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Actualités cliniques en immuno-oncologie Digestif

Journées d'immuno-onco du Cancéropôle Est

Aurélien Lambert

Immunothérapie et oesogastrique

RESEARCH SUMMARY

Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer

Kelly RJ et al. DOI: 10.1056/NEJMoa2032125

CLINICAL PROBLEM

For patients with locally advanced esophageal or gastroesophageal junction cancer, neoadjuvant chemoradiotherapy followed by surgery is a standard treatment. However, the risk of recurrence is high, especially among the 70 to 75% of patients without a pathological complete response, and clinicians lack proven adjuvant therapies for these patients.

CLINICAL TRIAL

A phase 3, double-blind, randomized, placebo-controlled trial to evaluate the efficacy of the checkpoint inhibitor nivolumab as adjuvant treatment after standard therapy.

794 adults who had received standard therapy for stage II or III esophageal or gastroesophageal junction cancer but had residual pathological disease were assigned within 4 to 16 weeks after surgery to intravenous nivolumab (30-minute infusions of 240 mg every 2 weeks for 16 weeks and then 480 mg monthly) or placebo for a maximum of 1 year. Median follow-up was 24.4 months.

RESULTS

Efficacy:

Median disease-free survival was 22.4 months with nivolumab and 11.0 months with placebo. Adjuvant nivolumab was also associated with longer metastasis-free survival.

Safety:

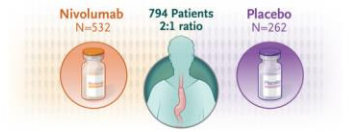
The safety profile of nivolumab was similar to that seen in other types of solid tumors. The most common high-grade nivolumab-related adverse events with potential immunologic cause were pneumonitis and rash.

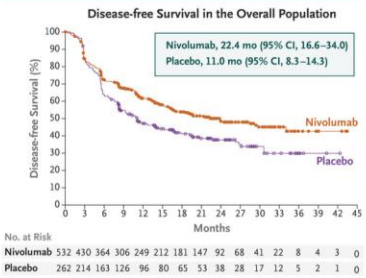
REMAINING QUESTIONS

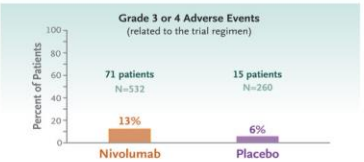
Further study is required to understand the following:

- The longer-term effects of nivolumab on overall survival
- Whether standard chemotherapy would be more effective if given with checkpoint inhibitors

Links: Full article | NEJM Quick Take | Editorial







CONCLUSIONS

Adjuvant nivolumab significantly prolonged disease-free survival among patients with an incomplete pathological response after standard therapy for esophageal or gastroesophageal junction cancer.

Immunothérapie et oesogastrique

Articles

CE + CPS > 10

CE

CE/ADK + CPS > 10

CE/ADK

CPS < 10

Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study

*Jong-Mu Sun, Lin Shen, Manish A Shah, Peter Enzinger, Antoine Adenis, Toshihiko Doi, Takashi Kojima, Jean-Philippe Metges, Zhigang Li, Sung-Bae Kim, Byoung Chul Cho, Wasat Mansoor, Shau-Hsuan Li, Patrapim Sunpaweravong, Maria Alsina Maqueda, Eray Goekkurt, Hiroki Hara, Luis Antunes, Christos Fountzilas, Akihito Tsuji, Victor Castro Oliden, Qi Liu, Sukrut Shah, Pooja Bhagia, Ken Kato, on behalf of the KEYNOTE-590 Investigators**

Summary

Background First-line therapy for advanced oesophageal cancer is currently limited to fluoropyrimidine plus platinum-based chemotherapy. We aimed to evaluate the antitumour activity of pembrolizumab plus chemotherapy versus chemotherapy alone as first-line treatment in advanced oesophageal cancer and Siewert type 1 gastro-oesophageal junction cancer.

Methods We did a randomised, placebo-controlled, double-blind, phase 3 study across 168 medical centres in 26 countries. Patients aged 18 years or older with previously untreated, histologically or cytologically confirmed, locally advanced, unresectable or metastatic oesophageal cancer or Siewert type 1 gastro-oesophageal junction cancer (regardless of PD-L1 status), measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1, and Eastern Cooperative Oncology Group performance status of 0–1, were randomly assigned (1:1) to intravenous pembrolizumab 200 mg or placebo, plus 5-fluorouracil and cisplatin (chemotherapy), once every 3 weeks for up to 35 cycles. Randomisation was stratified by geographical region, histology, and performance status. Patients, investigators, and site staff were masked to group assignment and PD-L1 biomarker status. Primary endpoints were overall survival in patients with oesophageal squamous cell carcinoma and PD-L1 combined positive score (CPS) of 10 or more, and overall survival and progression-free survival in patients with oesophageal squamous cell carcinoma, PD-L1 CPS of 10 or more, and in all randomised patients. This trial is registered with ClinicalTrials.gov, NCT03189719, and is closed to recruitment.

Lancet 2021; 398: 759–71

See Comment page 726

*KEYNOTE-590 Investigators are listed in the appendix (pp 2–5)

Samsung Medical Center, Sungkyunkwan University, Seoul, South Korea (J-M Sun MD); **Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital & Institute, Beijing, China** (L Shen MD); **Weill Cornell Medical College, New York City, NY, USA** (Prof M A Shah MD); **Dana Farber Cancer Institute, Boston, MA, USA** (P Enzinger MD); **Institut de**

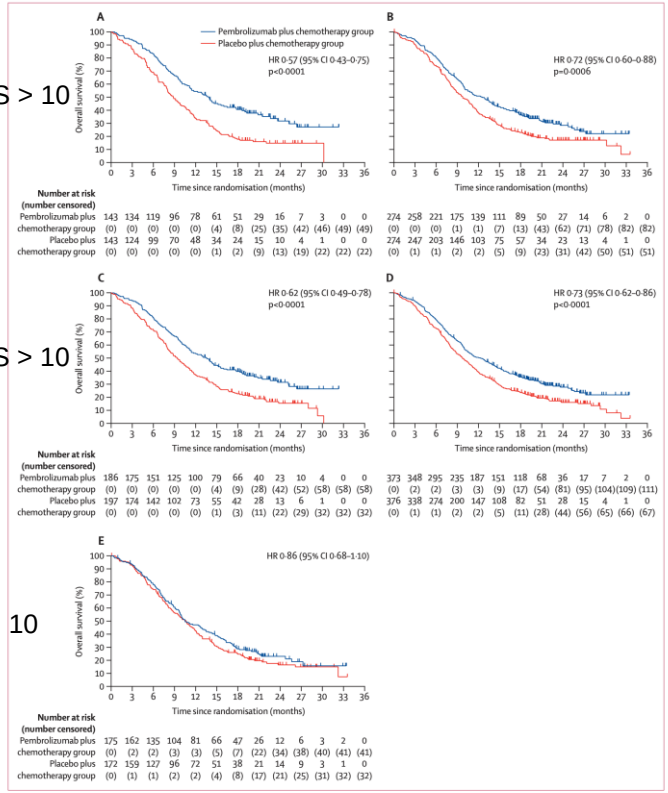


Figure 2: Kaplan-Meier estimates of overall survival
(A) Patients with oesophageal squamous cell carcinoma and PD-L1 CPS of 10 or more. (B) Patients with oesophageal squamous cell carcinoma. (C) Patients with PD-L1 CPS of 10 or more. (D) All randomised patients. (E) Patients with PD-L1 CPS of less than 10 (post-hoc analysis). Tick marks represent data censored at the time of last imaging assessment. CPS=combined positive score. HR=hazard ratio.

Immunothérapie et oesogastrique

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma

Y. Doki, J.A. Ajani, K. Kato, J. Xu, L. Wyrwicz, S. Motoyama, T. Ogata, H. Kawakami, C.-H. Hsu, A. Adenis, F. El Hajbi, M. Di Bartolomeo, M.I. Braghiroli, E. Holtved, S.A. Ostoich, H.R. Kim, M. Ueno, W. Mansoor, W.-C. Yang, T. Liu, J. Bridgewater, T. Makino, I. Xynos, X. Liu, M. Lei, K. Kondo, A. Patel, J. Gricar, I. Chau, and Y. Kitagawa, for the CheckMate 648 Trial Investigators*

ABSTRACT

BACKGROUND

First-line chemotherapy for advanced esophageal squamous-cell carcinoma results in poor outcomes. The monoclonal antibody nivolumab has shown an overall survival benefit over chemotherapy in previously treated patients with advanced esophageal squamous-cell carcinoma.

METHODS

In this open-label, phase 3 trial, we randomly assigned adults with previously untreated, unresectable advanced, recurrent, or metastatic esophageal squamous-cell carcinoma in a 1:1:1 ratio to receive nivolumab plus chemotherapy, nivolumab plus the monoclonal antibody ipilimumab, or chemotherapy. The primary end points were overall survival and progression-free survival, as determined by blinded independent central review. Hierarchical testing was performed first in patients with tumor-cell programmed death ligand 1 (PD-L1) expression of 1% or greater and then in the overall population (all randomly assigned patients).

The authors' full names, acade
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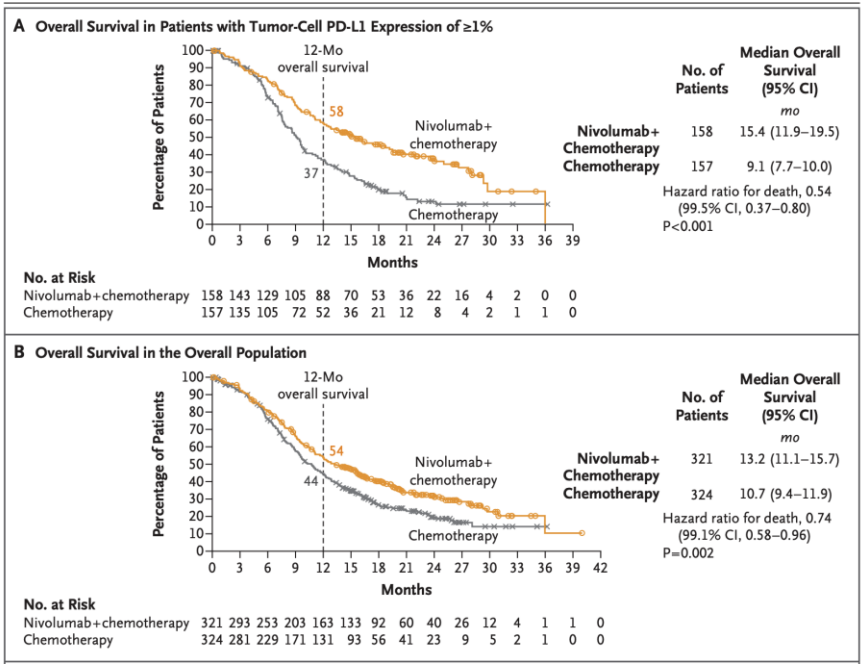
Oncology, National Cancer Cen
pital, Chuo City, Tokyo, 104-0045

*A complete list of the sites an
tigators in the CheckMate 64
provided in the Supplementary
dix, available at NEJM.org.

Drs. Doki and Ajani contributed equally to this article.

N Engl J Med 2022;386:449-62.
DOI: 10.1056/NEJMoa2111380



Checkmate 648

Immunothérapie et oesogastrique

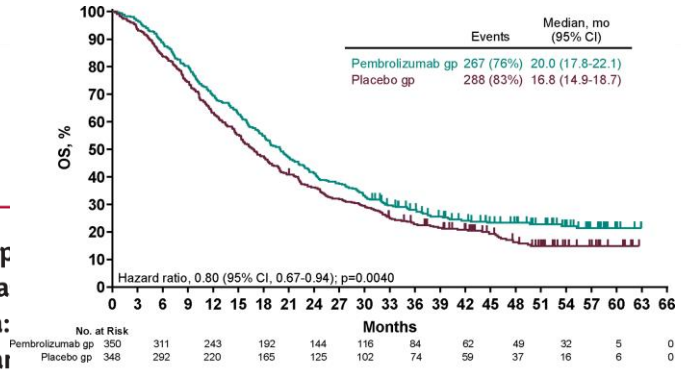
Pembrolizumab p
HER2-positive ga
adenocarcinoma:
KEYNOTE-811 ra

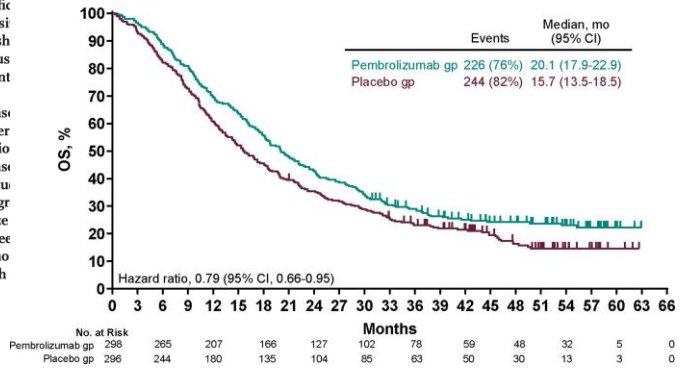
Yelena Y Janjigian, Akihito Kawazoe, Yuxi
Yuriy Ostapenko, Mehmet Bilici, Hyun Ch
Pooja Bhagia, Sun Young Rha, on behalf o

Summary

Background Evidence for the effic
and overall survival in HER2-posi
phase 3 KEYNOTE-811 study sh
when added to trastuzumab plus
protocol-specified subsequent int

Methods The randomised, phas
Patients aged 18 years or older
adenocarcinoma, without previo
voice-response and web-respons
with standard chemotherapy (flu
to 35 cycles or until disease progr
Randomisation used a block size
endpoints were progression-free
randomly assigned patients who
KEYNOTE-811 is registered with





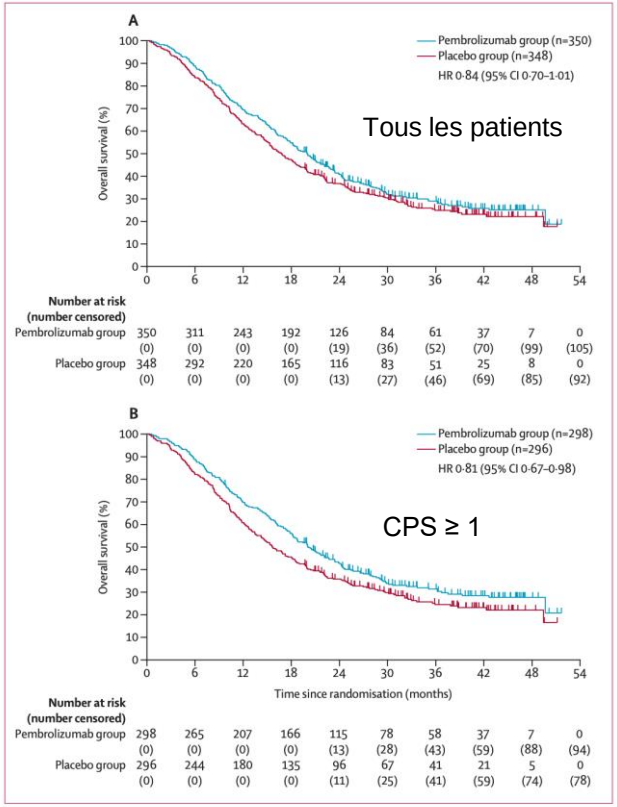


Figure 4: **Overall survival in patients in the intention-to-treat population at the third interim analysis**
Kaplan-Meier estimates of overall survival in all patients (A) and in the subgroup of patients with tumours with a PD-L1 combined positive score of 1 or more (B). The HR for death is provided on each graph. Tick marks represent data censored at the time of last imaging assessment. HR=hazard ratio.

Immunothérapie et oesogastrique

F. Lordick et al.

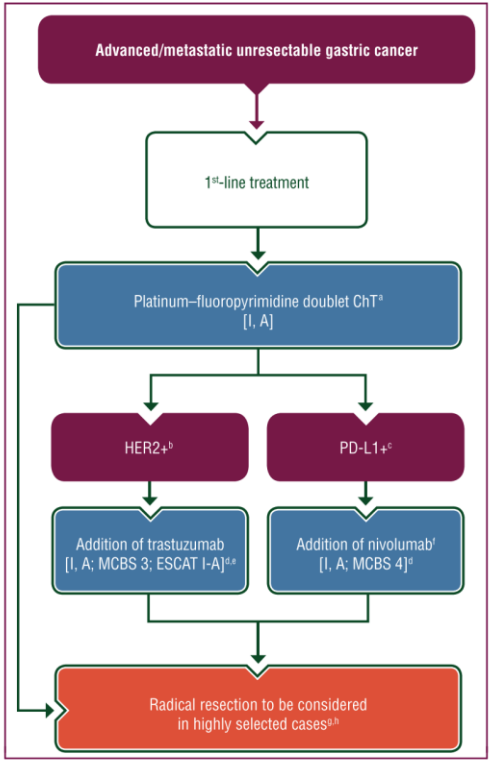


Figure 2. Treatment algorithm for first-line treatment of advanced/metastatic unresectable gastric cancer.

R. Obermannová et al.

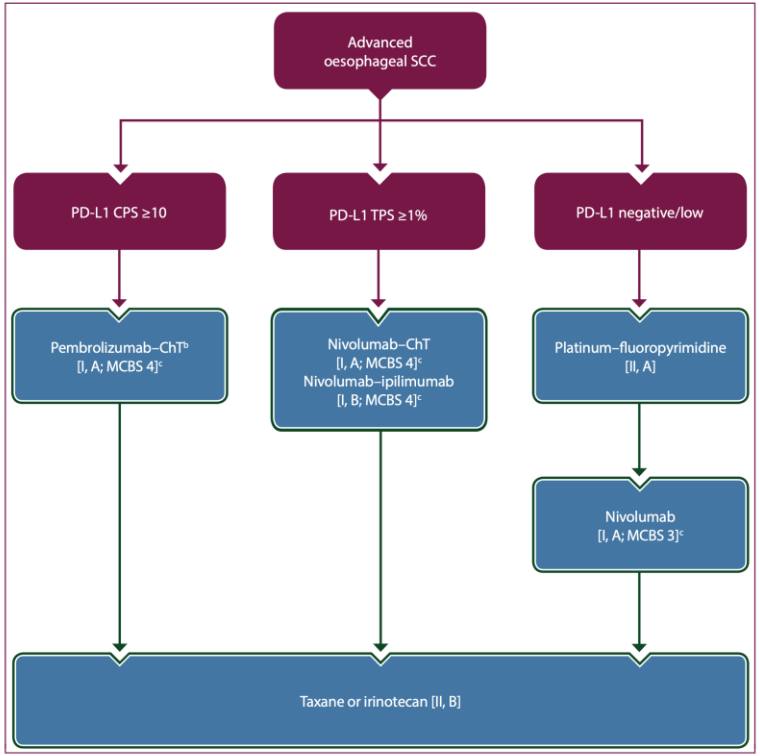


Figure 2. Treatment algorithm for advanced oesophageal SCC.[a]

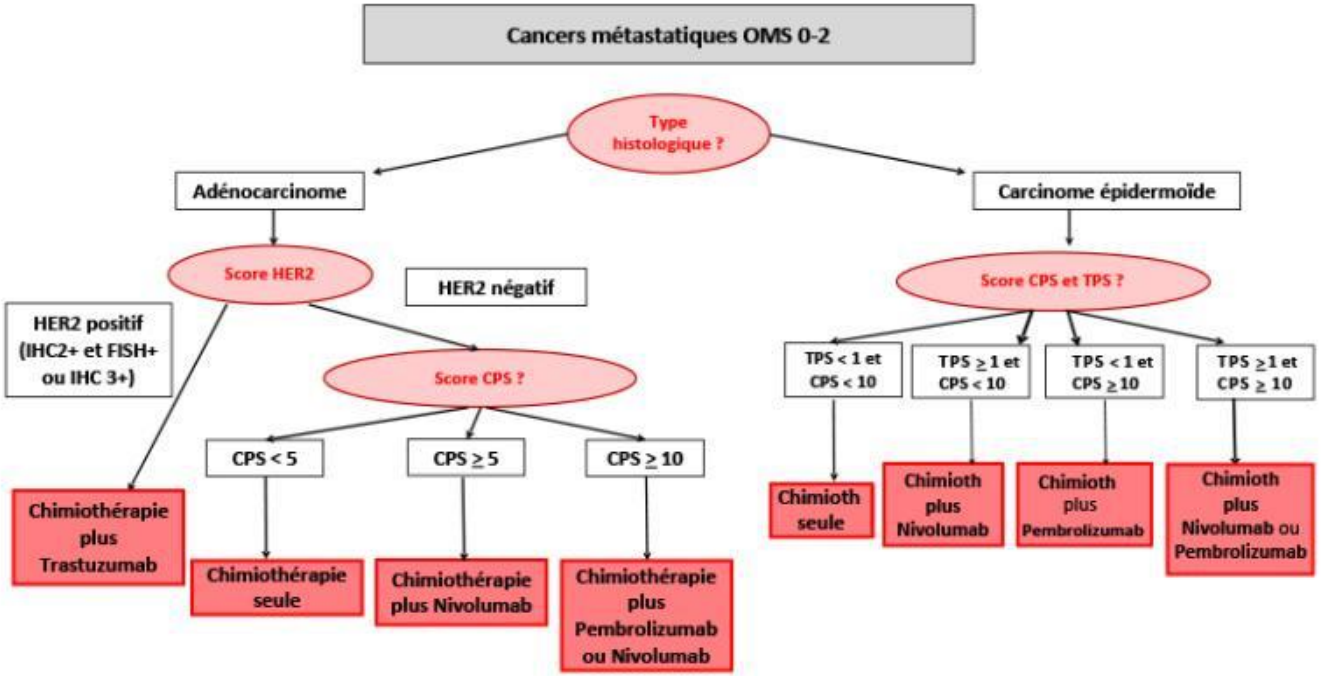
Purple: general categories or stratification; blue: systemic anticancer therapy. AC, adenocarcinoma; ChT, chemotherapy; CPG, Clinical Practice Guideline; CPS, combined positive score; EMA, European Medicines Agency; FDA, Food and Drug Administration; MCBS, Magnitude of Clinical Benefit Score; OGJ, oesophagogastric junction; PD-L1, programmed death-ligand 1; SCC, squamous-cell carcinoma; TPS, tumour proportion score.

[a]For treatment of oesophageal AC and OGJ cancer, see the ESMO CPG for gastric cancer.[20]

[b]EMA approval is for tumours with PD-L1 CPS ≥10, FDA approval is irrespective of PD-L1 expression.

[c]ESMO-MCBS v1.1[21] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).

Immunothérapie et oesogastrique



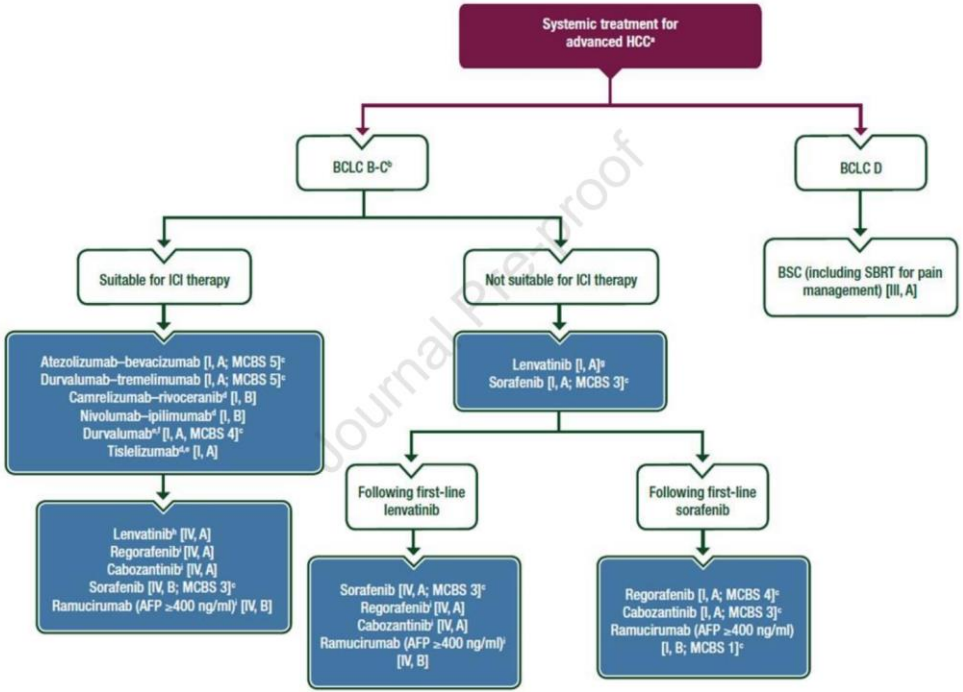
Immunothérapie et CHC

Journal Pre-proof

Hepatocellular carcinoma: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up†

A. Vogel, S.L. Chan, L.A. Dawson, R.K. Kelley, J.M. Llovet, T. Meyer, J. Ricke, L. Rimassa, G. Sapisochin, V. Vilgrain, J. Zucman-Rossi, M. Ducreux, on behalf of the ESMO Guidelines Committee

Figure 2. Management of advanced HCC.



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Immunothérapie et CCRm

VOLUME 36 · NUMBER 8 · MARCH 10, 2018

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Check for updates

Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair–Deficient/Microsatellite Instability–High Metastatic Colorectal Cancer

Michael J. Overman, Sara Lonardi, Ka Yeung Mark Wong, Heinz-Josef Lenz, Fabio Gelsomino, Massimo Aglietta, Michael A. Morse, Eric Van Cutsem, Ray McDermott, Andrew Hill, Michael B. Sawyer, Alain Hendlisz, Bart Neyns, Magali Svrcek, Rebecca A. Moss, Jean-Marie Ledeine, Z. Alexander Cao, Shital Kamble, Scott Kopetz, and Thierry André

Author affiliations and support information (if applicable) appear at the end of this article.

Published at jco.org on January 20, 2018.

Clinical trial information: NCT02060188.

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0732-183X/18/3608w-773w/$20.00

ABSTRACT

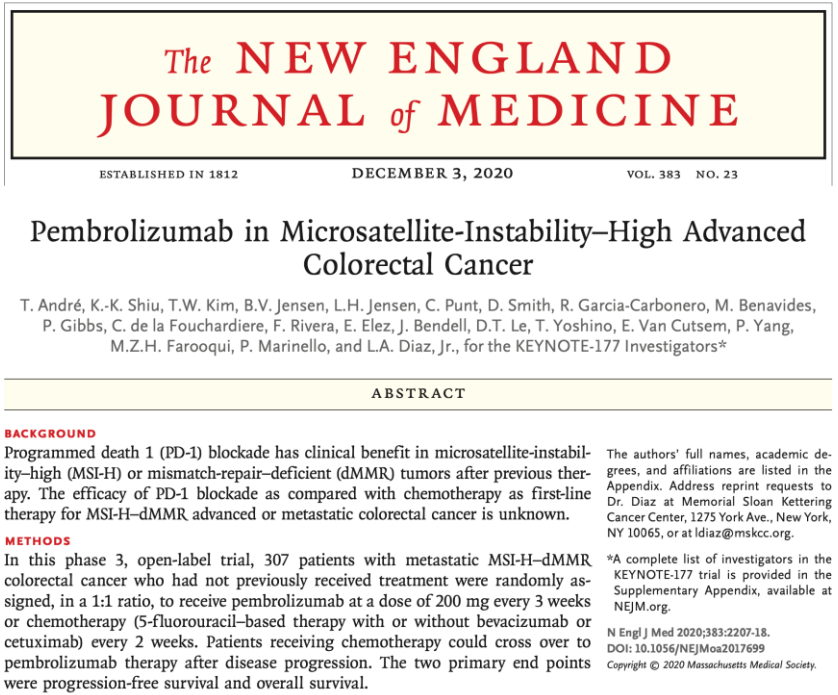
Purpose
Nivolumab provides clinical benefit (objective response rate [ORR], 31%; 95% CI, 20.8 to 42.9; disease control rate, 69%; 12-month overall survival [OS], 73%) in previously treated patients with DNA mismatch repair–deficient (dMMR)/microsatellite instability–high (MSI-H) metastatic colorectal cancer (mCRC); nivolumab plus ipilimumab may improve these outcomes. Efficacy and safety results for the nivolumab plus ipilimumab cohort of CheckMate-142, the largest single-study report of an immunotherapy combination in dMMR/MSI-H mCRC, are reported.

Patients and Methods
Patients received nivolumab 3 mg/kg plus ipilimumab 1 mg/kg once every 3 weeks (four doses) followed by nivolumab 3 mg/kg once every 2 weeks. Primary end point was investigator-assessed ORR.

Results
Of 119 patients, 76% had received ≥ two prior systemic therapies. At median follow-up of 13.4 months, investigator-assessed ORR was 55% (95% CI, 45.2 to 63.8), and disease control rate for ≥ 12 weeks was 80%. Median duration of response was not reached; most responses (94%) were ongoing at data cutoff. Progression-free survival rates were 76% (9 months) and 71% (12 months); respective OS rates were 87% and 85%. Statistically significant and clinically meaningful improvements were observed in patient-reported outcomes, including functioning, symptoms, and quality of life. Grade 3 to 4 treatment-related adverse events (AEs) occurred in 32% of patients and were manageable. Patients (13%) who discontinued treatment because of study drug-related AEs had an ORR (63%) consistent with that of the overall population.

Conclusion
Nivolumab plus ipilimumab demonstrated high response rates, encouraging progression-free survival and OS at 12 months, manageable safety, and meaningful improvements in key patient-reported outcomes. Indirect comparisons suggest combination therapy provides improved efficacy relative to anti–programmed death-1 monotherapy and has a favorable benefit-risk profile. Nivolumab plus ipilimumab provides a promising new treatment option for patients with dMMR/MSI-H mCRC.

J Clin Oncol 36:773-779. © 2018 by American Society of Clinical Oncology



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 3, 2020 VOL. 383 NO. 23

Pembrolizumab in Microsatellite-Instability–High Advanced Colorectal Cancer

T. André, K.-K. Shiu, T.W. Kim, B.V. Jensen, L.H. Jensen, C. Punt, D. Smith, R. Garcia-Carbonero, M. Benavides, P. Gibbs, C. de la Fouchardiere, F. Rivera, E. Elez, J. Bendell, D.T. Le, T. Yoshino, E. Van Cutsem, P. Yang, M.Z.H. Farooqui, P. Marinello, and L.A. Diaz, Jr., for the KEYNOTE-177 Investigators*

ABSTRACT

BACKGROUND
Programmed death 1 (PD-1) blockade has clinical benefit in microsatellite-instability–high (MSI-H) or mismatch-repair–deficient (dMMR) tumors after previous therapy. The efficacy of PD-1 blockade as compared with chemotherapy as first-line therapy for MSI-H–dMMR advanced or metastatic colorectal cancer is unknown.

METHODS
In this phase 3, open-label trial, 307 patients with metastatic MSI-H–dMMR colorectal cancer who had not previously received treatment were randomly assigned, in a 1:1 ratio, to receive pembrolizumab at a dose of 200 mg every 3 weeks or chemotherapy (5-fluorouracil–based therapy with or without bevacizumab or cetuximab) every 2 weeks. Patients receiving chemotherapy could cross over to pembrolizumab therapy after disease progression. The two primary end points were progression-free survival and overall survival.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Diaz at Memorial Sloan Kettering Cancer Center, 1275 York Ave., New York, NY 10065, or at ldiaz@mskcc.org.

*A complete list of investigators in the KEYNOTE-177 trial is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2020;383:2207-18.
DOI: 10.1056/NEJMoa2017699

Immunothérapie et CCRm

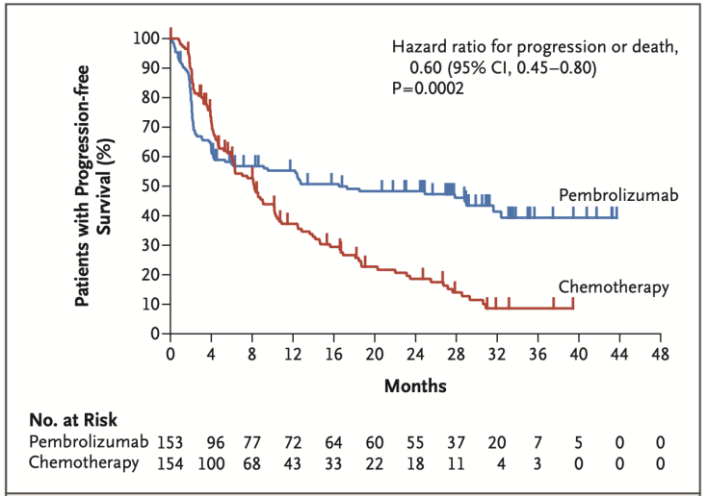


Figure 1. Progression-free Survival in Patients with MSI-H–dMMR Metastatic Colorectal Cancer.

Shown are Kaplan–Meier estimates of progression-free survival among patients with microsatellite-instability–high (MSI-H) or mismatch-repair–deficient (dMMR) colorectal cancer. The analysis was performed in the intention-to-treat population. Tick marks represent data censored at the time of the last imaging assessment. Progression-free survival was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, by independent central reviewers who were unaware of the group assignments. The P value shown met the prespecified statistical criterion (P=0.0117) for superiority of pembrolizumab over chemotherapy.

Immunothérapie et CCRm

Nivolumab plus ipilimumab versus nivolumab in microsatellite instability-high metastatic colorectal cancer (CheckMate 8HW): a randomised, open-label, phase 3 trial

Thierry André, Elena Elez, Heinz-Josef Lenz, Lars Henrik Jensen, Yann Touchefeu, Eric Van Cutsem, Rocio Garcia-Carbonero, David Tougeron, Guillermo Ariel Mendez, Michael Schenker, Christelle de la Fouchardiere, Maria Luisa Limon, Takayuki Yoshino, Jin Li, Jose Luis Manzano Mozo, Laetitia Dahan, Giampaolo Tortora, Myriam Chalabi, Eray Goekkurt, Maria Ignez Braghiroli, Rohit Joshi, Timucin Cil, Francine Aubin, Elvis Cela, Tian Chen, Ming Lei, Lixian Jin, Steven I Blum, Sara Lonardi

Summary

Background CheckMate 8HW prespecified dual primary endpoints, assessed in patients with centrally confirmed microsatellite instability-high or mismatch repair-deficient status: progression-free survival with nivolumab plus ipilimumab compared with chemotherapy as first-line therapy and progression-free survival with nivolumab plus ipilimumab compared with nivolumab alone, regardless of previous systemic treatment for metastatic disease. In our previous report, nivolumab plus ipilimumab showed superior progression-free survival versus chemotherapy in first-line microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer in the CheckMate 8HW trial. Here, we report results from the prespecified interim analysis for the other primary endpoint of progression-free survival for nivolumab plus ipilimumab versus nivolumab across all treatment lines.

Methods CheckMate 8HW is a randomised, open-label, international, phase 3 trial at 128 hospitals and cancer centres across 23 countries. Immunotherapy-naive adults with unresectable or metastatic colorectal cancer across different lines of therapy and microsatellite instability-high or mismatch repair-deficient status per local testing were randomly assigned (2:2:1) to nivolumab plus ipilimumab (nivolumab 240 mg, ipilimumab 1 mg/kg, every 3 weeks for four doses; then nivolumab 480 mg every 4 weeks; all intravenously), nivolumab (240 mg every 2 weeks for six doses, then 480 mg every 4 weeks; all intravenously), or chemotherapy with or without targeted therapies. The dual independent primary endpoints were progression-free survival by blinded independent central review with nivolumab plus ipilimumab versus chemotherapy (first line) and progression-free survival by blinded independent central review with nivolumab plus ipilimumab versus nivolumab (all lines) in patients with centrally confirmed microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer. This study is registered with ClinicalTrials.gov (NCT04008030).

Lancet 2025; 405: 383–95

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See Comment page 354

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Immunothérapie et CCRm

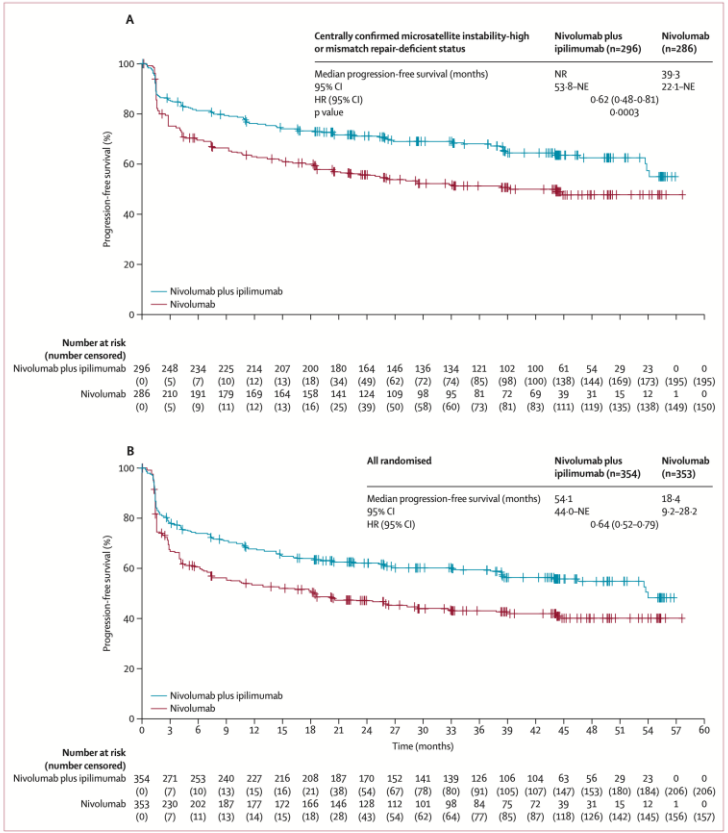
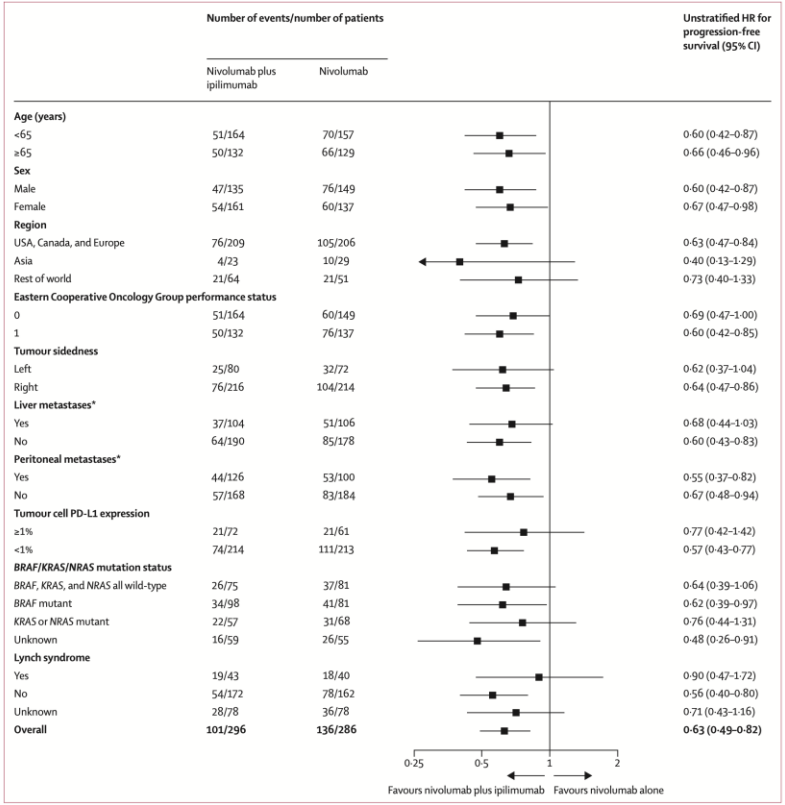


Figure 2: **Progression-free survival by blinded independent central review with nivolumab plus ipilimumab versus nivolumab**
(A) Patients with centrally confirmed microsatellite instability-high or mismatch repair-deficient status. The boundary for statistical significance was p<0·0095. (B) All patients who underwent randomisation. For both patient populations, stratified Cox proportional hazard model by tumour sidedness (left vs right) and previous lines of therapy (0 vs 1 vs ≥2) per interactive response technology was used. Vertical dashes indicate censored data. HR=hazard ratio. NE=not estimable. NR=not reached.

Immunothérapie et CCRm



	Number of events/number of patients		Unstratified HR for progression-free survival (95% CI)
	Nivolumab plus ipilimumab	Nivolumab	
Age (years)			
<65	51/164	70/157	0·60 (0·42–0·87)
≥65	50/132	66/129	0·66 (0·46–0·96)
Sex			
Male	47/135	76/149	0·60 (0·42–0·87)
Female	54/161	60/137	0·67 (0·47–0·98)
Region			
USA, Canada, and Europe	76/209	105/206	0·63 (0·47–0·84)
Asia	4/23	10/29	0·40 (0·13–1·29)
Rest of world	21/64	21/51	0·73 (0·40–1·33)
Eastern Cooperative Oncology Group performance status			
0	51/164	60/149	0·69 (0·47–1·00)
1	50/132	76/137	0·60 (0·42–0·85)
Tumour sidedness			
Left	25/80	32/72	0·62 (0·37–1·04)
Right	76/216	104/214	0·64 (0·47–0·86)
Liver metastases*			
Yes	37/104	51/106	0·68 (0·44–1·03)
No	64/190	85/178	0·60 (0·43–0·83)
Peritoneal metastases*			
Yes	44/126	53/100	0·55 (0·37–0·82)
No	57/168	83/184	0·67 (0·48–0·94)
Tumour cell PD-L1 expression			
≥1%	21/72	21/61	0·77 (0·42–1·42)
<1%	74/214	111/213	0·57 (0·43–0·77)
***BRAF*/*KRAS*/*NRAS* mutation status**			
BRAF, *KRAS*, and *NRAS* all wild-type	26/75	37/81	0·64 (0·39–1·06)
BRAF mutant	34/98	41/81	0·62 (0·39–0·97)
KRAS or *NRAS* mutant	22/57	31/68	0·76 (0·44–1·31)
Unknown	16/59	26/55	0·48 (0·26–0·91)
Lynch syndrome			
Yes	19/43	18/40	0·90 (0·47–1·72)
No	54/172	78/162	0·56 (0·40–0·80)
Unknown	28/78	36/78	0·71 (0·43–1·16)
Overall	**101/296**	**136/286**	**0·63 (0·49–0·82)**

Figure 3: **Progression-free survival by blinded independent central review in key subgroups of patients with centrally confirmed microsatellite instability-high or mismatch repair-deficient status**

Unstratified HRs are reported for patient subgroup analyses. Based on Kaplan–Meier estimates; rates not computed for subgroups with less than ten patients per treatment group. HR=hazard ratio. *Metastatic sites were determined by blinded independent central review and were not reported in three patients in the nivolumab plus ipilimumab group and two patients in the nivolumab group; patients could have more than one site of metastasis.

Immunothérapie et CCRm

	Nivolumab plus ipilimumab group (n=352)		Nivolumab group (n=351)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Any treatment-related adverse event	285 (81%)	78 (22%)	249 (71%)	50 (14%)
Treatment-related serious adverse event	65 (18%)	55 (16%)	29 (8%)	24 (7%)
Treatment-related adverse event leading to discontinuation of any drug in the regimen	48 (14%)	33 (9%)	21 (6%)	14 (4%)
Treatment-related deaths*	2 (1%)	..	1 (<1%)	..

Immunothérapie et CCR

The NEW ENGLAND JOURNAL of MEDICINE

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Neoadjuvant Immunotherapy in Locally Advanced Mismatch Repair–Deficient Colon Cancer

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ABSTRACT

BACKGROUND

Mismatch repair–deficient (dMMR) tumors can be found in 10 to 15% of patients with nonmetastatic colon cancer. In these patients, the efficacy of chemotherapy is limited. The use of neoadjuvant immunotherapy has shown promising results, but data from studies of this approach are limited.

METHODS

We conducted a phase 2 study in which patients with nonmetastatic, locally advanced, previously untreated dMMR colon cancer were treated with neoadjuvant nivolumab plus ipilimumab. The two primary end points were safety, defined by timely surgery (i.e., ≤2-week delay of planned surgery owing to treatment-related toxic events), and 3-year disease-free survival. Secondary end points included pathological response and results of genomic analyses.

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CME

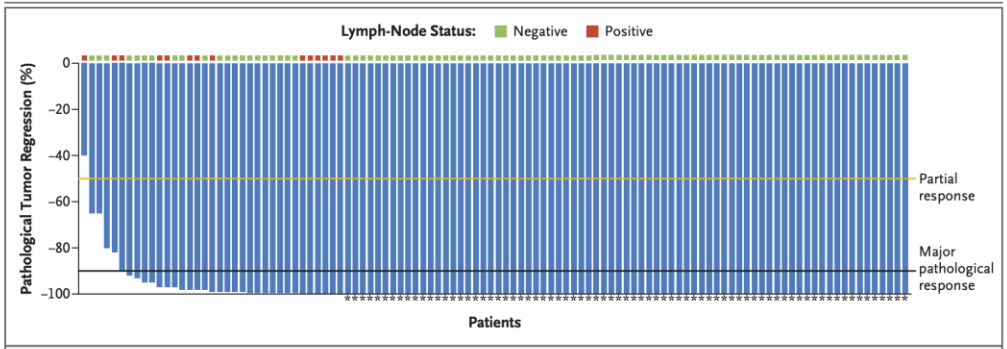

Figure 2. Pathological Responses among Patients in the Efficacy Analysis.

The waterfall plot shows the percentage of pathological tumor regression per tumor among the 110 tumors that could be evaluated for a pathological response. Boxes above each bar indicate the corresponding pathological lymph-node status. Patients with a pathological complete response in both the primary tumor and the lymph nodes are indicated by an asterisk. The black horizontal line indicates the threshold for a major pathological response, specified as at least 90% tumor regression. The yellow line indicates the threshold for a partial response, specified as at least a 50% regression.

Nivolumab + ipilimumab

Immunothérapie et CCR

nature medicine

Article

https://doi.org/10.1038/s41591-024-03250-w

Neoadjuvant nivolumab and relatlimab in locally advanced MMR-deficient colon cancer: a phase 2 trial

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Published online: 15 September 2024

Check for updates

A list of authors and their affiliations appears at the end of the paper

Mismatch repair deficiency (dMMR) is found in approximately 15% of non-metastatic colon cancers (CCs) and is characterized by a defective DNA mismatch repair system, resulting in hypermutated and highly immunogenic tumors. Although patients with dMMR CC have limited benefit from chemotherapy, these tumors have been shown to respond exceptionally well to neoadjuvant anti-PD-1 plus anti-CTLA-4, with high rates of pathologic responses. Here, based on data from melanoma studies, we postulated a high efficacy and favorable toxicity profile of anti-PD-1 plus anti-LAG-3. In the NICHE-3 study, a total of 59 patients with locally advanced dMMR CC were treated with two 4-weekly cycles of nivolumab (480 mg) plus relatlimab (480 mg) before surgery. Pathologic response was observed in 57 of 59 (97%; 95% confidence interval (CI): 88–100%) patients, meeting the primary endpoint. Responses included 54 (92%; 95% CI: 81–97%) major pathologic responses (≤10% residual viable tumor) and 40 (68%; 95% CI: 54–79%) pathologic complete responses. With a median follow-up of 8 months (range, 2–19), one patient had recurrence of disease. The treatment displayed an acceptable safety profile, with all-grade and grade 3–4 immune-related adverse events (irAEs) occurring in 80% and 10% of patients, respectively. The most common irAEs were infusion-related reactions (29%), thyroid dysfunction (22%) and fatigue (20%). In conclusion, our results show that neoadjuvant nivolumab/relatlimab induces high rates of pathologic responses and that further investigation of this treatment in larger studies is warranted. These data add to the body of evidence in support of neoadjuvant immunotherapy regimens in dMMR CC. ClinicalTrials.gov identifier: NCT03026140.

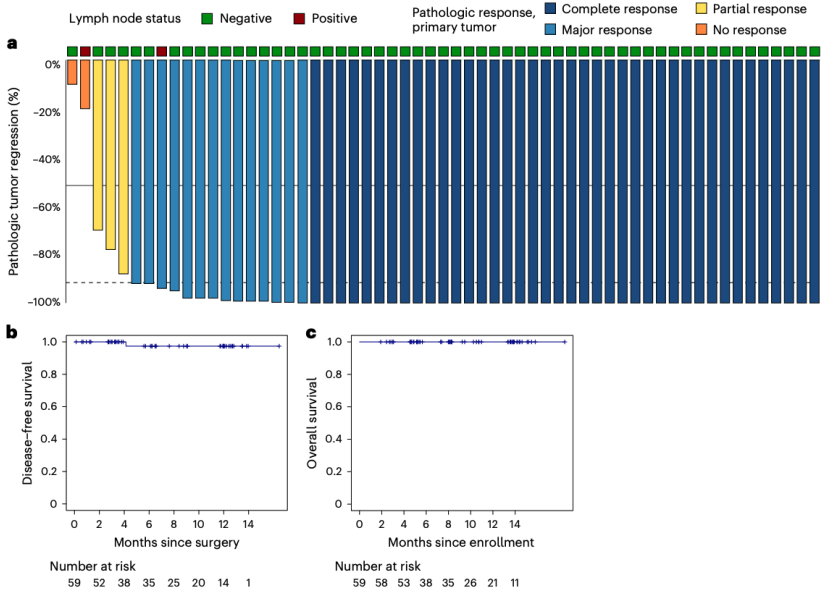


Fig. 2 | Pathologic response and outcome after neoadjuvant nivolumab plus relatlimab. a, Percentage of pathologic regression in the primary tumor bed shown per tumor. The horizontal black line depicts the threshold of 50% regression for a pathologic response, and the horizontal dashed line depicts the threshold of 90% regression for an MPR. Boxes above each bar indicate the corresponding pathologic lymph node status. **b**, Kaplan–Meier plot for DFS. **c**, Kaplan–Meier plot for overall survival.

Nivolumab + relatlimab

Immunothérapie et CCR

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

Cercek A et al. DOI: 10.1056/NEJMoa2201445

CLINICAL PROBLEM

Standard treatment for locally advanced rectal cancer includes neoadjuvant chemotherapy and radiation, followed by surgical resection of the rectum. This approach, however, is associated with substantial complications and toxic effects. Research suggests that immune checkpoint blockade alone is highly effective in patients with mismatch repair–deficient metastatic colorectal cancer; whether this strategy is effective in mismatch repair–deficient, locally advanced rectal cancer is unknown.

CLINICAL TRIAL

Design: A prospective, phase 2, single-group study examined the efficacy and safety of neoadjuvant therapy with the programmed death 1 (PD-1) inhibitor dostarlimab in patients with mismatch repair–deficient stage II or III rectal adenocarcinoma.

Intervention: Adult patients received intravenous dostarlimab every 3 weeks for 6 months, to be followed by chemoradiotherapy and total mesorectal excision. Patients with a clinical complete response to dostarlimab could forgo chemoradiotherapy and surgery. A key primary end point was overall response to dostarlimab alone or to dostarlimab plus chemoradiotherapy, determined on the basis of rectal magnetic resonance imaging, endoscopic visualization, and digital rectal examination.

RESULTS

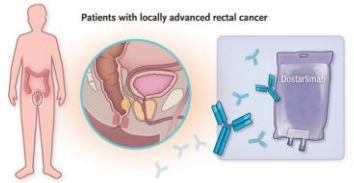
Efficacy: 12 of 16 enrolled patients have already completed 6 months of dostarlimab. All 12 had a clinical complete response, with no evidence of tumor on any diagnostic test. During a median follow-up of 12 months, no patient received chemoradiotherapy or underwent surgery, and none had disease progression or recurrence.

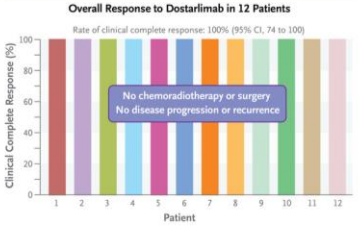
Safety: No adverse events of grade 3 or higher have occurred. The most common adverse events of grade 1 or 2 included rash or dermatitis, pruritus, fatigue, and nausea.

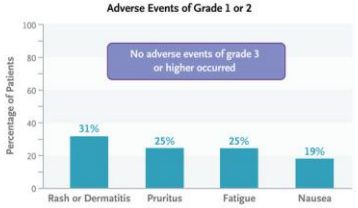
LIMITATIONS AND REMAINING QUESTIONS

- The study was small and limited to a single institution, and most of the patients were White.
- Longer-term follow-up is needed to evaluate the duration of response.

Links: Full Article | NEJM Quick Take | Editorial







CONCLUSIONS

All patients with mismatch repair–deficient, locally advanced rectal cancer who were treated with the PD-1 inhibitor dostarlimab alone for 6 months had a clinical complete response, although longer follow-up is warranted.

Dostarlimab

Immunothérapie et pancréas

Combining CD40 agonist mitazalimab with mFOLFIRINOX in previously untreated metastatic pancreatic ductal adenocarcinoma (OPTIMIZE-1): a single-arm, multicentre, phase 1b/2 study

Jean-Luc Van Laethem, Ivan Borbath, Hans Prenen, Karen Paula Geboes, Aurélien Lambert, Emmanuel Mitry, Philippe Alexandre Cassier, Jean-Frédéric Blanc, Lorenzo Pilla, Jaime Feliu Batlle, Mercedes Rodriguez Garrote, Roberto Antonio Pazo-Cid, Inmaculada Gallego, Karin Enell Smith, Peter Ellmark, Yago Pico de Coaña, Sumeet Vijay Ambarkhane, Teresa Macarulla

Summary

Background Current systemic therapies for metastatic pancreatic ductal adenocarcinoma are associated with poor outcomes with a 5-year overall survival rate under 5%. We aimed to assess the safety and antitumour activity of mitazalimab, a human CD40 agonistic IgG1 antibody, with modified FOLFIRINOX (mFOLFIRINOX; fluorouracil, leucovorin, oxaliplatin, and irinotecan), in chemotherapy-naive patients with metastatic pancreatic ductal adenocarcinoma.

Methods OPTIMIZE-1 was a single-arm, multicentre, phase 1b/2 study which enrolled adults with histologically-confirmed metastatic pancreatic ductal adenocarcinoma and European Cooperative Oncology Group performance status 0 or 1 in 14 university hospitals in Belgium, France, and Spain. The primary endpoint of phase 1b was to determine the recommended phase 2 dose of intravenous mitazalimab (450 µg/kg or 900 µg/kg) when combined with intravenous mFOLFIRINOX (oxaliplatin 85 mg/m², leucovorin 400 mg/m², irinotecan 150 mg/m², fluorouracil 2400 mg/m²). In the first 21-day treatment cycle, mitazalimab was administered on days 1 and 10, and mFOLFIRINOX on day 8. In subsequent 14-day cycles mitazalimab was administered 2 days after mFOLFIRINOX. The phase 2 primary endpoint was objective response rate. Activity and safety analyses were conducted on the full analysis set (all patients who received the combination of mitazalimab at the recommended phase 2 dose and mFOLFIRINOX for at least two treatment cycles) and safety set (all patients who received any study treatment), respectively. Enrolment is complete, and data represents a primary analysis of the ongoing trial. The trial is registered at Clinicaltrials.gov (NCT04888312).

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See Comment page 824

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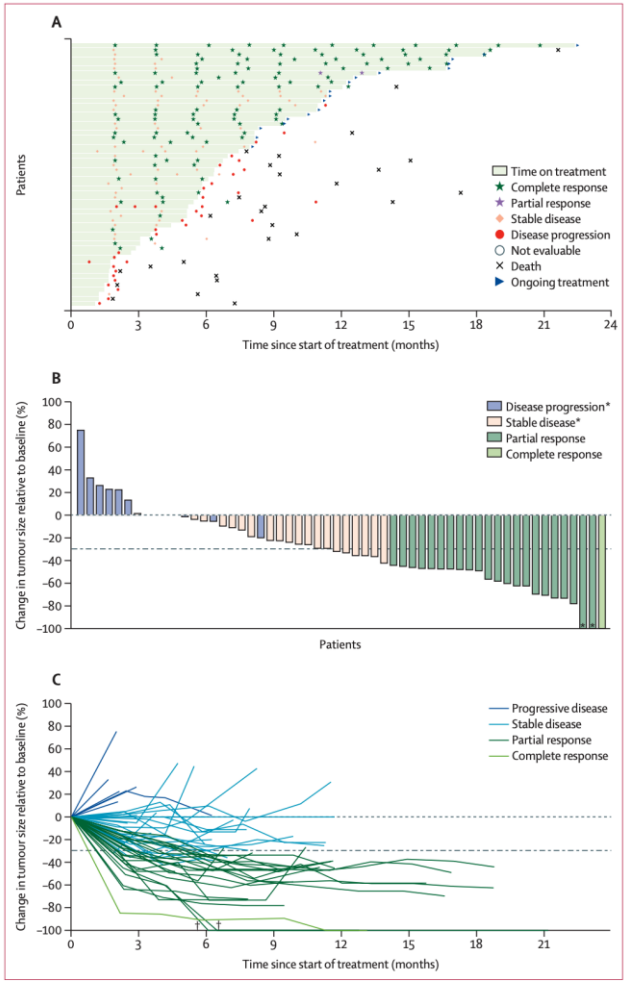

Figure 2: **Depth and duration of response in the full analysis set**

Immunothérapie et mMMR/MSI

BARCELONA 2024 ESMO congress

IMHOTEP : a phase II trial of neoadjuvant PEMBROLIZUMAB in dMMR/MSI localized tumors

Results of the colorectal cancer cohort

IMHOTEP

Christelle de la Fouchardière[1], A.Zaanan, R.Cohen, S.Le Sourd, D.Tougeron, E.Soularue, O.Dubreuil, N.Williet, E.Samalin-Scalzi, G.Piessen, V.Hautefeuille, M.Jary, M.Ben Abdelghani, L.Evesque, P.Rochigneux, E.Blanc, F.Bibeau, A. DeMontfort, C.Coutzac.

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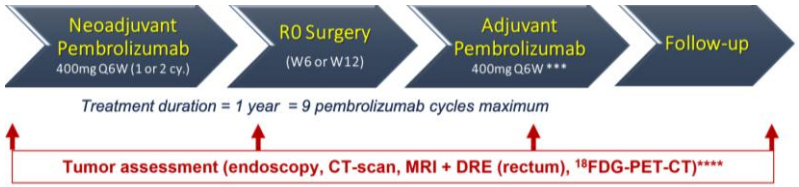
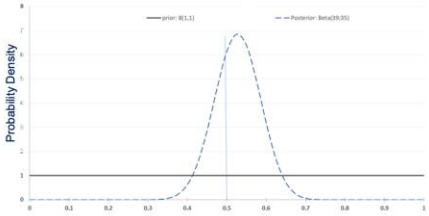


Results: primary endpoint, pCR (per-protocol population/operated patients - N=72)

	Colon (N=63)	Rectum (N=9)	All CRC (N=72)
pCR (ypT0N0) rate	35 (55.6%)	3 (33.3%)	38 (52.8%)



Bayesian estimation of pCR: 52.7% (95% CI* [41.4% ; 63.9%])**

Proba (pCR > 50%) = 0.68

* Credible Interval

** Assuming a non-informative prior distribution [Beta (1,1) ⇨ pCR rate of 50%]

Results: primary endpoint, pCR (per-protocol population/operated patients - N=72)

	Colon (N=63)		Rectum (N=9)		All CRC (N=72)	
pCR (ypT0N0) rate	35/63	(55.6%)	3/9	(33.3%)	38/72	(52.8%)
↳ After 1 pembrolizumab cycle	21/45	(46.7%)	2/5	(40.0%)	23/50	(46.0%)
↳ After 2 pembrolizumab cycles	14/18	(77.8%)	1/4	(25.0%)	**15/22**	**(68.2%)**

*

* Multivariate logistic analysis **p=0.034**

Effet abscopal avec la radiothérapie ?

Cancer Cell

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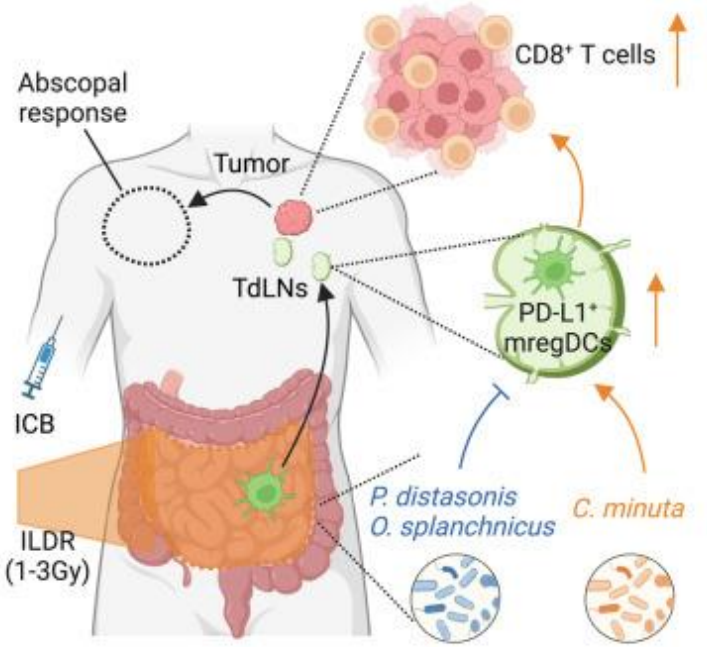
Article

Low-dose irradiation of the gut improves the efficacy of PD-L1 blockade in metastatic cancer patients

Jianzhou Chen,[1,2,3,10,36] Antonin Levy,[2,5,6,36] Ai-Ling Tian,[1,2,3] Xuehan Huang,[10] Guoxin Cai,[1,2,3] Marine Fidelle,[1,3,4] Conrad Rauber,[1,2,3,11] Pierre Ly,[1,2,3] Eugénie Pizzato,[1,2,3] Lisa Sitterle,[6] Gianmarco Piccinno,[12] Peng Liu,[7,8] Sylvère Durand,[7] Misha Mao,[7,8,25,26] Liwei Zhao,[7,8] Valerio Iebba,[1] Hannah Felchle,[7,8,27] Anne-Laure Mallard de La Varende,[1,2,3] Julius Clemens Fischer,[7,8,27] Simon Thomas,[1,2,3] Tim F. Greten,[28] Jennifer C. Jones,[29,30] Cecilia Monge,[28] Sandra Demaria,[13] Silvia Formenti,[13] Lorenzo Belluomini,[31] Valeria Dionisi,[32] Christophe Massard,[2,6,14] Pierre Blanchard,[2,6] Charlotte Robert,[6] Clément Quevrin,[6]



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