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MEETING SUMMARY
ASCO 2020, VIRTUAL MEETING

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HIGHLIGHTS FROM GI CONNECT
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PEMBROLIZUMAB VERSUS CHEMOTHERAPY FOR MICROSATELLITE INSTABILITY-HIGH/MISMATCH REPAIR DEFICIENT METASTATIC COLORECTAL CANCER: THE PHASE 3 KEYNOTE-177 STUDY

Andre T, et al.

ASCO 2020. Abstract #LBA4. Oral presentation

BACKGROUND

Introduction

A subset of CRC are characterised by dMMR→ resulting in MSI

CRCs with MSI-H → high levels of lymphocyte infiltrates

→ high expression of PD-1 and PD-L1[1]

KEYNOTE-016 study (Phase 2)

Pembrolizumab (anti–PD-1 antibody) showed **ORR of 40% in patients with progressive dMMR mCRC** vs 0% in patients with MMR-proficient mCRC[2]

KEYNOTE-177 (Phase 3)

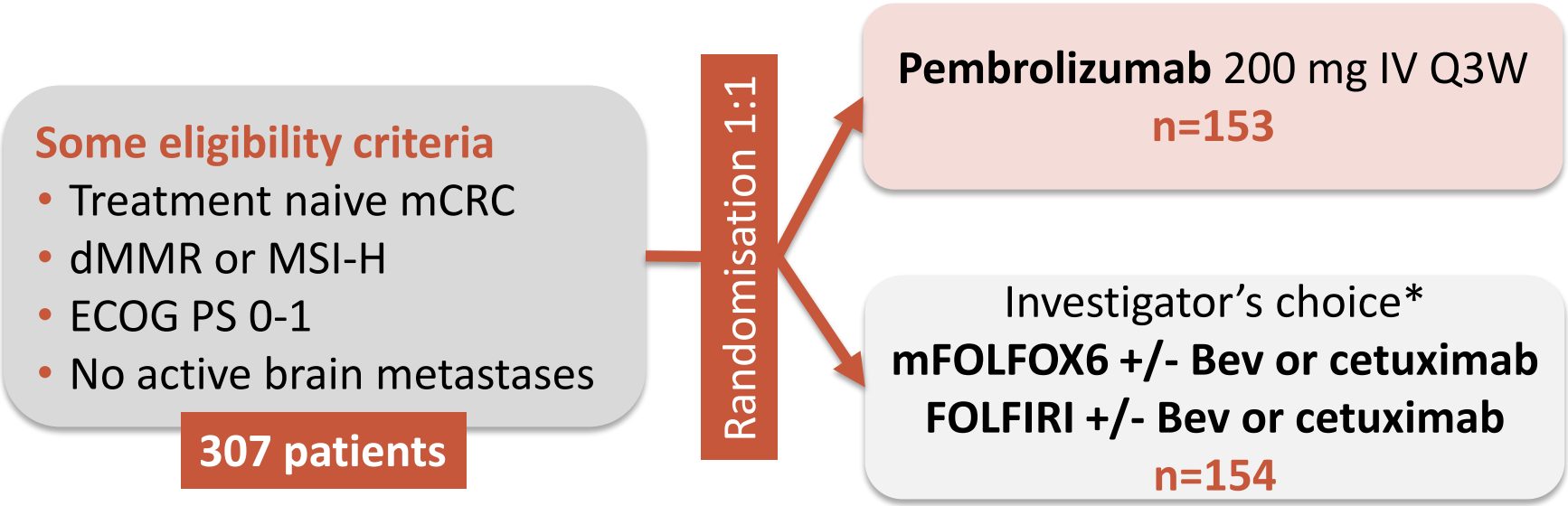
Designed to evaluate the efficacy and safety of pembrolizumab vs standard-of-care chemotherapy as first-line therapy for dMMR or MSI-H mCRC

CRC, colorectal cancer; dMMR, mismatch repair deficiency; mCRC, metastatic colorectal cancer; MSI, microsatellite instability; MSI-H, microsatellite instability-high; ORR, overall response rate; PD-1, programmed death-1; PD-L1, programmed death ligand-1

1. Llosa NJ, et al Cancer Discov 2015;5:43-51
2. Le DT, et al. N Engl J Med 2015;372(26):2509-20

TRIAL DESIGN

KEYNOTE-177 (NCT02563002): 2-arm, randomised, open-label, phase 3 study



Treatment Duration: until PD, unacceptable toxicity, patient/investigator decision to withdraw, or completion of 35 cycles (pembrolizumab only)

Primary endpoints: **PFS** (RECIST v1.1, central review) and **OS**

Secondary endpoints: **ORR** (RECIST v1.1, central review) and **safety**

* Patients with progressive disease have the option of receiving pembrolizumab 200 mg IV q3wk

Bev, bevacizumab; ECOG PS, Eastern Cooperative Oncology Group performance status; dMMR, mismatch repair deficiency; FOLFIRI, leucovorin + irinotecan + 5- fluorouracil; IV, intravenously; mFOLFOX6, modified oxaliplatin + leucovorin + 5-fluorouracil; MSI-H, microsatellite instability-high; ORR; overall response rate; OS, overall survival; PD, disease progression; PFS, progression-free survival; Q3W, every 3 weeks; RECIST, Response evaluation criteria in solid tumours

RESULTS

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Data cut-off date: Feb 19, 2020

Primary endpoint	Pembro	Chemo
Median PFS (months)	**16.5**	**8.2**
HR (95% CI)	**0.60 (0.45-0.80)**	
P-value	**0.0002**	
12-months PFS rates	55.3%	37.3%
24-months PFS rates	48.3%	18.6%

Secondary endpoints	Pembro	Chemo
ORR	43.8%	33.1%
Median DoR (months)	NR	10.6
Grade 3-5 TRAE rates	22%	66%*

* One patient in the chemo arm died due to a treatment-related AE.

CI, confidence interval; chemo, chemotherapy; DoR, duration of response; HR, hazard ratio; ORR; overall response rate; pembro, pembrolizumab; PFS; progression-free survival; TRAE, treatment-related adverse event

CONCLUSIONS

PEMBROLIZUMAB = THE NEW STANDARD OF CARE IN 1-L FOR mCRC PATIENTS WITH dMMR OR MSI-H?

- Pembrolizumab provided a clinically meaningful and statistically significant improvement in PFS versus chemotherapy as first-line therapy for patients with MSI-H/dMMR mCRC, with fewer treatment-related AEs observed
- The study is ongoing in order to evaluate the OS

1-L, first line; AEs, adverse events; dMMR, mismatch repair deficiency; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; OS, overall survival; PFS, progression-free survival

PEMBROLIZUMAB VERSUS PACLITAXEL FOR PREVIOUSLY TREATED PATIENTS WITH PD-L1–POSITIVE ADVANCED GASTRIC OR GASTROESOPHAGEAL JUNCTION CANCER (GC): UPDATE FROM THE PHASE III KEYNOTE-061 TRIAL

Fuchs CS, et al.
ASCO 2020. Abstract #4503. Oral presentation

PD-L1, programmed death ligand-1

BACKGROUND

- **Standard second-line therapy** for gastric/GEJ cancer:
  - **Combination therapy:** ramucirumab + paclitaxel
  - **Monotherapy:** docetaxel, paclitaxel or irinotecan

KEYNOTE-061 (NCT02370498) is a global phase 3 study of pembrolizumab vs paclitaxel as second-line therapy for gastric/GEJ cancer

Results (primary analysis: Oct 26, 2017)[1]:

- In patients with CPS ≥1:
  - **pembrolizumab did not significantly prolong OS** vs paclitaxel (9.1 vs 8.3 months)
  - **DoR: substantially longer with pembrolizumab** vs paclitaxel (18.0 vs 5.2 months)

→ Longer-term results after additional 2 years of follow up are presented; CPS ≥1, CPS ≥5 and CPS ≥10 patient data are also assessed

CPS, combined positive score; DoR; duration of response; GC, gastric cancer; GEJ, gastroesophageal junction; OS, overall survival

1. Shitara K, et al. Lancet 2018;392:123-33

RESULTS: EFFICACY BY CPS

Data cut-off date: Oct 7, 2019

	Pembro CPS ≥1 n=196	Paclitaxel CPS ≥1 n=199	Pembro CPS ≥5 n=95	Paclitaxel CPS ≥5 n=91	Pembro CPS ≥10 n=53	Paclitaxel CPS ≥10 n=55
OS, deaths, n (%)	176 (89.8)	190 (95.5)	84 (88.4)	86 (94.5)	44 (83.0)	51 (92.7)
OS, months, median (95% CI)	**9.1 (6.2-10.7)**	**8.3 (7.6-9.0)**	**10.4 (6.7-15.5)**	**8.3 (6.8-9.4)**	**10.4 (5.9-18.3)**	**8.0 (5.1-9.9)**
HR (95% CI)	**0.81 (0.66-1.00)**		**0.72 (0.53-0.99)**		**0.69 (0.46-1.05)**	
P value	**0.03**		**0.02**		**0.04**	
PFS, months, median (95% CI)	1.5 (1.4-2.0)	4.1 (3.2-4.3)	1.6 (1.4-2.8)	4.0 (2.8-4.4)	2.7 (1.4-4.3)	4.0 (2.7-4.4)
HR (95% CI)	1.25 (1.02-1.54)		0.98 (0.71-1.34)		0.79 (0.51-1.21)	
ORR, % (n)	**16.3 (32)**	**13.6 (27)**	**20.0 (19)**	**14.3 (13)**	**24.5 (13)**	**9.1 (5)**
DoR, months, (range)	**19.1 (1.4+ to 47.1+)**	**5.2 (1.3+ to 16.8)**	**32.7 (4.1 to 47.1+)**	**4.8 (1.3+ to 15.3)**	**NR (4.1 to 47.1+)**	**6.9 (2.6 to 6.9)**

CI, confidence interval; CPS, combined positive score; DoR, duration of response; HR, hazard ratio; ORR; overall response rate; OS, overall survival; NR, not reached; Pembro, pembrolizumab; PFS, progression-free survival

CONCLUSIONS

AS 2-L THERAPY, PEMBROLIZUMAB CAN BE BENEFICIAL FOR PD-L1-POSITIVE GC PATIENTS

- **After 2 additional years of follow up: pembrolizumab did not significantly improve OS and PFS** over paclitaxel (consistent with primary analysis)
- **Response rates were numerically higher and more durable** with pembrolizumab
- Treatment with pembrolizumab resulted in **fewer treatment-related AEs**

- With **increasing PD-L1 enrichment** among **GC patients:**
  - Second-line pembrolizumab **prolonged OS**
  - Pembrolizumab treatment **effect increased for ORR and DoR**

2-L, second line; AEs, adverse events; DoR, duration of response; GC, gastric cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PD-L1, programmed death ligand-1

REGOMUNE: A PHASE II STUDY OF REGORAFENIB PLUS AVELUMAB IN SOLID TUMOURS—RESULTS OF THE NON-MSI-H METASTATIC COLORECTAL CANCER (mCRC) COHORT

Cousin S, et al.

ASCO 2020. Abstract #4019. Poster presentation

MSI-H, microsatellite instability-high

BACKGROUND

Regorafenib has anti-immunosuppressive property[1]

Synergy between regorafenib and anti–PD-1/PD-L1 antibodies has been shown in pre-clinical models[1]

Combination strategy studies initiated with regorafenib and anti-PD-1/PD-L1:

Studies	Phase	Location	Status
REGONIVO: **regorafenib and nivolumab** simultaneous combination therapy (NCT03406871)	1b	Japan	36% ORR CRC[2] 44% ORR GC[2]
REGOMUNE: a phase I/II study of **regorafenib plus avelumab** in solid tumours (NCT03475953)	1/2	France	Data on mCRC presented here
Regorafenib and pembrolizumab in treating participants with advanced or metastatic colorectal cancer (NCT03657641)	1/2	USA	Ongoing

CRC, colorectal cancer; GC, gastric cancer; ORR, objective response rate; PD-1, programmed death-1; PD-L1, programmed death ligand-1

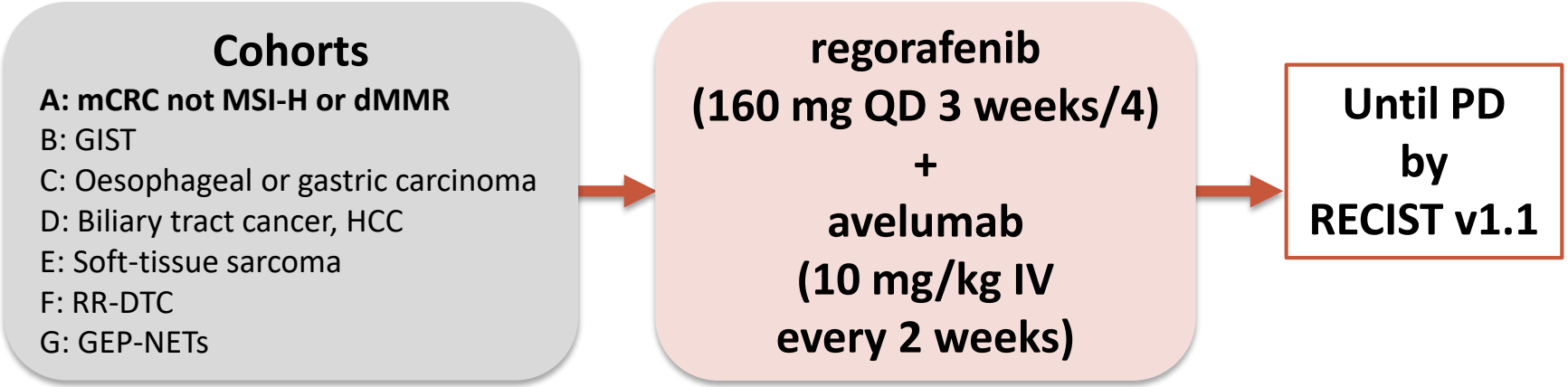
1. Arai H, et al. Cancer Treat Rev 2019;81:101912; 2. Fukuoka S, et al. J Clin Oncol 2020;JCO1903296

TRIAL DESIGN

REGOMUNE (NCT03475953): Single arm, open-label, phase 1/2 study

Phase 1: defined the recommended phase II dose of regorafenib with avelumab

Phase 2: assessment of the antitumour activity of regorafenib with avelumab in various cohorts



Primary endpoint: **6-months ORR** (RECIST v1.1, central review)
Secondary endpoints: **best overall response**, **6-month PFS**, **PFS**, **OS** and **safety**

dMMR, mismatch repair deficiency; GEP-NETS, Neuroendocrine gastroenteropancreatic tumours; GIST, gastrointestinal stromal tumour; HCC; hepatocellular carcinoma; IV, intravenously; mCRC, metastatic colorectal cancer; MSI-H, microsatellite-instability high; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, every day; RECIST, Response evaluation criteria in solid tumours; RR-DTC, Radioiodine-refractory differentiated thyroid cancer

RESULTS

Period of investigation: Nov. 2018 to Oct. 2019

Cohort assessed: Cohort A: mCRC patients

Number of patients enrolled: 48 patients

- The most common grade 3/4 AEs:
  - palmar-plantar erythrodysesthesia syndrome (30%)
  - hypertension (23%)
  - diarrhoea (13%)
- Overall population:
  - Best response: SD in 23 pts (53.5%) and PD in 17 pts (39.5%)
  - Median PFS: 3.6 months (CI 95%: 1.8–5.4)
  - Median OS: 10.8 months (CI 95%: 5.9–NA)
- Subgroup with low TAMs infiltration and low tumour cells to CD8+ T-cells distance:
  - Median PFS: 5.3 vs 1.9 months (p=0.037)
  - Median OS: NR vs 5.3 months (p=0.02)

AEs, adverse events; CI, confidence interval; mCRC, metastatic colorectal cancer; NA, not available; OS, overall survival; PD, disease progression; PFS, progression-free survival; pts, patients; SD, stable disease; TAMs, tumour-associated macrophages

CONCLUSIONS

- **Regorafenib + avelumab** achieved PFS and OS that compared favourably with historical data of regorafenib alone in this clinical setting

- High-resolution analysis of tumour samples identified a composite score based on **TAMs infiltration and tumour cell to CD8+ T-cells distance which could be used as a biomarker** in further studies investigating this approach in mCRC patients

mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression-free survival; TAMs, tumour-associated macrophages

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