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Kolorektální karcinom

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NIVOLUMAB PLUS LOW-DOSE IPILIMUMAB IN PREVIOUSLY TREATED PATIENTS WITH MICROSATELLITE INSTABILITY-HIGH/ MISMATCH REPAIR-DEFICIENT METASTATIC COLORECTAL CANCER: 4-YEAR FOLLOW-UP FROM CHECKMATE 142

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CheckMate 142 NIVO3 + IPI1 2L+ cohort study design

- CheckMate 142 is an ongoing, multicohort, nonrandomized phase 2 trial evaluating the efficacy and safety of NIVO-based therapies in patients with mCRC[a]

- Histologically confirmed metastatic/recurrent CRC
- MSI-H/dMMR per local laboratory
- ≥ 1 prior line of therapy

N = 119

NIVO3 + IPI1 Q3W
(4 doses, then NIVO3 Q2W)[b]

Primary endpoint:
ORR per investigator assessment (RECIST v1.1)

Other key endpoints:
ORR per BICR, DCR,[c] DOR, PFS, OS, and safety

- At data cutoff (October 2020), the median duration of follow-up was 50.9 months (range, 46.9-62.7)[d]

[a]ClinicalTrials.gov number. NCT02060188; [b]Until disease progression or discontinuation in patients receiving study therapy beyond progression, discontinuation due to toxicity, withdrawal of consent, or the study end; [c]Patients with CR, PR, or SD for ≥ 12 weeks divided by the number of treated patients; [d]Median follow-up was defined as time from first dose to data cutoff.

Response, disease control, and durability

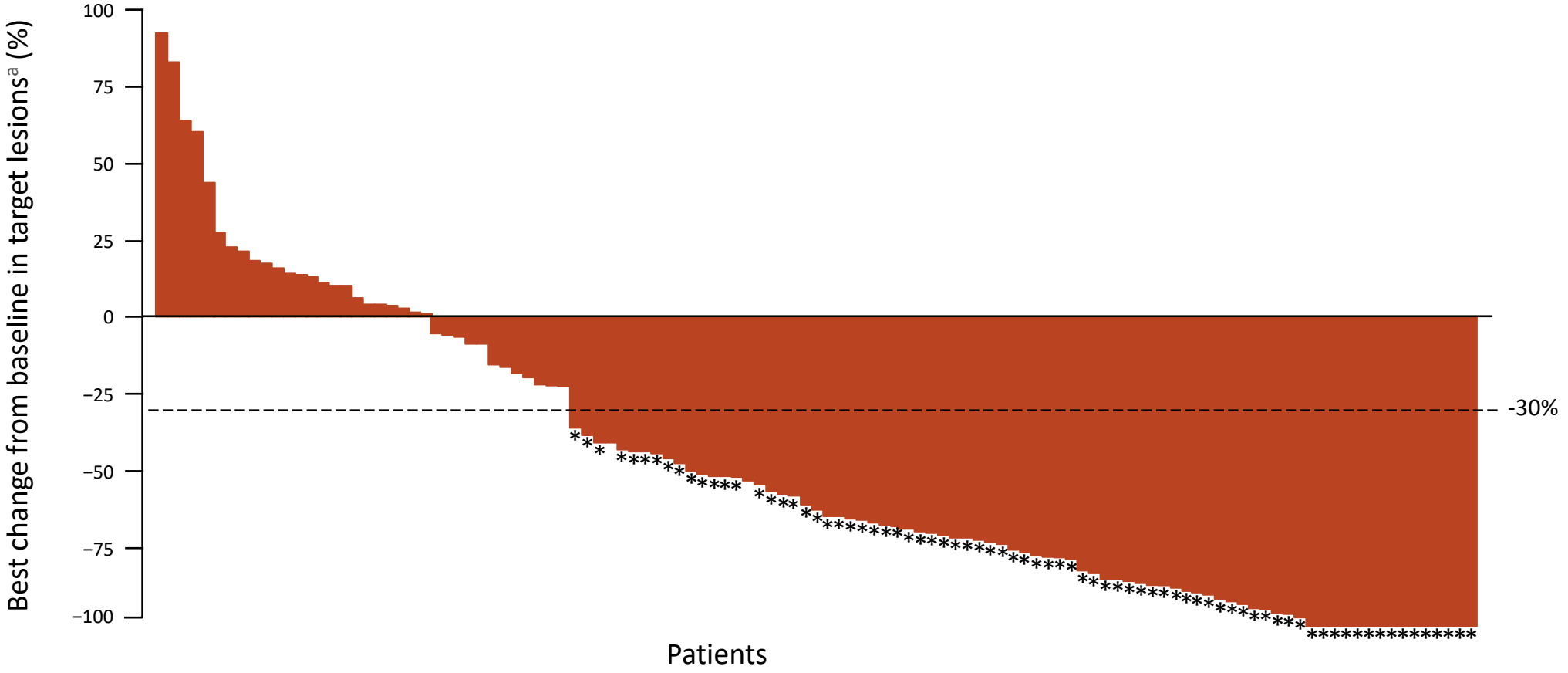
Outcome[a]	NIVO3 + IPI1 2L+ (N = 119)		
	13.4-month follow-up[1,b]	25.4-month follow-up[2,b]	50.9-month follow-up[b]
ORR,[c] n (%) 95% CI, %	65 (55) 45–64	69 (58) 49–67	**77 (65)** **55-73**
Best overall response, n (%)			
CR	4 (3)	7 (6)	**15 (13)**
PR	61 (51)	62 (52)	**62 (52)**
SD	37 (31)	33 (28)	**25 (21)**
PD	14 (12)	14 (12)	**14 (12)**
Unable to determine	3 (3)	3 (3)	**3 (3)**
Disease control, n (%)[d] 95% CI, %	95 (80) 72–87	96 (81) 72–87	**96 (81)** **72-87**
Median TTR (range), months	2.8 (1.1–14.0)	2.8 (1.1–24.4)	**2.8 (1.1–37.1)**
Median DOR (range), months	NR (NE)	NR (1.4+ to 32.5+)	**NR (1.4+ to 58.0+)**

- The rate and depth of responses increased between 13.4 and 50.9 months of follow up
  - ORR from 55% to 65%; CR from 3% to 13%
- The rate of PD as best response was 12%. Of 14 patients with BOR of PD, 6 were identified as MSS per central testing and another 6 were confirmed as MSI-H[e]

[a]Investigator assessed; [b]Median follow-up, defined as time from first dose to data cutoff; [c]Patients with BOR of CR or PR divided by the number of treated patients; [d]Patients with CR, PR, or SD for ≥ 12 weeks divided by the number of treated patients; [e]1 patient each had missing or inconsistent MSI status by central testing.

1. Overman MJ, et al. *J Clin Oncol* 2018;8:773–779; 2. Overman MJ, et al. Poster presentation at ASCO-GI; January 17–19, 2019; San Francisco, CA. Abstract 635.

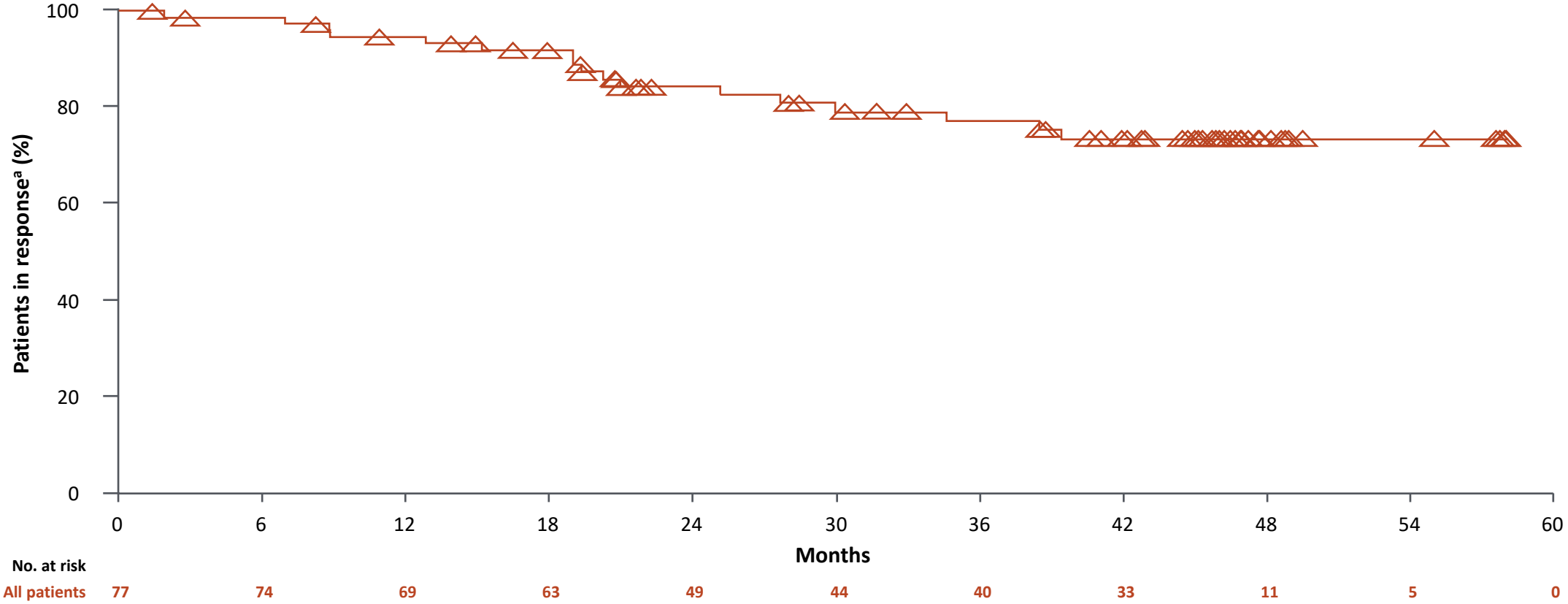
Best change in target lesions



- Most patients (79%) had a reduction in tumor burden from baseline

[a]Per investigator assessment. Evaluable patients with a target lesion at baseline and at least 1 on-treatment tumor assessment. Best change is based on evaluable target lesion measurements up to progression or start of subsequent therapy. *Confirmed response per investigator assessment (RECIST v1.1). Horizontal reference line indicates the 30% reduction consistent with a response per RECIST v1.1.

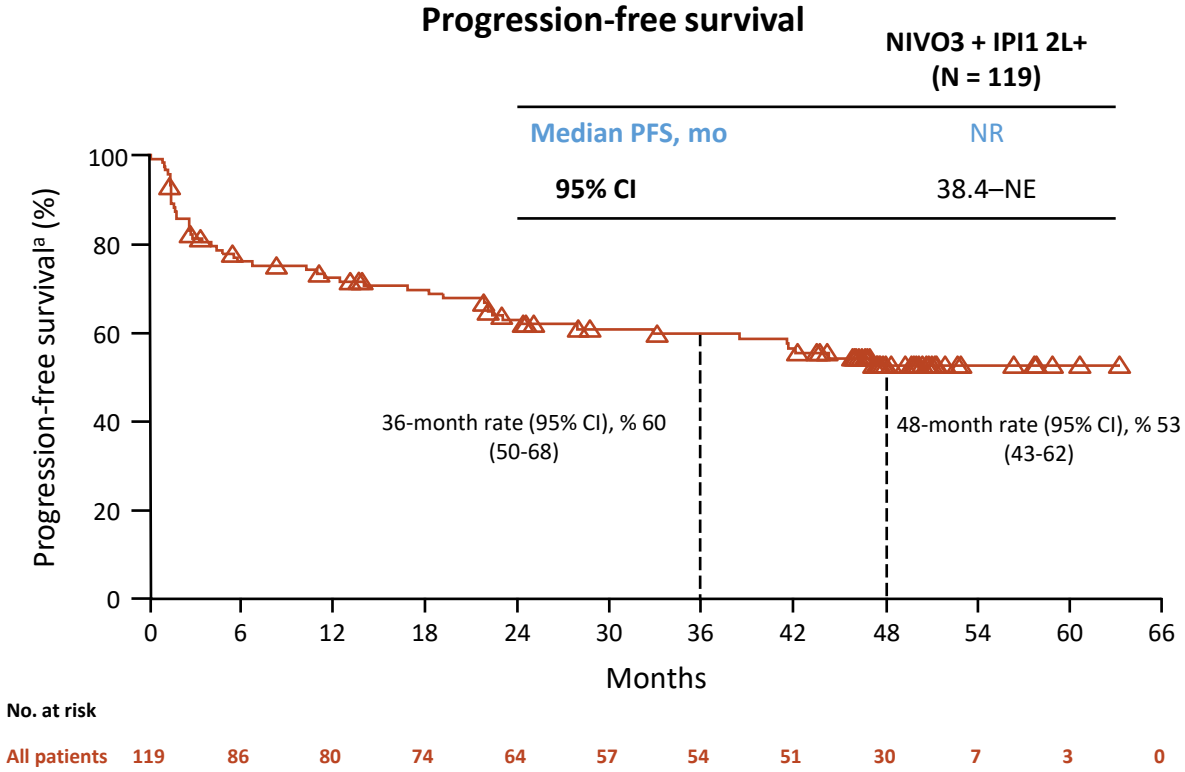
Duration of response

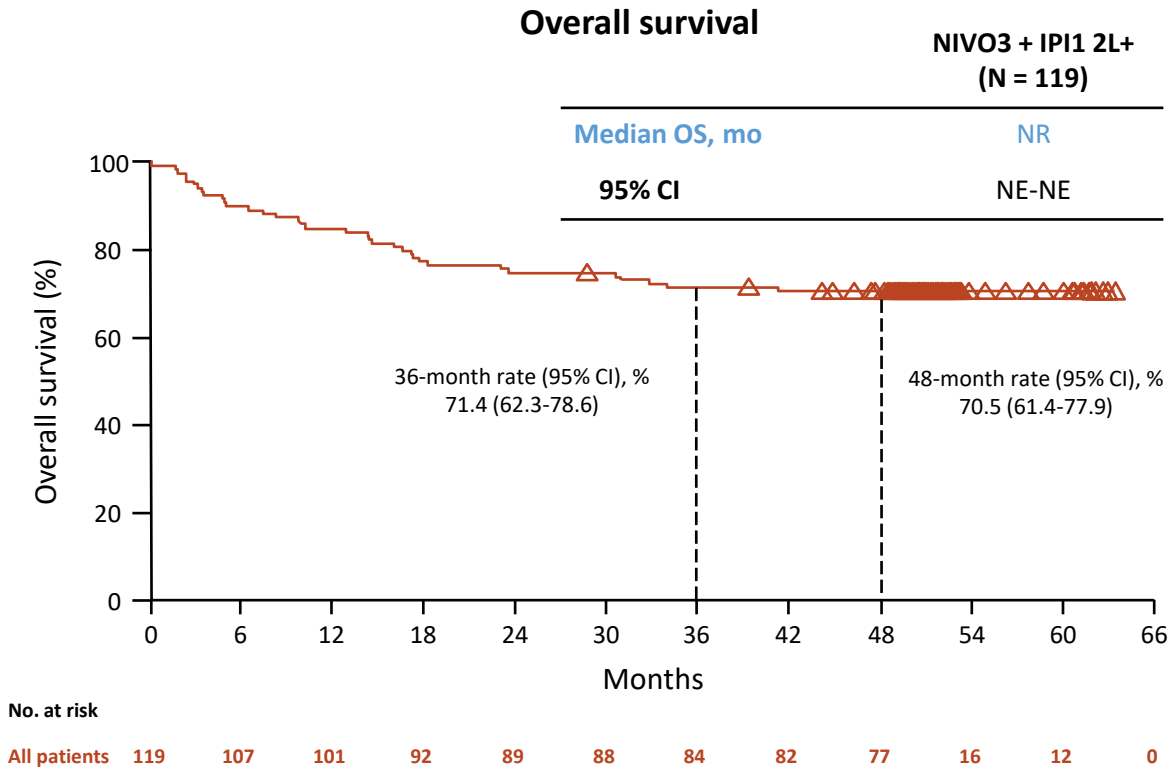


- Median duration of response was not reached
- Responses lasting ≥ 12, ≥ 24, and ≥ 36 months were observed in 90%, 64%, and 52% of patients, respectively

[a]Response per investigator assessment. Ongoing response includes responders who had neither progressed nor initiated subsequent therapy at the time of analysis and excludes responders censored prior to 8 weeks of the clinical data cutoff date if a patient is still in the first 24 weeks of follow-up period, otherwise, the window is 14 weeks. Overall, 60 patients (78%) were censored.

Progression-free survival and overall survival





- Median PFS was not reached; the 48-month PFS rate was 53%
- Median OS was not reached; the 48-month OS rate was 70.5%

[a]Per investigator assessment.

Final Overall Survival for the Phase III KN177 Study: Pembrolizumab Versus Chemotherapy in Microsatellite Instability–High/Mismatch Repair Deficient Metastatic Colorectal Cancer

ASCO 2021

Phase III KN177

- The open-label phase 3 KEYNOTE-177 trial compared pembrolizumab vs chemotherapy as first-line therapy in 307 patients with MSI-H/dMMR stage IV CRC.
- Pembrolizumab was administered at 200 mg every 3 weeks for up to 35 cycles.

- **Chemotherapy** consisted of the investigator's choice of leucovorin, 5-fluorouracil, and oxaliplatin (FOLFOX) or leucovorin, 5-fluorouracil, and irinotecan (FOLFIRI), plus bevacizumab or cetuximab, administered in 2-week cycles.

Phase III KN177

- Median PFS was 16.5 months with pembrolizumab vs 8.2 months with chemotherapy (hazard ratio [HR], 0.59; 95% CI, 0.45-0.79; *P*=.0002;)

- The **3-year PFS rate was 42% with pembrolizumab vs 11% with chemotherapy**.

- The objective response rate **(ORR)** was **45.1%** with pembrolizumab vs **33.1%** with chemotherapy, and the complete response (CR) rate **was 13.1% vs 3.9%,** respectively.

- The median OS was not reached in the pembrolizumab arm (95% CI, 49.2 months to not reached) vs 36.7 months in the chemotherapy arm (95% CI, 27.6 months to not reached; HR, 0.74; 95% CI, 0.53-1.03; *P*=.0359).

Single-Arm, Phase 2 Study of Regorafenib Plus Nivolumab in Patients With Mismatch Repair Proficient/Microsatellite Stable Colorectal Cancer

ASCO 2021

Phase 2 Study of Regorafenib Plus Nivolumab

- An open-label, single-arm phase 2 study investigated the safety and efficacy of regorafenib plus nivolumab in patients with **MSS/pMMR CRC**.
- Prior therapy had to include fluoropyrimidines, irinotecan, oxaliplatin, vascular endothelial growth factor (VEGF) inhibitors, and, for patients with extended *RAS* wild-type disease, endothelial growth factor receptor (EGFR) inhibitors.
- The phase 2 study enrolled 70 patients, whose median age was 57 years (range, 34-85). The site of the primary cancer was **the right side of the colon in 36%, the left side of the colon in 47%, and the rectum in 17%. The *KRAS* or *NRAS* mutation was present in 61% of patients, and the *BRAF* mutation was reported in 4%.**
- ***KRAS*, *NRAS*, and *BRAF* were wild type in 31% of patients**.

Phase 2 Study of Regorafenib Plus Nivolumab

- The median duration of treatment was **2.2 months for regorafenib** (range, 0.7-11.7) and **1.9 months for nivolumab** (range, 0.03-11.1).
- CR = 0 pts . PR = 5 patients, all without liver metastases, yielding an ORR of 7% for the entire study population.
- Among the 23 patients without liver metastases, the ORR was 22%, and 22 of the patients (31%) achieved stable disease.
- Among the 70 patients, the **median OS was 11.9 months** (95% CI, 7.0 months to not evaluable).. The median OS was 11.0 months (95% CI, 7.9-11.9) among patients without liver metastases vs 10.7 months (95% CI, 6.1 months to not evaluable) among those with liver metastases.

Regorafenib Combined With PD-1 Inhibition as Salvage Treatment and in a Real-World Study of Patients with Metastatic Colorectal Cancer

ASCO 2021

ONC-FR-2100213-NP-Juillet 2021

BMS-REF-31026

Regorafenib Combined With PD-1 Inhibition

- A prospective, open-label, single-arm study investigated the combination of **regorafenib** (80 mg daily) plus **sintilimab (200 mg every 3 weeks)** in patients **with non–MSI-H metastatic CRC.**
- The primary endpoint was the ORR. The study enrolled 24 patients. Half had wild-type *RAS*. Most patients (83.3%) had received 2 prior lines of treatment, and 58.3% had liver metastases.

- The primary endpoint was OS. Among the 52 patients, 35 (67%) had liver metastases. Regorafenib plus a PD-1 inhibitor was administered to 48 patients (92%) as third-line or later treatment; 11 patients (21%) were receiving treatment at the time of the report.
- After a median follow-up of 4.9 months, the median OS was 17.3 months (95% CI, 10.2 months to not reached) and the median **PFS was 3.1 months** (95% CI, 2.5-5.0 months).

Otázky

- Lynch syndrom - 5% nemocných ?
- Role chemoterapie a check point inhibitoprů

- Nemocní s proficientní MMR ? O 80% nižší účinnost check point inhibitorů . Jejich role ?

- III stádium CRC dMMR - role kombinace chemo + atezolizumabu