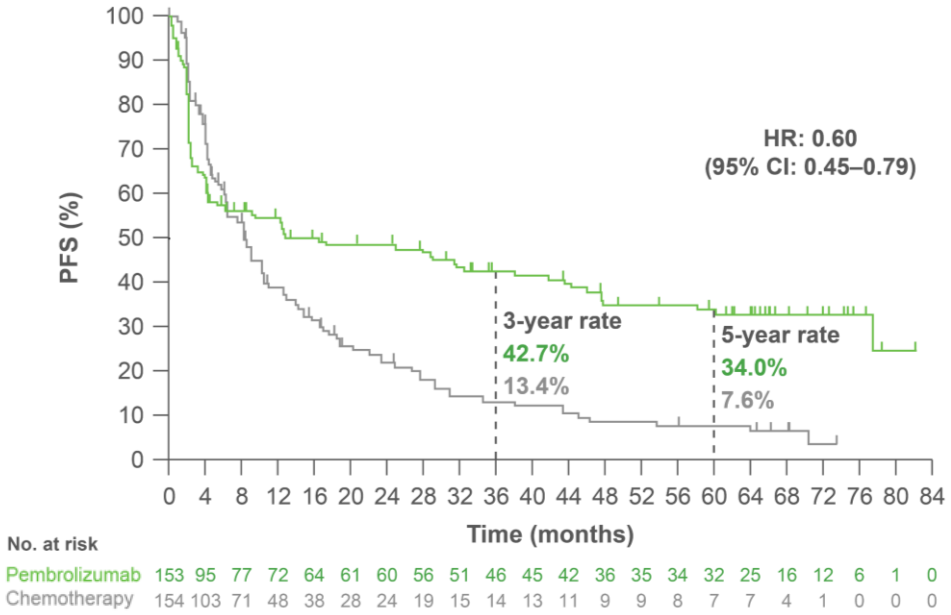
Data cut-off: 19 February 2020. Median follow up: 32.4 months.

Figure adapted from André T et al. *N Engl J Med* 2020.

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; WT, wild-type; Yr, years.

1. André T et al. *N Engl J Med* 2020;383:2207–2218 (plus protocol).

KEYNOTE-177: PFS[a] (5-year updated analysis)

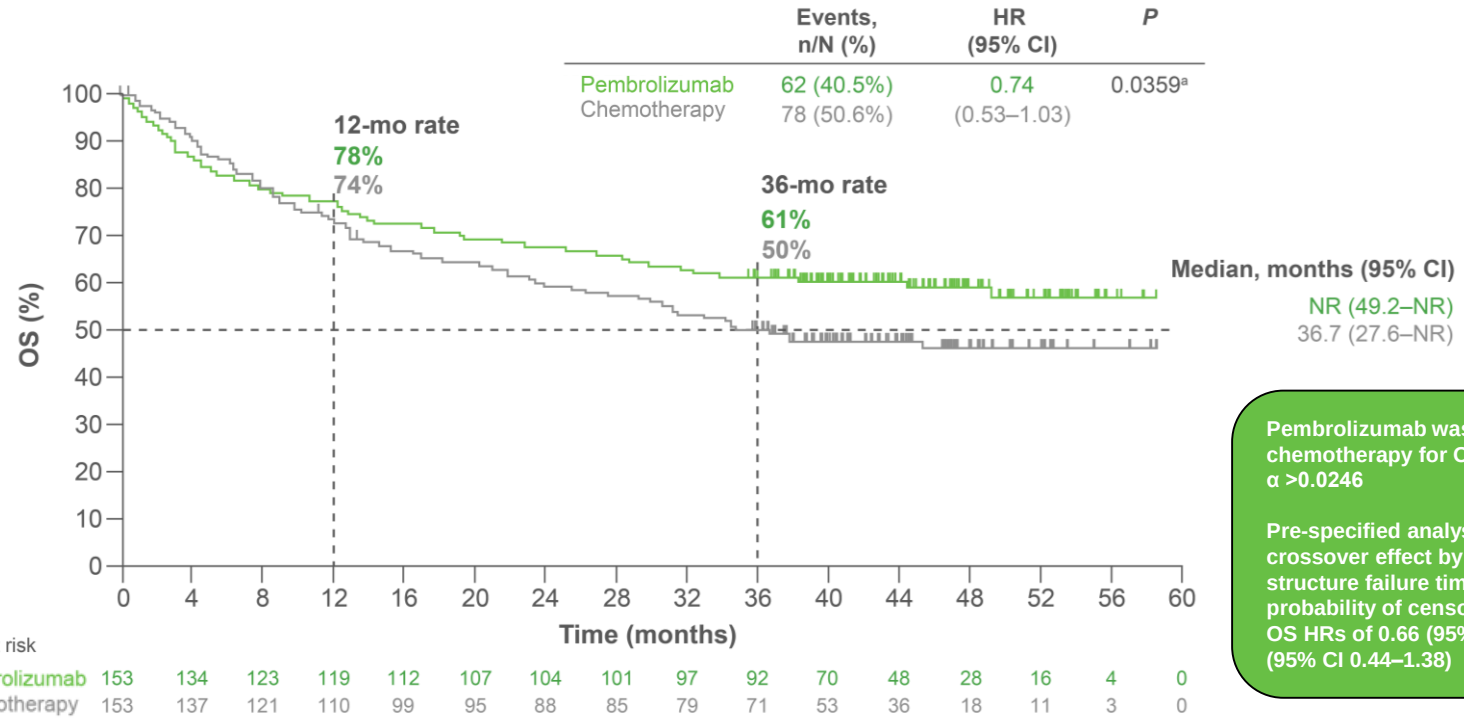


PFS	Pembrolizumab	Chemotherapy
Patients with event, n/N (%)	94/153 (61.4)	122/154 (79.2)
Median (95% CI), months	16.5 (5.4–38.1)	8.2 (6.2–10.3)

This was an exploratory analysis; significance was not tested and no statistical conclusions can be drawn from this analysis

Data cut-off: 17 July 2023. Median (range) follow up: 73.3 (64.9–89.2) months.
Figure and table adapted from Shiu K-K et al. 2023.
[a]PFS was assessed according to RECIST v1.1, per BICR.
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors Version 1.1.
Shiu K-K et al. Presented at the European Society for Medical Oncology (ESMO) Congress 2023, 20–24 October 2023.

KEYNOTE-177: OS in the ITT population



Pembrolizumab was not superior to chemotherapy for OS as one-sided α >0.0246

Pre-specified 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: 19 February 2021.
Figure adapted from André T at al. *J Clin Oncol* 2021.
CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat.
André T et al. *J Clin Oncol* 2021;39:suppl_15.

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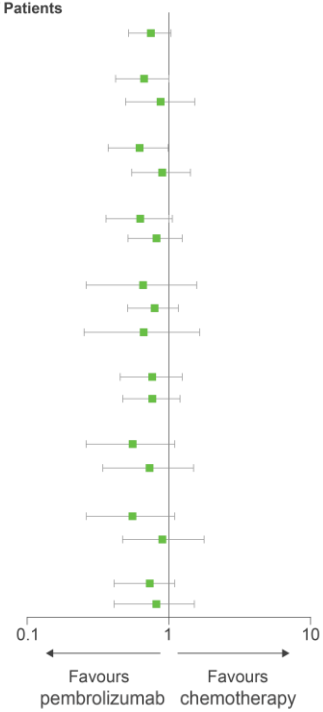
KEYNOTE-177: OS in key subgroups

Subgroup	No. of events/No. of Patients	Hazard ratio (95% CI)
Overall	140/307	0.74 (0.53–1.30)
Age		
≤70 yr	89/217	0.66 (0.43–1.00)
>70 yr	51/90	0.86 (0.50–1.50)
Gender		
Male	70/153	0.61 (0.38–0.99)
Female	70/154	0.88 (0.55–1.41)
ECOG PS		
0	59/159	0.62 (0.37–1.05)
1	81/148	0.80 (0.52–1.24)
Geographic region		
Asia	22/48	0.65 (0.27–1.55)
Western Europe/North America	99/222	0.78 (0.52–1.16)
Rest of the world	19/37	0.65 (0.26–1.62)
Stage		
Recurrent metachronous	63/154	0.75 (0.46–1.23)
Newly diagnosed	77/153	0.75 (0.48–1.19)
BRAF		
BRAF WT	32/81	0.55 (0.27–1.10)
$BRAF^{V600E}$	32/81	0.48 (0.35–1.47)
KRAS/NRAS		
KRAS/NRAS all WT	32/81	0.55 (0.27–1.10)
KRAS or *NRAS* mutant	38/74	0.92 (0.48–1.75)
Site of primary tumour		
Right	94/209	0.72 (0.48–1.09)
Left	39/88	0.80 (0.42–1.49)



Endpoint was not powered for statistical comparison in subgroups

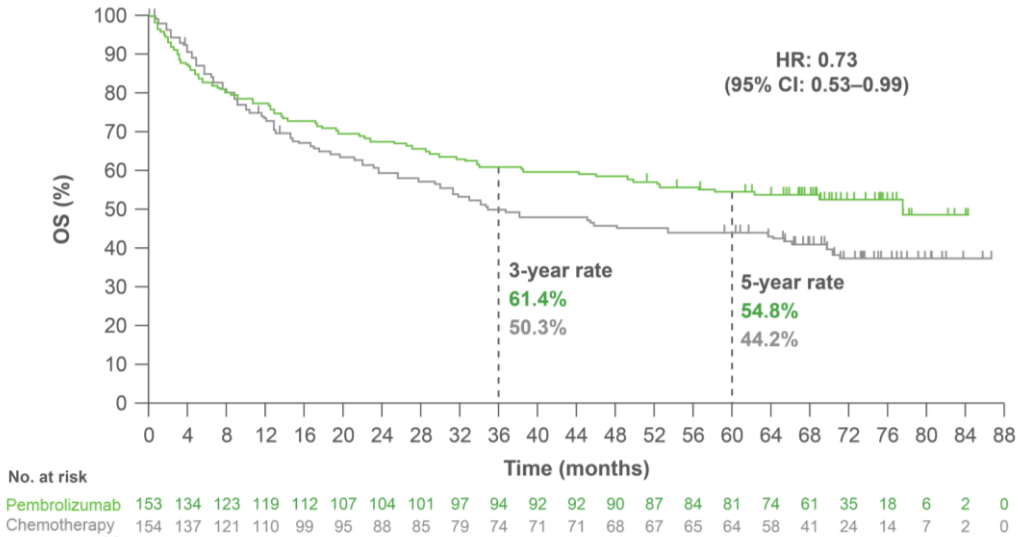
Data cut-off: 19 February 2021.

Figure adapted from André T at al. *J Clin Oncol* 2021.

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; WT, wild-type; Yr, years.

André T et al. *J Clin Oncol* 2021;39:suppl_15.

KEYNOTE-177: OS[a] (5-year updated analysis)



OS	Pembrolizumab	Chemotherapy
Patients with event, n/N (%)	72/153 (47.1)	90/154 (58.4)
Median (95% CI), months	77.5 (49.2–NR)	36.7 (27.6–65.3)

When last formally tested at the final analysis in 2021, the OS improvement did not reach statistical significance and was not formally re-tested. Results should therefore be interpreted with caution.

Data cut-off: 17 July 2023. Median (range) follow up: 73.3 (64.9–89.2) months.
Figure and table adapted from Shiu K-K et al. 2023.
[a]OS did not reach statistical significance in this analysis.
CI, confidence interval; HR, hazard ratio; NR, not reached; OS, overall survival.
Shiu K-K et al. Presented at the European Society for Medical Oncology (ESMO) Congress 2023, 20–24 October 2023.

KEYNOTE-177: ORR, best overall response and time to response

Variable	Pembrolizumab (n=153)	Chemotherapy (n=154)
Overall response[a]		
No. of patients	67	51
% (95% CI)	43.8 (35.8–52.0)	33.1 (25.8–41.1)
Best response, n (%)[b]		
Complete response	17 (11.1)	6 (3.9)
Partial response	50 (32.7)	45 (29.2)
Stable disease	32 (20.9)	65 (42.2)
Progressive disease	45 (29.4)	19 (12.3)
Could not be evaluated or no assessment made[c]	9 (5.9)	19 (12.3)
Median time to response (range), months	2.2 (1.8 to 18.8)	2.1 (1.7 to 24.9)
Median DoR (range), months[d]	NR (2.3+ to 41.4+)	10.6 (2.8 to 37.5+)
Response duration of ≥24 months, %[d]	82.6	35.3

Data cut-off: 19 February 2020. Median follow up: 32.4 months.

Table adapted from André T et al. *N Engl J Med* 2020.

[a]Defined as a confirmed complete response or partial response. The denominators for the percentages are patients in the intention-to-treat population, which included all patients who underwent randomisation. Patients who could not be evaluated, who had no assessment available, or who did not start either therapy (11 patients in the chemotherapy group) were not excluded from this analysis. [b]Percentages may not total 100% because of rounding. [c]Includes patients for whom no post baseline imaging was performed. [d]The Kaplan–Meier method for censored data was used to calculate duration. A plus sign indicates no progressive disease by the time of the last assessment.

CI, confidence interval; DoR, duration of response; NR, not reached; ORR, objective response rate.

André T et al. *N Engl J Med* 2020;383:2207–2218.

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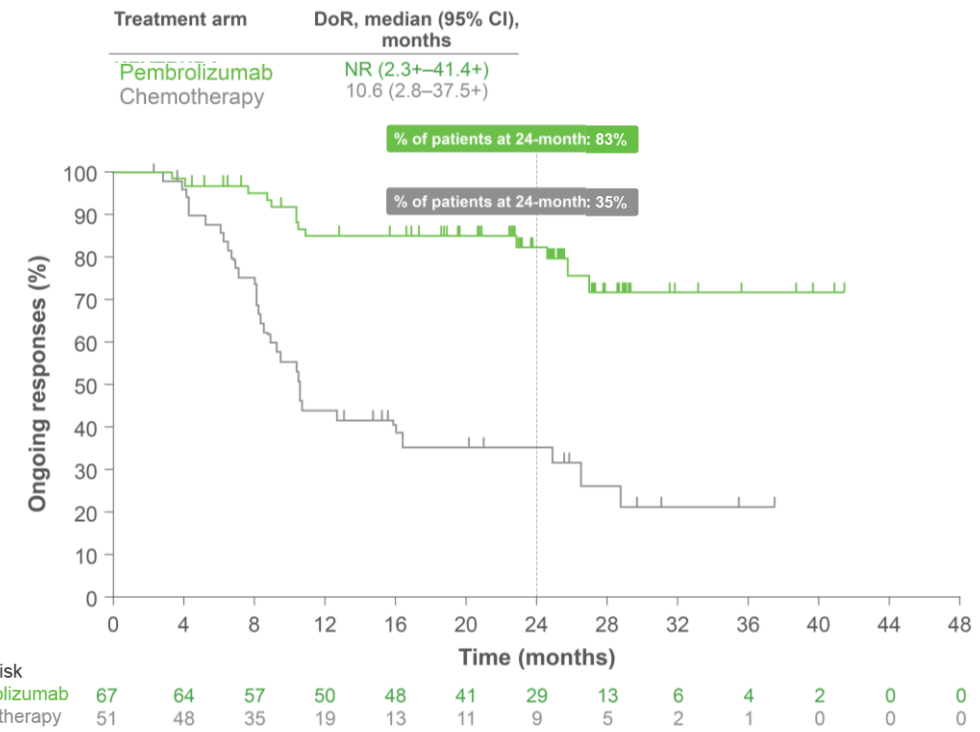
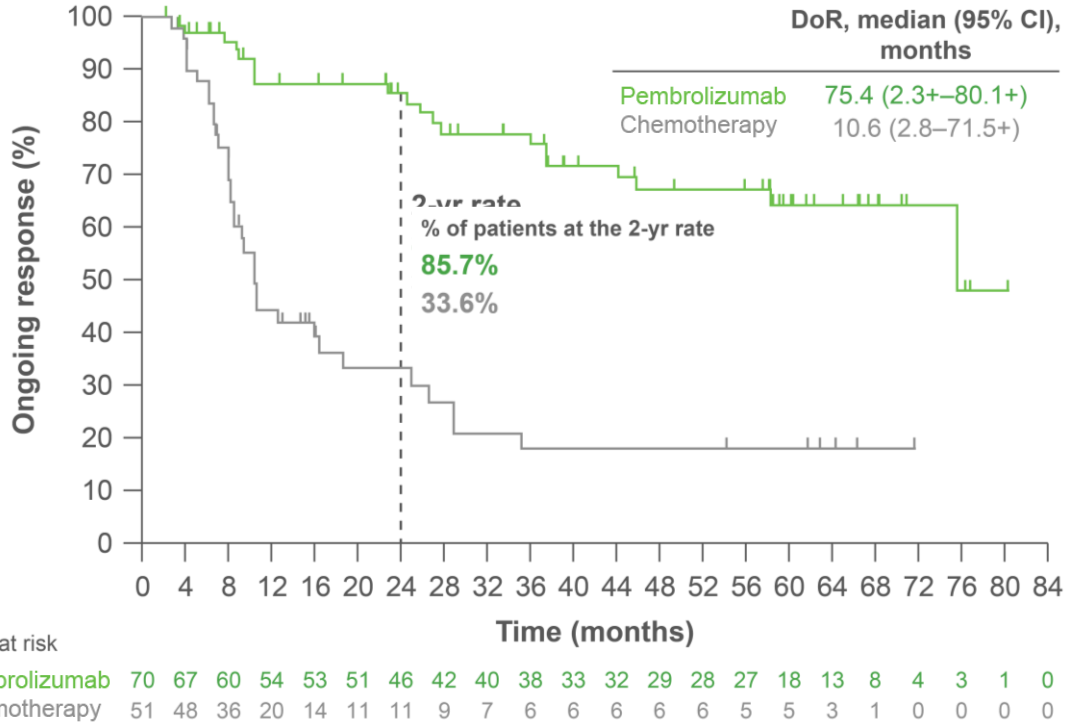
KEYNOTE-177: DoR (exploratory endpoint)



Exploratory endpoint was not powered for statistical comparison

Data cut-off: 19 February 2020. Median follow up: 32.4 months.
Figure adapted from André T et al. *N Engl J Med* 2020 (suppl. appx.).
DoR, duration of response; mDoR, median duration of response; NR, not reached.
André T et al. *N Engl J Med* 2020;383:2207–2218.(suppl. appx.).

KEYNOTE-177: DoR (exploratory endpoint) (5-year updated analayis)



Exploratory endpoint was not powered for statistical comparison

Data cut-off: 17 July 2023.

[a]DoR was assessed per RECIST v1.1 by BICR; [b] "+" indicates no PD by time of last assessment.

BICR, Blinded Independent Central Review; CI, confidence interval; DoR, duration of response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors Version 1.1; yr, year.

Shiu KK et al. Presented at the European Society for Medical Oncology (ESMO) Congress 2023, 20–24 October 2023, Madrid, Spain.

KEYNOTE-177: Summary of AEs in the as-treated population (1)[a,1,2]

Event, n (%)	Pembrolizumab (n=153)	Chemotherapy (n=143)
All AEs	149 (97)	142 (99)
Treatment related	122 (80)	141 (99)
Grade ≥3	33 (22)	94 (66)
Discontinued[2]	15 (10)	10 (7)
Death[2]	0 (0)	1 (1)[b]
Immune-mediated and infusion reactions	47 (31)	21 (15)
Grade ≥3	14 (9)	3 (2)
Discontinued	10 (7)	1 (1)
Death	0 (0)	0 (0)

For further guidance on the management of AEs, refer to the pembrolizumab SmPC. For a complete list of AEs, click here

Data cut-off: 19 February 2020. Median follow up: 32.4 months.

Table adapted from André T et al. *N Engl J Med* 2020 (suppl. appx.) and André T et al. Presented at the American Society for Clinical Oncology (ASCO) Virtual Annual Meeting 2021, 4–8 April 2021.

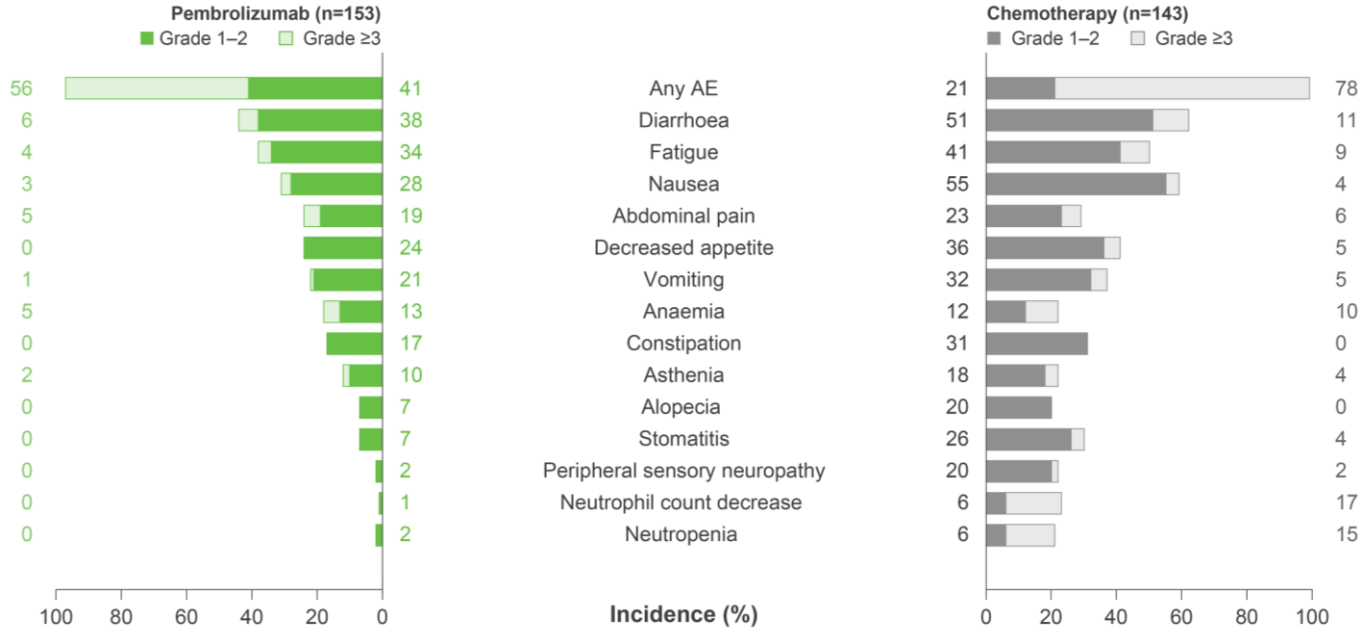
[a]The as-treated population included all patients who underwent randomisation and received at least one trial treatment. [b]One Grade 5 event of intestinal perforation.

AE, adverse event.

1. André T et al. *N Engl J Med* 2020;383:2207–2218 (plus supplementary appendix); 2. André T et al. Presented at the American Society for Clinical Oncology (ASCO) Virtual Annual Meeting 2021, 4–8 April 2021.

KEYNOTE-177: Summary of AEs in the as-treated population (2)[a]

AEs incidence with pembrolizumab or chemotherapy



For further guidance on the management of AEs, refer to the pembrolizumab SmPC. For a complete list of AEs, click here

Data cut-off: 19 February 2020. Median follow up: 32.4 months.

Figure adapted from André T et al. *N Engl J Med* 2020.

[a]The as-treated population included all patients who underwent randomisation and received at least one trial treatment.

AE, adverse event; PPE, palmar-plantar erythrodysesthesia.

André T et al. *N Engl J Med* 2020;383:2207–2218.

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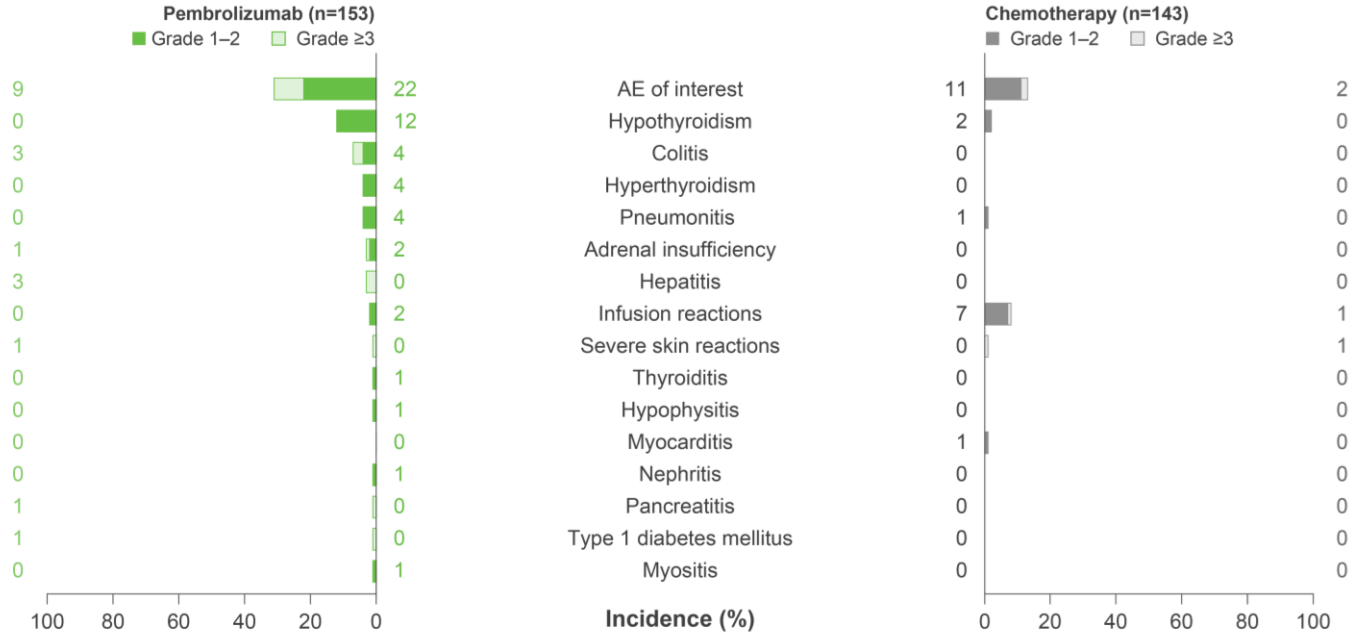
KEYNOTE-177: AEOSIs in the as-treated population[a]

AEOSIs with pembrolizumab or chemotherapy



For further guidance on the management of AEs, refer to the pembrolizumab SmPC. For a complete list of AEs, click here

Data cut-off: 19 February 2020. Median follow up: 32.4 months.

Figure adapted from André T et al. *N Engl J Med* 2020.

[a]The as-treated population included all patients who underwent randomisation and received at least one trial treatment.

AE, adverse event; AEOSI, adverse event of special interest.

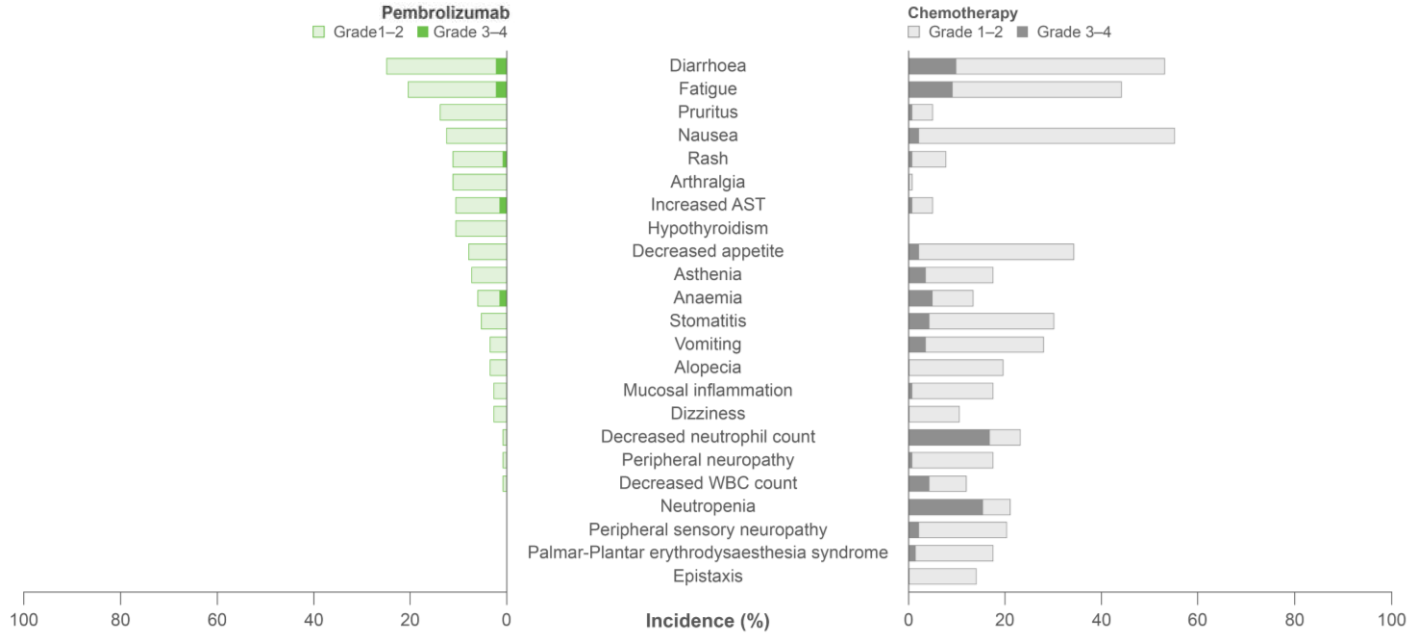
André T et al. *N Engl J Med* 2020;383:2207–2218.

KEYNOTE-177: AEs in the as-treated population (5-year updated analysis)[1]

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

Data cut-off: 17 July 2023. Median (range) follow up: 73.3 (64.9–89.2) months. The as-treated population included all patients who were randomised and received ≥1 dose of study treatment.[2]
Table adapted from Shiu K-K et al. 2023.
AE, adverse event; TRAE, treatment-related adverse event.
1. Shiu K-K et al. Presented at the European Society for Medical Oncology (ESMO) Congress 2023, 20–24 October 2023; 2. André T et al. *N Engl J Med* 2020;383:2207–2218.

KEYNOTE-177: TRAEs in ≥10% of patients in any treatment arm (5-year updated analysis)[1]



The safety profile was similar to that reported in the final analysis (median [IQR] follow up: 44.5 [39.7–49.8] months)[2]

Data cut-off: 17 July 2023. Median (range) follow up: 73.3 (64.9–89.2) months. The as-treated population included all patients who were randomised and received ≥1 dose of study treatment.[3]

Table adapted from Shiu K-K et al. 2023, Diaz LA et al. 2022 and Andre T et al. 2020.

AST, aspartate aminotransferase; IQR, interquartile range; TRAE, treatment-related adverse event; WBC, white blood cell.

1. Shiu K-K et al. Presented at the European Society for Medical Oncology (ESMO) Congress 2023, 20–24 October 2023; 2. Diaz LA et al. *Lancet Oncol* 2022;23:659–670; 3. André T et al. *N f J Med* 2020;383:2207–2218.

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KEYTRUDA dosing and administration

KEYTRUDA offers flexible dosing:

Administered as an IV infusion

Over 30 minutes

200 mg Q3W or 400 mg Q6W

The 200 mg Q3W regimen has been assessed in Phase 2 and 3 registration studies across a multitude of indications of KEYTRUDA. An exposure-response evaluation, using modelling and simulation, led to the approval of the 400 mg Q6W dosing for monotherapy and combination therapy

Please refer to the KEYTRUDA SmPC and Risk Minimisation Materials before prescribing KEYTRUDA.
Q3W, every 3 weeks; Q6W, every 6 weeks; SmPC, Summary of Product Characteristics.
KEYTRUDA (pembrolizumab) Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/2498/smpc#gref (GB) and https://www.emcmedicines.com/en-gb/northernireland/medicine?id=ce680467-8438-4e60-ab4f-dfab6767ccbe&type=smpc (NI). Accessed November 2023.

GB PI NI PI

KEYNOTE-177: Summary

1

Pembrolizumab monotherapy is the **first** licensed immunotherapy for adults with MSI-H/dMMR metastatic CRC[1]

2

Pembrolizumab monotherapy **doubled** median PFS vs chemotherapy in patients with MSI-H/dMMR metastatic CRC (16.5 months vs 8.2 months respectively [HR: 0.60, 95% CI: 0.45–0.80; p=0.0002]) and continued to provide a clinically meaningful improvement in PFS at 5 years of follow up (HR: 0.60 [95% CI: 0.45–0.79])[2,3]

OS was 77.5 months with pembrolizumab vs 36.7 months with chemotherapy (HR: 0.73 [95% CI: 0.53–0.99]) after 5 years of follow up[3]

- No formal statistical analysis was conducted after 5 years to assess differences between the two regimens

3

The safety profile of pembrolizumab in this trial was consistent with that observed across multiple tumour types and was similar to that reported at the final analysis[2–4]

- The incidence of Grade 3–5 TRAEs was 21.6% (33/153) with pembrolizumab vs 67.1% (96/143) with chemotherapy at the 5-year updated analysis[3]
- Pembrolizumab was associated with a higher rate of immune-mediated AEs vs chemotherapy[2,3]
  - The rate of any immune-mediated AE or infusion reaction was 33.3% (51/153) with pembrolizumab vs 16.1% (23/143) with chemotherapy at the 5-year updated analysis[3]

AE, adverse event; CI, confidence interval; CRC, colorectal cancer; DoR, duration of response; HR, hazard ratio; MSI-H, microsatellite instability-high; NR, not reached; ORR, objective response rate; PFS, progression-free survival; TRAE, treatment-related adverse event.

1. KEYTRUDA (pembrolizumab) Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/2498/smpc#gref (GB) and https://www.emcmedicines.com/en-gb/northernireland/medicine?id=ce680467-8438-4e60-ab4f-dfab6767ccbe&type=smpc (NI). Accessed November 2023; 2. André T et al. *N Engl J Med* 2020;383:2207–2218; 3. Shiu K-K et al. Presented at the European Society for Medical Oncology (ESMO) Congress 2023, 20–24 October 2023; 4. Diaz LA et al. *Lancet Oncol* 2022;23:659–670.

Appendix

- Identifying suitable patients
- Pembrolizumab monotherapy mechanism of action
- KEYNOTE-177: Patient disposition
- KEYNOTE-177: Standard of care chemotherapy
- KEYNOTE-177: Subsequent therapies
- KEYNOTE-177: PFS2
- KEYNOTE-177: Complete list of AEs (1)
- KEYNOTE-177: Complete list of AEs (2)
- KEYNOTE-177: Patient-reported outcomes (1)
- KEYNOTE-177: Patient-reported outcomes (2)

AE, adverse event; AEOSI, adverse event of special interest; dMMR, mismatch repair deficient; MSI-H, microsatellite instability-high; PFS2, progression-free survival after next-line therapy.

Identifying patients suitable for pembrolizumab monotherapy[1,2]

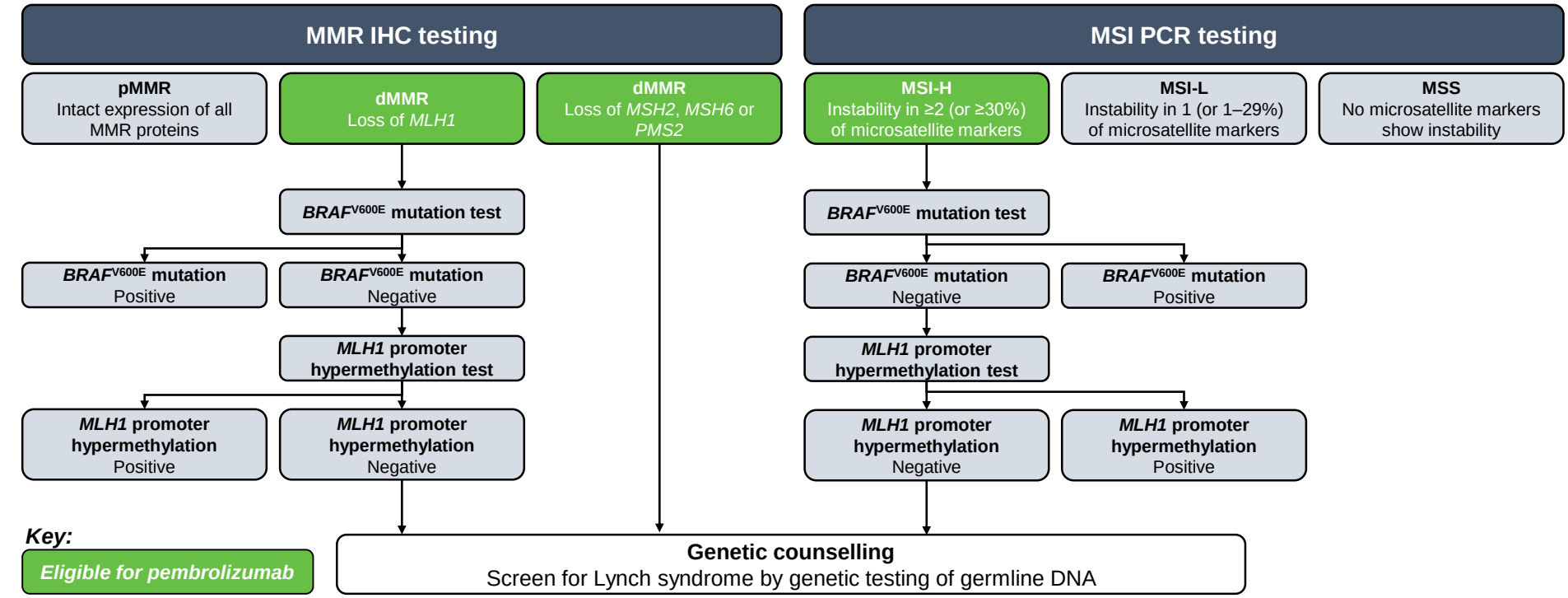
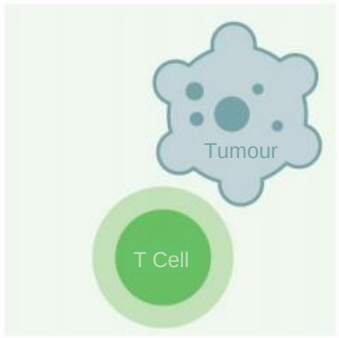


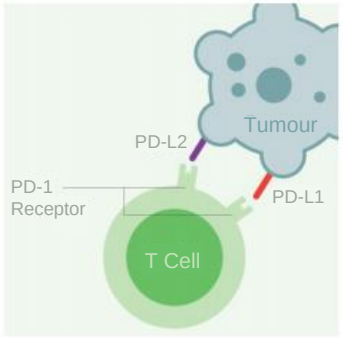
Figure adapted from NICE guidance 2017 and Kawakami H et al. *Curr Treat Options Oncol* 2015.
dMMR, mismatch repair deficient; IHC, immunohistochemistry; MMR, mismatch repair; MSI-H, microsatellite instability-high; MSI-L, microsatellite instability-low; MSS, microsatellite stable; PCR, polymerase chain reaction; pMMR mismatch repair proficient.

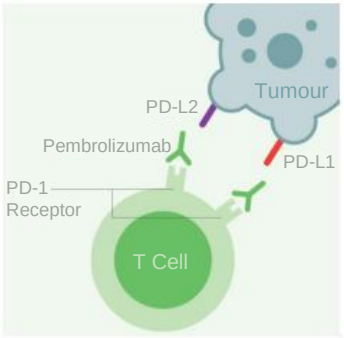
1. NICE diagnostics guidance. Published 22 February 2017; 2. Kawakami H et al. *Curr Treat Options Oncol* 2015;16:30.

Pembrolizumab monotherapy: Mechanism of action[1,2]

- Pembrolizumab is a selective monoclonal antibody that blocks the PD-1 protein pathway, potentiating T-cell responses, including anti-tumour responses
- When functioning properly, T cells are activated and can attack tumour cells
- Some tumours can evade the immune system through the PD-1 pathway. On the surface of tumour cells, the dual PD-1 ligands, PD-L1 and PD-L2, bind to the PD-1 receptors on T cells to inactivate them, allowing tumour cells to evade detection
- By inhibiting this process, pembrolizumab reactivates tumour-specific cytotoxic T lymphocytes and anti-tumour immunity







For more information on the mechanism of action of pembrolizumab monotherapy, click here

Please note that clicking this link will redirect you to the promotional MSD Connect website.

Figure adapted from KEYTRUDA (pembrolizumab) SmPC.
MHC, major histocompatibility complex; PD-1, programmed death-1; PD-L1, programmed death ligand-1; PD-L2, programmed death ligand-2; TCR, T cell receptor.
1. Harvey R et al. *Clin Pharm Therapeutics* 2014:96;214-223; 2. KEYTRUDA (pembrolizumab) Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/2498/smpc#gref (GB) and https://www.emcmedicines.com/en-gb/northernireland/medicine?id=ce680467-8438-4e60-ab4f-dfab6767ccbe&type=smpc (NI). Accessed November 2023.
Please note that this link will redirect you to an external website, for which MSD does not review or control the content.

KEYNOTE-177: Patient disposition

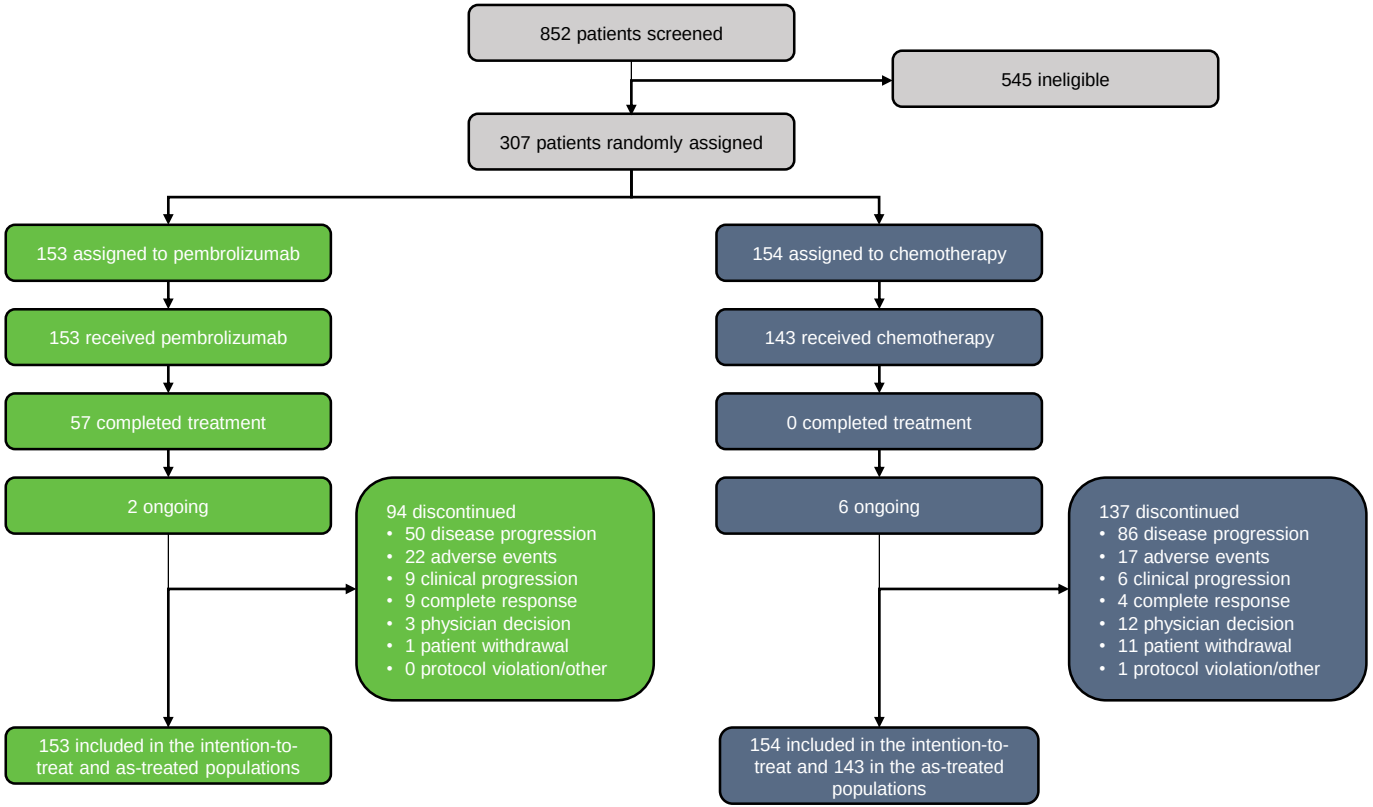


Figure adapted from André T et al. *N Engl J Med* 2020 (supplementary appendix).
André T et al. *N Engl J Med* 2020;383:2207–2218 (supplementary appendix).

KEYNOTE-177: Standard of care chemotherapy

Standard of care chemotherapy	n=143
Chemotherapy regimen	**n (%)[a]**
mFOLFOX6 alone	11 (8)
mFOLFOX6 + bevacizumab	64 (45)
mFOLFOX6 + cetuximab	5 (4)
FOLFIRI alone	16 (11)
FOLFIRI + bevacizumab	36 (25)
FOLFIRI + cetuximab	11 (8)

The choices of chemotherapy were as follows:

- mFOLFOX6, administered intravenously, consisting of oxaliplatin (85 mg per square meter of body-surface area delivered as a 2-hour infusion on day 1), leucovorin (400 mg per square meter administered as a 2-hour infusion on day 1), and 5-fluoropyrimidine (400 mg per square meter on day 1, followed by 1200 mg per square meter for 2 days for a total of 2400 mg per square meter delivered by continuous infusion over 46 to 48 hours)
- mFOLFOX6 plus bevacizumab (5 mg per kilogram of body weight administered intravenously on day 1)
- mFOLFOX6 plus cetuximab (400 mg per square meter administered intravenously over 2 hours [first infusion] followed by 250 mg per square meter administered as one 1-hour infusion weekly)
- FOLFIRI, administered intravenously, consisting of irinotecan (180 mg per square meter delivered over 30 to 90 minutes on day 1), leucovorin (400 mg per square meter delivered by infusion over 30 to 90 minutes on day 1), and 5-fluoropyrimidine (400 mg per square meter administered as a bolus on day 1, followed by 1200 mg per square meter per day for 2 days for a total of 2400 mg per square meter delivered by continuous infusion over 46 to 48 hours)
- FOLFIRI plus bevacizumab (bevacizumab administered at the same dose as listed above with mFOLFOX6)
- FOLFIRI plus cetuximab (cetuximab administered at the same dose as listed above with mFOLFOX6)

All the chemotherapy regimens were repeated every 2 weeks. The investigator's choice of chemotherapy combination was determined before randomization.

Table adapted from André T et al. *N Engl J Med* 2020.
[a]Percentages may not total 100% because of rounding.
FOLFIRI, leucovorin, 5-fluorouracil and irinotecan; FOLFOX, leucovorin, 5-fluorouracil and oxaliplatin; mFOLFOX6, modified leucovorin, 5-fluorouracil and oxaliplatin.
André T et al. *N Engl J Med* 2020;383:2207–2218.

KEYNOTE-177: Subsequent therapies

Patients, n (%)	Pembrolizumab (n=153)	Chemotherapy (n=154)
Crossed over from SoC to pembrolizumab	0	56 (36.4)
Did not cross over but received subsequent anti-cancer therapies[a]	44 (28.8)	44 (28.6)
Pembrolizumab	6 (3.9)	14 (9.1)
Nivolumab	0	4 (2.6)
Nivolumab + ipilimumab	0	3 (1.9)
Durvalumab	0	2 (1.3)
Atezolizumab + bevacizumab	0	1 (0.6)
Avelumab	0	1 (0.6)
Anti-PD-L1 unspecified	0	2 (1.3)
FOLFIRI/XELIRI	4 (2.6)	2 (1.3)
FOLFIRI + bevacizumab	7 (4.6)	3 (1.9)
FOLFIRI + panitumumab	1 (0.7)	1 (0.6)
FOLFOXIRI/FOLFOXIRI + bevacizumab	2 (1.3)	0
XELIRI/irinotecan + cetuximab	2 (1.3)	0
FOLFOX	7 (4.6)	1 (0.6)
FOLFOX/XELOX + bevacizumab	9 (5.9)	2 (1.3)
FOLFOX/XELOX + panitumumab	1 (0.7)	0
5-fluorouracil	1 (0.7)	0
5-fluorouracil + bevacizumab	0	3 (1.9)
Panitumumab	1 (0.7)	2 (1.3)
ICOS inhibitor + pembrolizumab	1 (0.7)	0
Other[b]	2 (1.3)	3 (1.9)

Data cut-off: 19 February 2020. Median follow up: 32.4 months.

Tables adapted from André T et al. Presented at the American Society for Clinical Oncology (ASCO) Virtual Annual Meeting 2021, 4–8 April 2021.

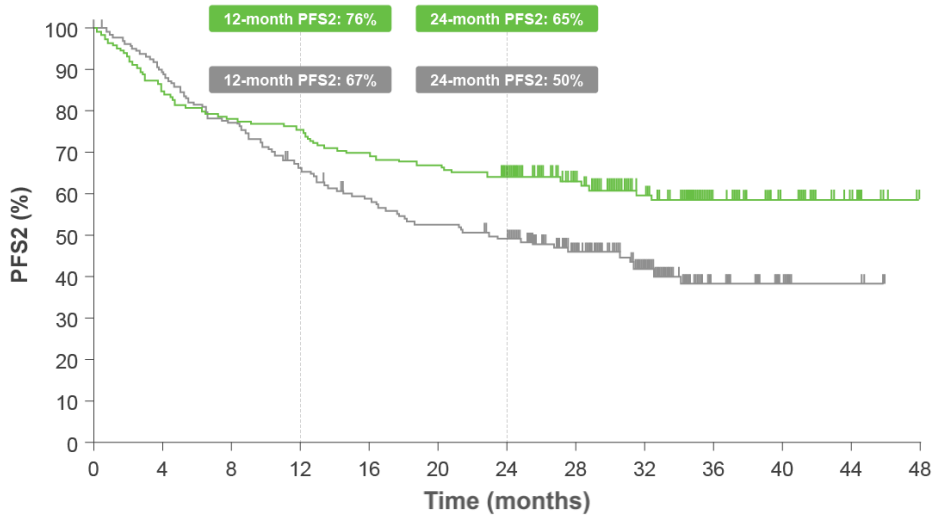
[a]Including second-course treatment for patients randomised to pembrolizumab. [b]Other includes patients who receive bevacizumab (n=1), bevacizumab +oxaliplatin (n=1), bevacizumab + tipiracil HCL (n=1), fluorouracil + mitomycin (n=1), or oxaliplatin only (n=1).

FOLFIRI, leucovorin, 5-fluorouracil and irinotecan; FOLFOX, folinic acid, fluorouracil and oxaliplatin; FOLFOXIRI, folinic acid, 5-fluorouracil, irinotecan and oxaliplatin; HCL, hydrochloride; ICOS, inducible T-cell co-stimulator; PD-L1, programmed death ligand-1; SoC, standard of care; XELIRI, irinotecan and capecitabine; XELOX, capecitabine and oxaliplatin.

André T et al. Presented at the American Society for Clinical Oncology (ASCO) Virtual Annual Meeting 2021, 4–8 April 2021.

KEYNOTE-177: Progression-free survival after next-line therapy (PFS2) (exploratory endpoint)

Treatment arm	Events (%)	Median, months	HR (95% CI)
Pembrolizumab	39	NR (NR–NR)	0.63 (0.45–0.88)
Chemotherapy	55	23.5 (16.6–32.6)	—



No. at risk												
Pembrolizumab	153	131	120	116	107	103	98	72	46	25	15	5	0
Chemotherapy	154	136	117	100	86	77	71	51	30	11	5	2	0

PFS2 was a post-hoc analysis and was not powered for statistical comparison

Data cut-off: 19 February 2020. Median follow up: 32.4 months.
Figure adapted from André T et al. Presented at the American Society for Clinical Oncology (ASCO) Virtual Annual Meeting 2021, 4–8 April 2021.
PFS2 was assessed according to the RECIST version 1.1, by investigator.
CI, confidence interval; HR, hazard ratio; NR, not reached; PFS2, progression-free survival after next-line therapy; RECIST v1.1, Response Evaluation Criteria in Solid Tumors Version 1.1.
André T et al. Presented at the American Society for Clinical Oncology (ASCO) Virtual Annual Meeting 2021, 4–8 April 2021.

KEYNOTE-177: Complete list of AEs (1/2)

Event, n (%)	Pembrolizumab (n=153)		Chemotherapy (n=154)	
	Any	Grade ≥3	Any	Grade ≥3
Any AE	149 (97)	86 (56)	142 (99)	111 (78)
Diarrhoea	68 (44)	9 (6)	89 (62)	16 (11)
Fatigue	58 (38)	6 (4)	72 (50)	13 (9)
Nausea	47 (31)	4 (3)	85 (59)	6 (4)
Abdominal pain	37 (24)	8 (5)	42 (29)	8 (6)
Decreased appetite	36 (24)	0	58 (41)	7 (5)
Vomiting	33 (22)	2 (1)	53 (37)	7 (5)
Arthralgia	28 (18)	1 (1)	7 (5)	0
Pyrexia	28 (18)	1 (1)	20 (14)	0
Anaemia	27 (18)	8 (5)	32 (22)	15 (10)
Pruritus	25 (16)	0	12 (8)	1 (1)
Back pain	26 (17)	2 (1)	24 (17)	1 (1)
Constipation	26 (17)	0	45 (31)	0

Event, n (%)	Pembrolizumab (n=153)		Chemotherapy (n=154)	
	Any	Grade ≥3	Any	Grade ≥3
Cough	26 (17)	0	23 (16)	0
Aspartate aminotransferase increase	24 (16)	4 (3)	12 (8)	3 (2)
Dizziness	24 (16)	0	27 (19)	3 (2)
Alanine aminotransferase increase	22 (14)	4 (3)	16 (11)	3 (2)
Blood alkaline phosphatase increase	22 (14)	4 (3)	6 (4)	2 (1)
Dyspnoea	21 (14)	1 (1)	15 (10)	0
Headache	21 (14)	0	22 (15)	0
Rash	20 (13)	1 (1)	16 (11)	1 (1)
Upper abdominal pain	20 (13)	2 (1)	11 (8)	1 (1)
Nasopharyngitis	20 (13)	0	10 (7)	0
Asthenia	19 (12)	3 (2)	31 (22)	6 (4)

Data cut-off: 19 February 2020. Median follow up: 32.4 months.
Tables adapted from André T et al. *N Engl J Med* 2020.
AE, adverse event.
André T et al. *N Engl J Med* 2020;383:2207–2218.

KEYNOTE-177: Complete list of AEs (2/2)

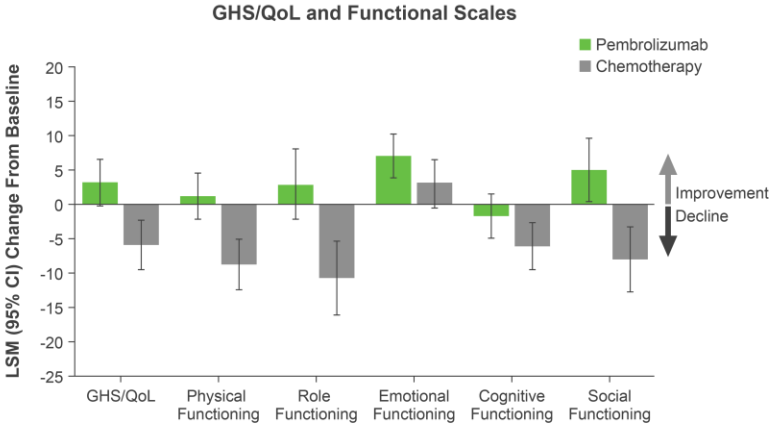
Event, n (%)	Pembrolizumab (n=153)		Chemotherapy (n=154)	
	Any	Grade ≥3	Any	Grade ≥3
Dry skin	19 (12)	0	13 (9)	0
Hypertension	19 (12)	11 (7)	16 (11)	7 (5)
Hypothyroidism	19 (12)	0	3 (2)	0
Pain in extremity	18 (12)	0	11 (8)	1 (1)
Peripheral oedema	18 (12)	0	12 (8)	2 (1)
Dry mouth	17 (11)	0	9 (6)	0
Upper respiratory tract infection	16 (10)	0	8 (6)	0
Urinary tract infection	14 (9)	1 (1)	16 (11)	4 (3)
Hypokalaemia	13 (8)	2 (1)	24 (17)	9 (6)
Alopecia	11 (7)	0	29 (20)	0
Stomatitis	10 (7)	0	43 (30)	6 (4)

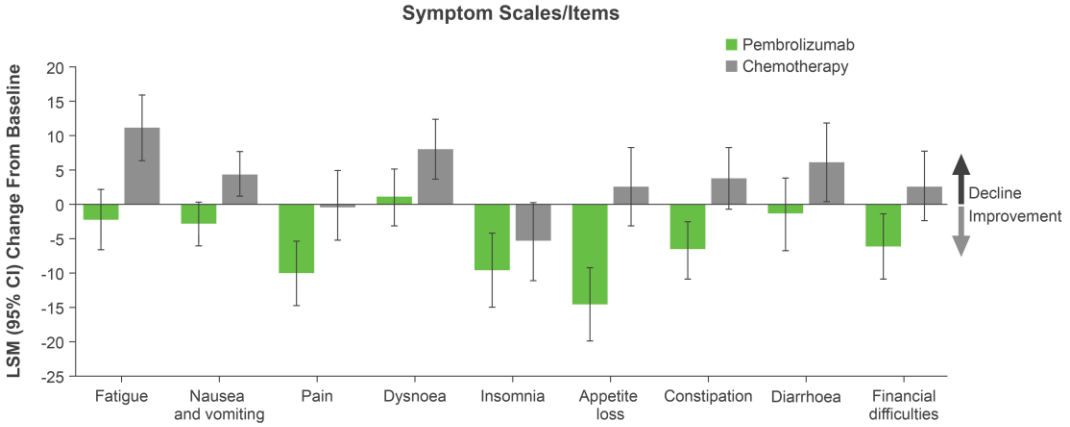
Event, n (%)	Pembrolizumab (n=153)		Chemotherapy (n=154)	
	Any	Grade ≥3	Any	Grade ≥3
Dyspepsia	9 (6)	0	16 (11)	0
Mucosal inflammation	7 (5)	0	27 (19)	1 (1)
Weight decreased	7 (5)	1 (1)	17 (12)	1 (1)
Peripheral sensory neuropathy	3 (2)	0	31 (22)	3 (2)
Neutrophil count decrease	2 (1)	0	33 (23)	24 (17)
Neutropenia	3 (2)	0	30 (21)	22 (15)
Epistaxis	2 (1)	0	23 (16)	0
Peripheral neuropathy	1 (1)	0	27 (19)	1 (1)
PPE syndrome	1 (1)	0	25 (17)	1 (1)
White cell count decrease	1 (1)	0	17 (12)	6 (4)

Data cut-off: 19 February 2020. Median follow up: 32.4 months.
Tables adapted from André T et al. *N Engl J Med* 2020.
AE, adverse event; PPE, palmar–plantar erythrodysesthesia syndrome.
André T et al. *N Engl J Med* 2020;383:2207–2218.

KEYNOTE-177: Patient-reported outcomes (exploratory analysis) (1/2)

EORTC QLQ-C30 GHS/QoL, functional and symptom scales/items[a]





QoL was a post-hoc analysis and was not powered for statistical comparison

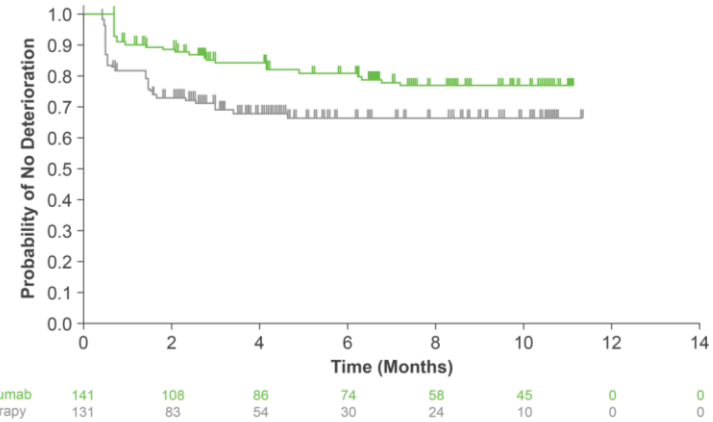
Data cut-off: 19 February 2020. Median follow up: 32.4 months.
Figure adapted from André T et al. Presented at the American Society for Clinical Oncology (ASCO) Virtual Annual Meeting 2021, 4–8 April 2021.
[a]Error bars indicate 95% CIs around the mean.
CI, confidence interval; EORTC QLQ, European Organisation for Research and Treatment of Cancer quality of life questionnaire version 3.0; GHS, global health status; LSM, least square mean; QoL quality of life.
André T et al. Presented at the American Society for Clinical Oncology (ASCO) Virtual Annual Meeting 2021, 4–8 April 2021.

KEYNOTE-177: Patient-reported outcomes (exploratory analysis) (2/2)

EORTC QLQ-C30 social functioning and fatigue[a]

Social Functioning

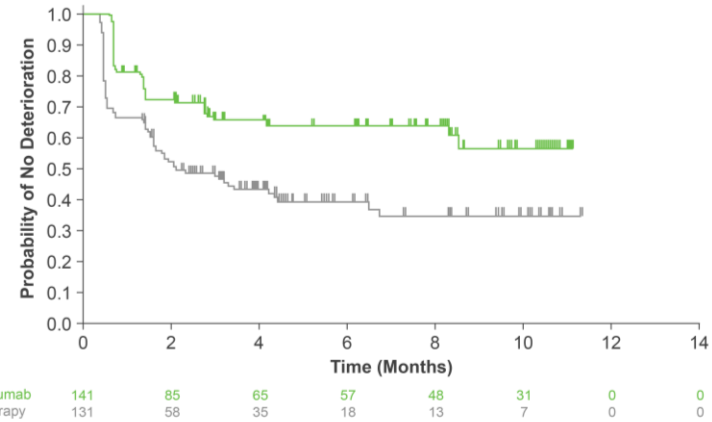
Treatment arm	No. of events	Median, months	HR (95% CI)	P value[b]
Pembrolizumab	27	NR (NR–NR)	0.53 (0.32–0.87)	0.0050
Chemotherapy	39	NR (NR–NR)	—	



No. at risk								
Pembrolizumab	141	108	86	74	58	45	0	0
Chemotherapy	131	83	54	30	24	10	0	0

Fatigue

Treatment arm	No. of events	Median, months	HR (95% CI)	P value[b]
Pembrolizumab	50	NR (8.5, NR)	0.48 (0.33–0.69)	<0.0001
Chemotherapy	72	2.1 (1.6, 4.4)	—	



No. at risk								
Pembrolizumab	141	85	65	57	48	31	0	0
Chemotherapy	131	58	35	18	13	7	0	0

Patient-reported outcomes was a post-hoc analysis and was not powered for statistical comparison

Data cut-off: 19 February 2020. Median follow up: 32.4 months.
Figure adapted from André T et al. Presented at the American Society for Clinical Oncology (ASCO) Virtual Annual Meeting 2021, 4–8 April 2021.
[a]Time to deterioration was defined as first onset of a ≥10-point change in score from baseline. [b]P values are 1-sided and nominal with no adjustment for multiplicity.
CI, confidence interval; EORTC QLQ, European Organisation for Research and Treatment of Cancer quality of life questionnaire version 3.0; HR, hazard ratio; NR, not reached.
André T et al. Presented at the American Society for Clinical Oncology (ASCO) Virtual Annual Meeting 2021, 4–8 April 2021.