PARIS 2022 ESMO congress

Avelumab versus standard second-line treatment in MSI metastatic colorectal cancer patients : the SAMCO-PRODIGE 54 randomised phase II trial.

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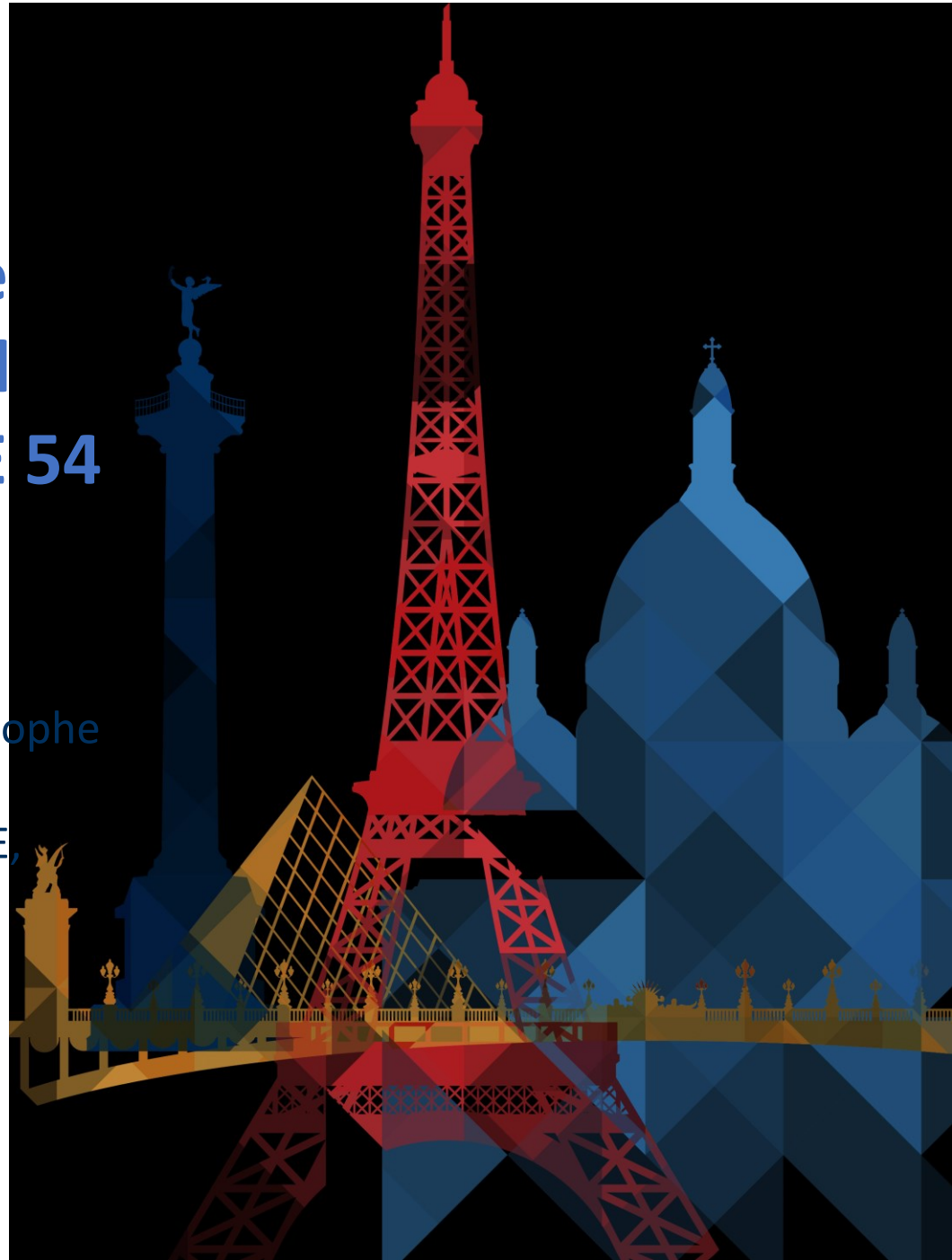
Julien TAIEB

Paris, France, September 12, 2022

PRODIGE PARTENARIAT DE RECHERCHE EN ONCOLOGIE DIGESTIVE

FFCD



DECLARATION OF INTERESTS

JT has received honoraria for consulting or speaker roles from :

AMGEN, Astellas, Astra-Zeneca, BMS, Merck, MSD, Novartis, Pierre Fabre, Servier

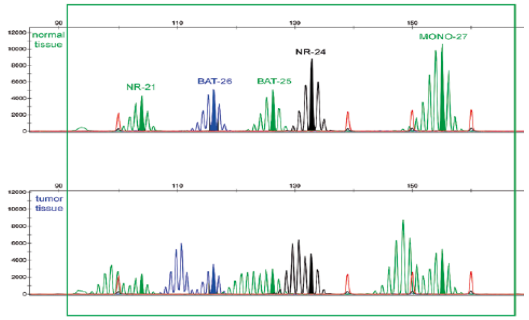
Background and goal

- Immune checkpoint inhibitors alone have failed in treating metastatic mCRC patients except those with MSI/dMMR tumours.

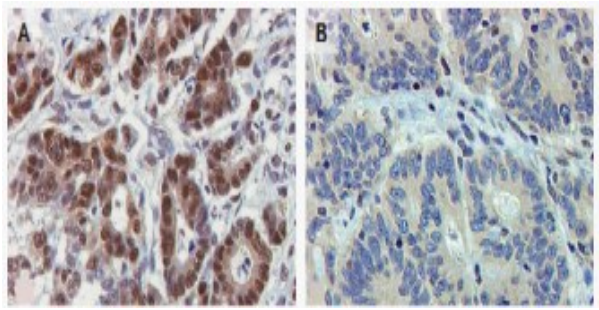
Grothey et al. ESMO 2018
Eng C, et al. Lancet Oncol. 2019

- Only one randomized trial, in the first-line setting, showed the superiority of an anti-programmed death1 (anti-PD-1) over standard treatment.

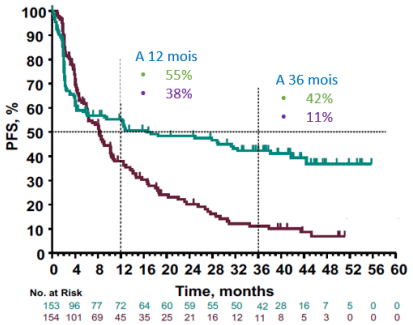
André et al NEJM 2020



Microsatellite instability (PCR)

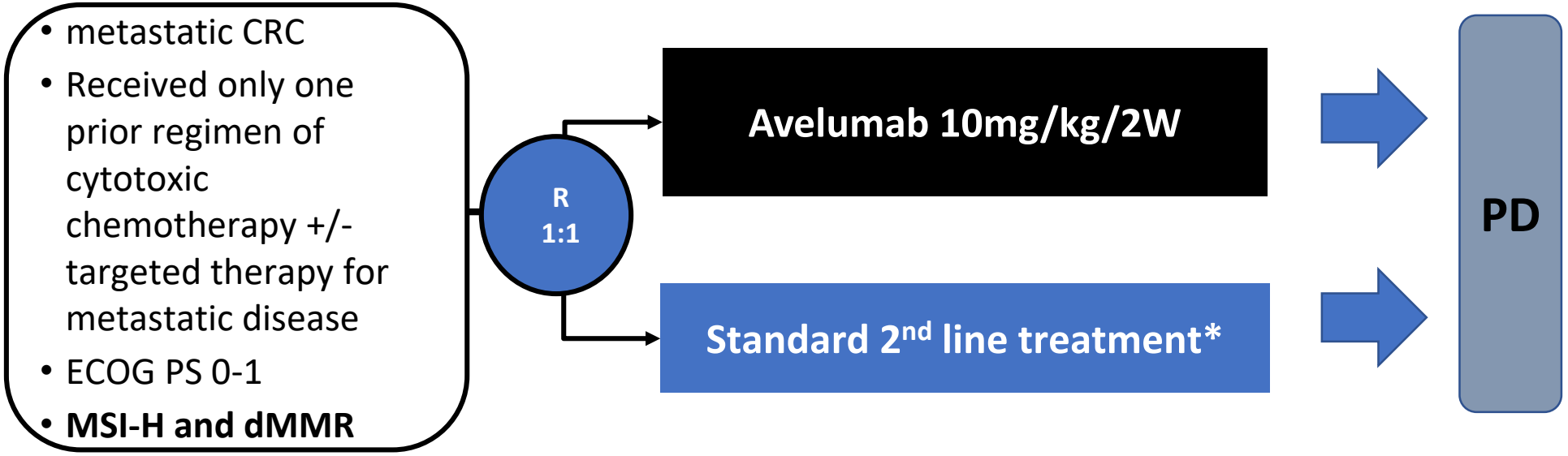


MMR protein deficiency (IHC)



- The SAMCO-PRODIGE 54 trial aimed, in the second-line setting, to evaluate efficacy and safety of an anti-programmed death ligand-1 (anti-PD-L-1) antibody in MSI/dMMR mCRC patients as compared to a second-line standard chemotherapy ± targeted therapy.

Study Design: SAMCO-PRODIGE 54



Stratification factors
- Age (> or<70)
- ECOG (0 vs 1)
- *BRAF* (mut vs wt)

Primary endpoint
- PFS

INV-assessed key secondary endpoints
- OS
- ORR
- DOR
- Tolerability

*FOLFOX or FOLFIRI depending on 1st line regimen +/- targeted agent (bevacizumab, aflibercept, ramucirumab, panitumumab, cetuximab)

Methodology & Statistics

- National, multi-center, open-label phase II comparative trial.
- **Primary endpoint: progression-free survival (PFS) according to RECIST 1.1 criteria and evaluated by investigators.**
- **Analyzes were planned on mITT** defined as all MSI/dMMR patients with a positive testing with IHC (4 MMR proteins) **and** tumor DNA (PCR) who received at least on cycle of planned treatment.
- statistical hypothesis were increase of PFS in favor of avelumab arm with a HR of 0.58, with 106 events needed to demonstrate this difference and **132 patients to enroll.**

Results : Baseline characteristics

- 132 pts were enrolled between 04/2018 and 04/2021, 10 pts (4+6) were excluded from the mITT population (5 Microsatellite Stable, 4 did not received any treatment (including 3 deaths), 1 consent withdrawal), **mITT= 122 patients.**

Characteristic	**Avelumab N = 61**	**chemotherapy N = 61**
Gender (M / F)	26 / **35**	31 / **30**
Median age (IQ range)	66 (54 – 75)	67 (60 – 75)
ECOG PS (0 /1 /2-%)	44 / 46 / **10**	49 / 43 / **8**
Right sided primary tumor (%)	**87%**	**77%**
BRAF V600E mutation (%)	**46%**	**40%**
***RAS* mutation** (%)	23%	21%
> 5 metastases (%)	41%	44%
>1 metastatic sites (%)	**46%**	**53%**
Previous treatment (FOLFOX/FOLFIRI/Others*- %)	62/12/26	69/19/12

* 5FU, capecitabine, FOLFIRINOX, CAPOX, CAPIRI

Results: best response RECIST1.1 investigator

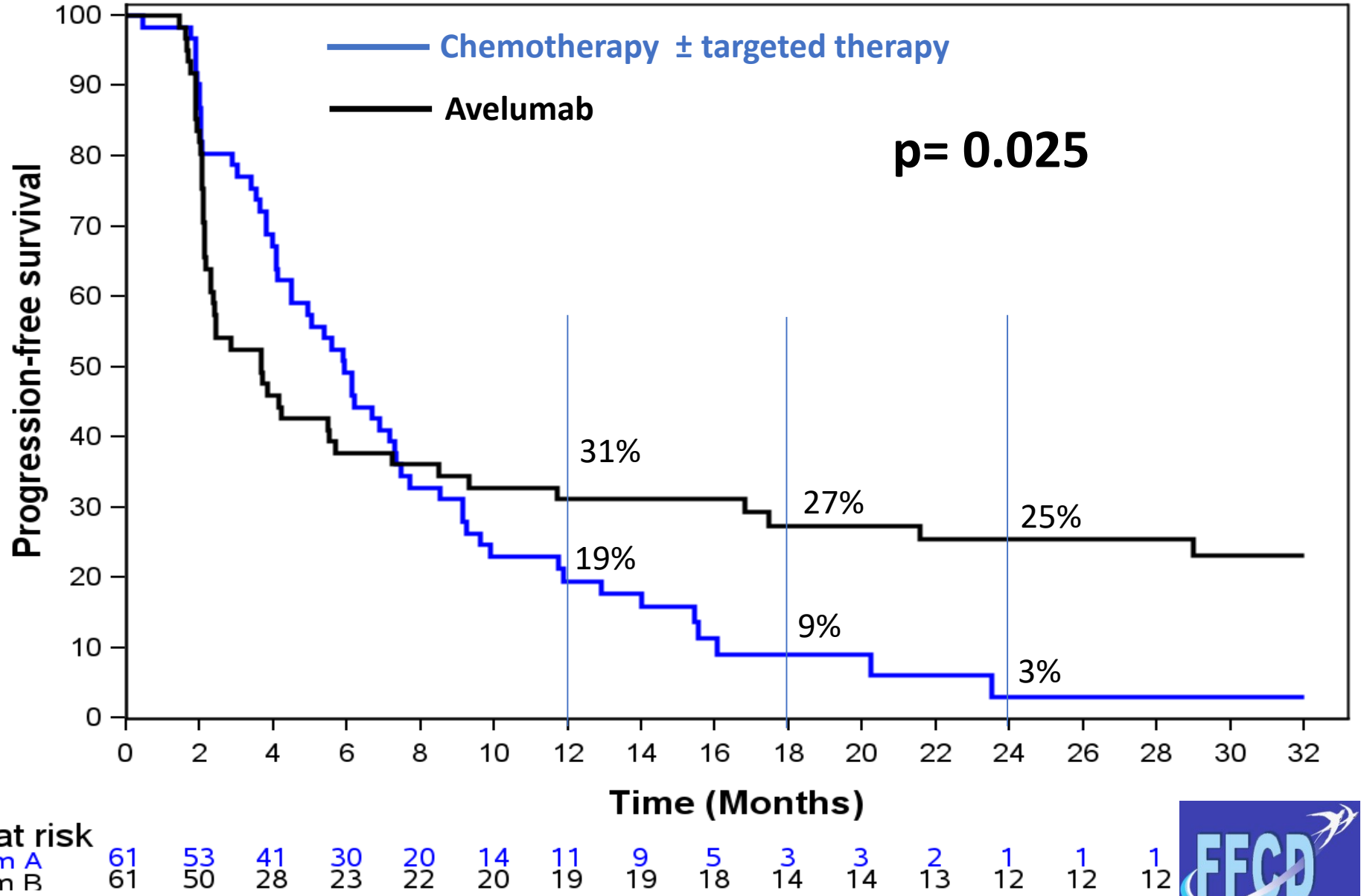
	Avelumab N = 61	Chemotherapy N = 61
Complete response	4 (6.5%)	3 (5%)
Partial response	14 (23%)	13 (21.3%)
ORR	**18 (29.5%)**	**16 (26.3%)**
Stable disease	25 (41%)	31 (51%)
DCR	**43 (70.5%)**	**47 (77.3%)**
Progressive disease	17 (28%)	10 (16.5%)
Time to best response (months)	2.99	1.94

Results: PFS

Median Follow-up:

33.3 months (28.3-34.8)

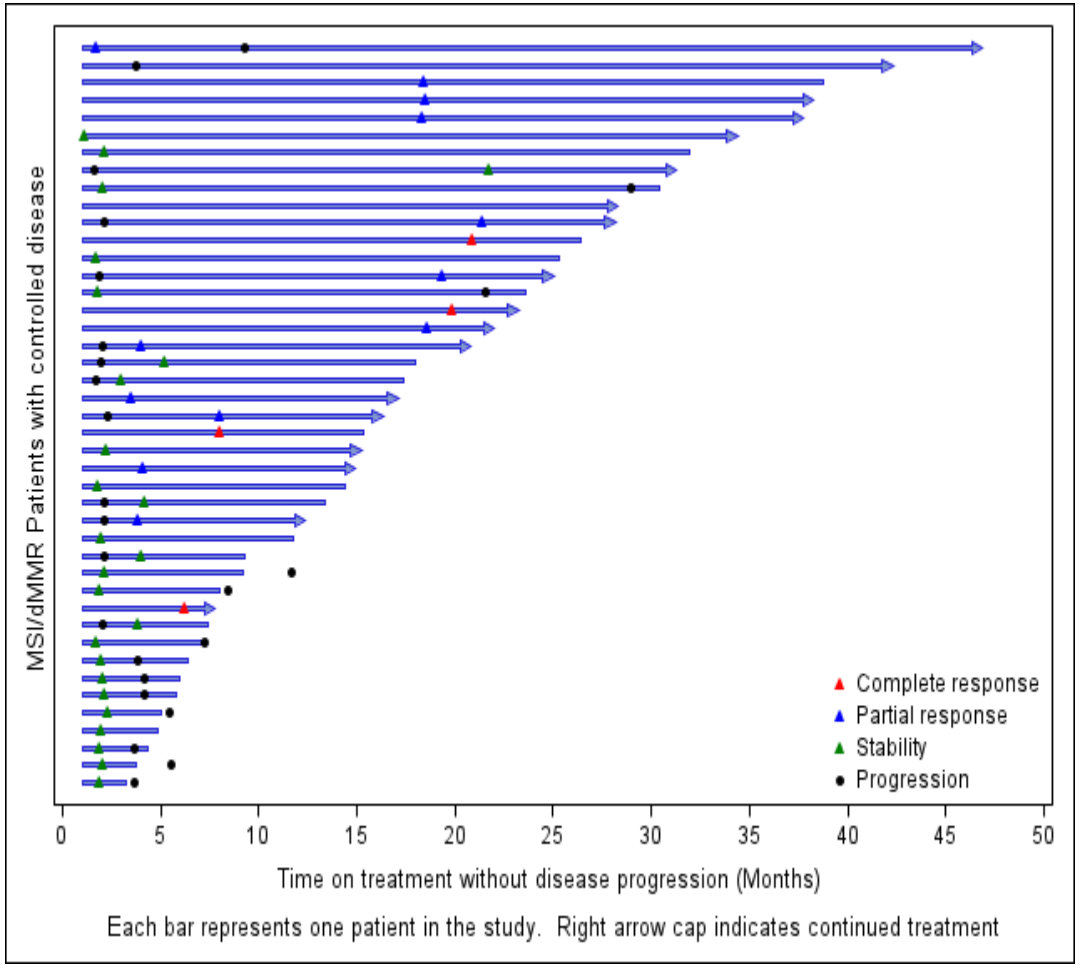
Due to KM curves crossing at 7.3 months, the Logrank test and HR of treatment are therefore not valid and not presented, Qiu and Sheng (1) test is then recommended.



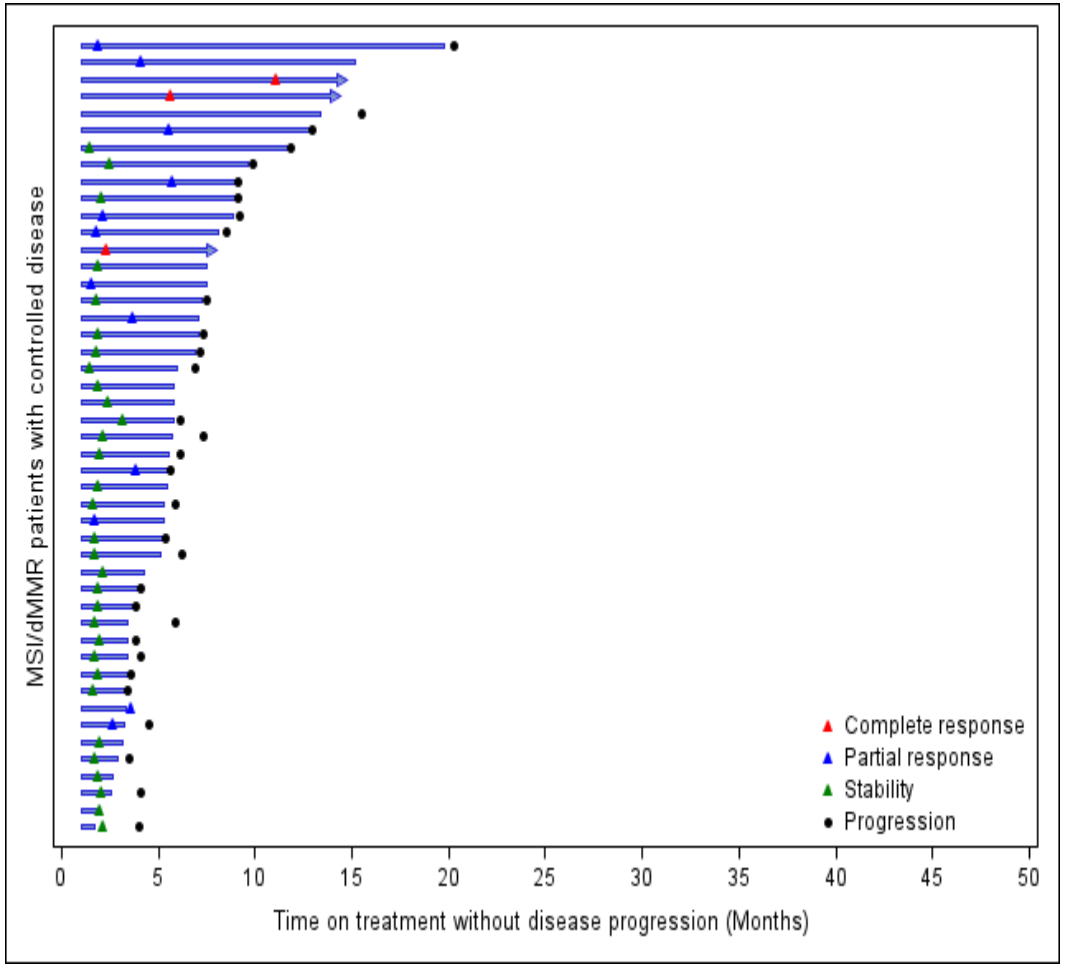
(1) Qiu, P., & Sheng, J. (2008). *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, *70*(1), 191-208.

Results: disease control duration

Avelumab



Chemotherapy +/- targeted agent



Results: safety profile

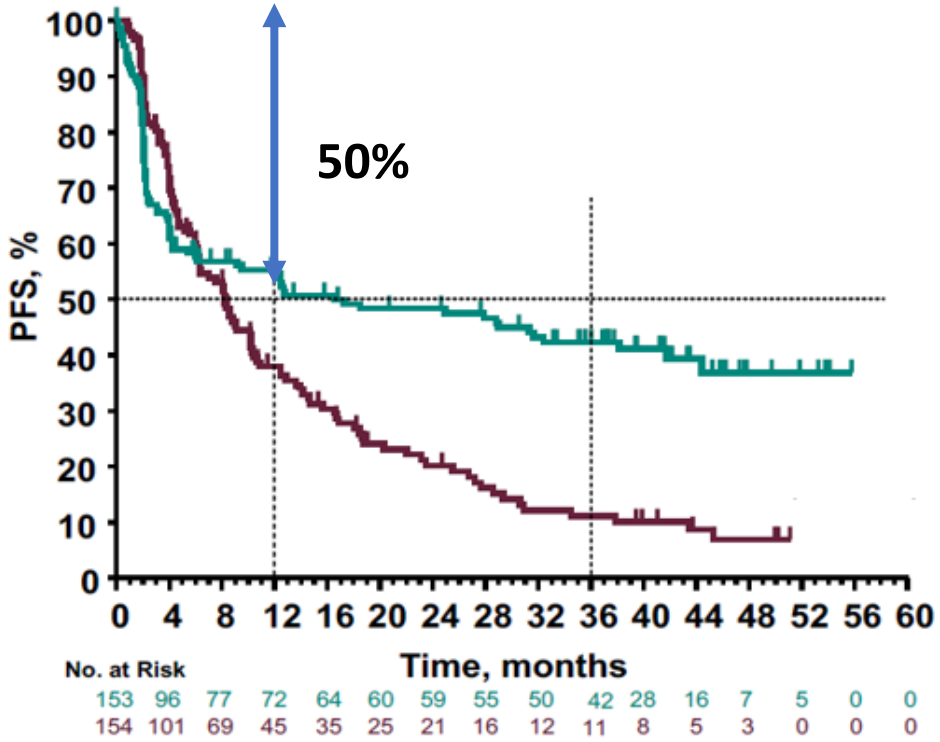
G3/4 adverse events, % patients	Avelumab (N = 63)	Chemotherapy (N = 64)
All grade ¾ toxicities	31.7%	53.1%
Nausea	0	1.6
Vomiting	0	1.6
Diarrhea	4.8	7.8
Stomatitis	0	3
Neutropenia	0	18.8
Neurotoxicity	0	3.2
Fatigue	0	10.9
Hypertension	1.6	10.9
Abnormal liver tests	9.5	1.6

Median number of cycle : chemotherapy : 11 (1-34) / Avelumab : 16 (1-92)

Discussion

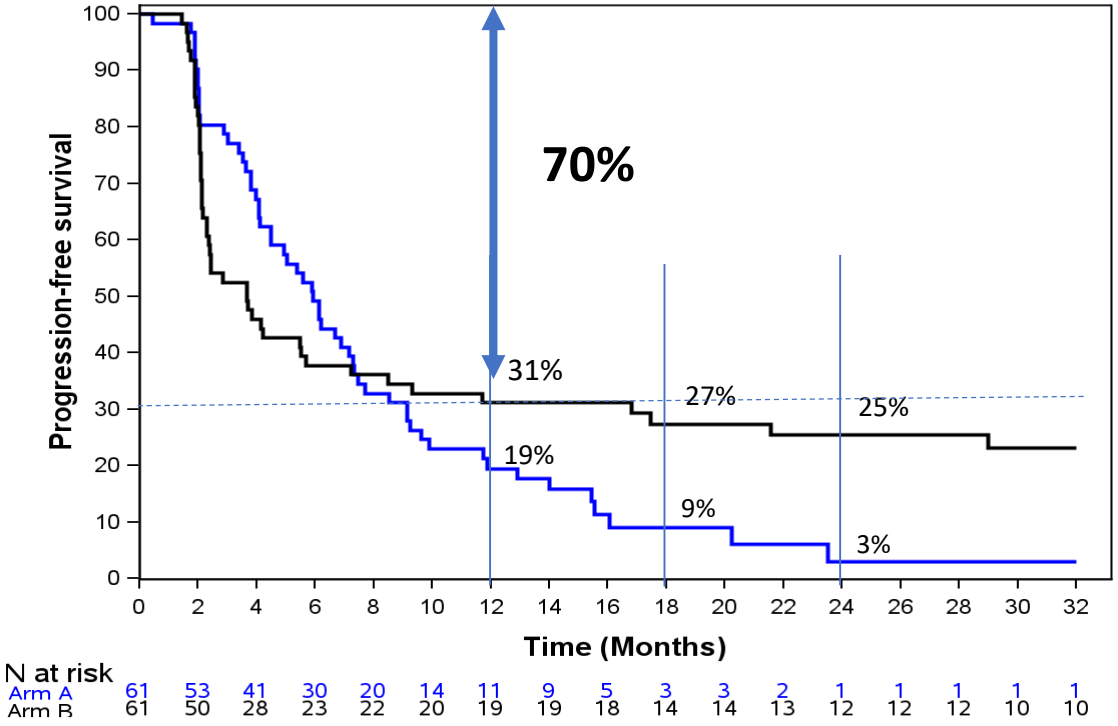
KEYNOTE 177

First line Pembrolizumab



PRODIGE 54-SAMCO

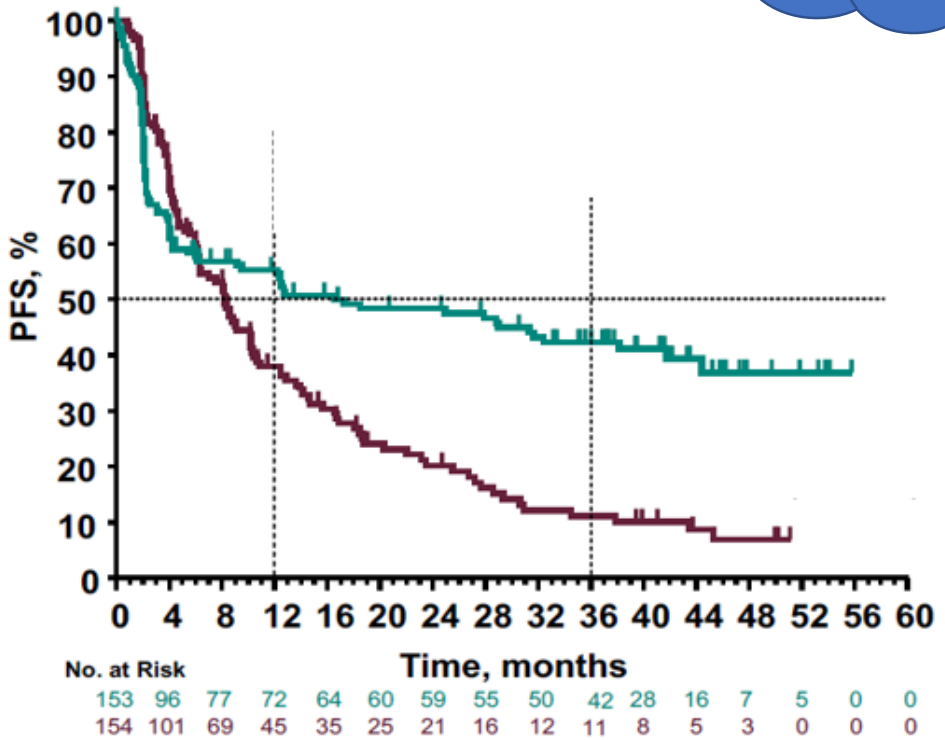
2nd-line Avelumab



Discussion

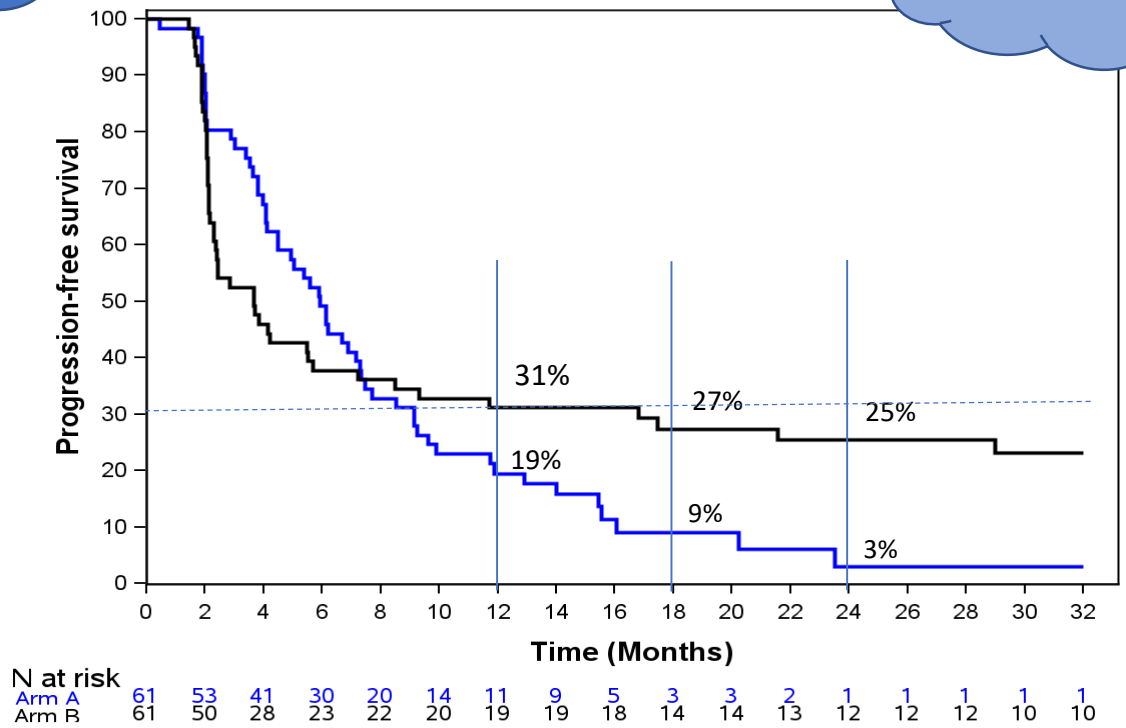
KEYNOTE 177

Anti-PD-1



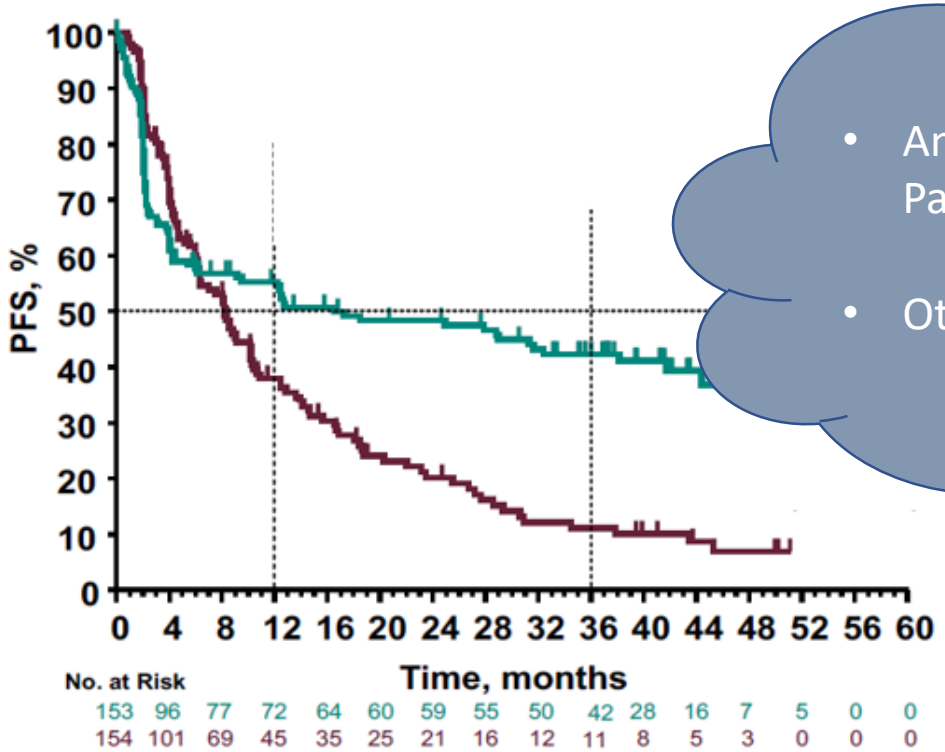
PRODIGE 54-SAMCO

Anti-PD-L-1



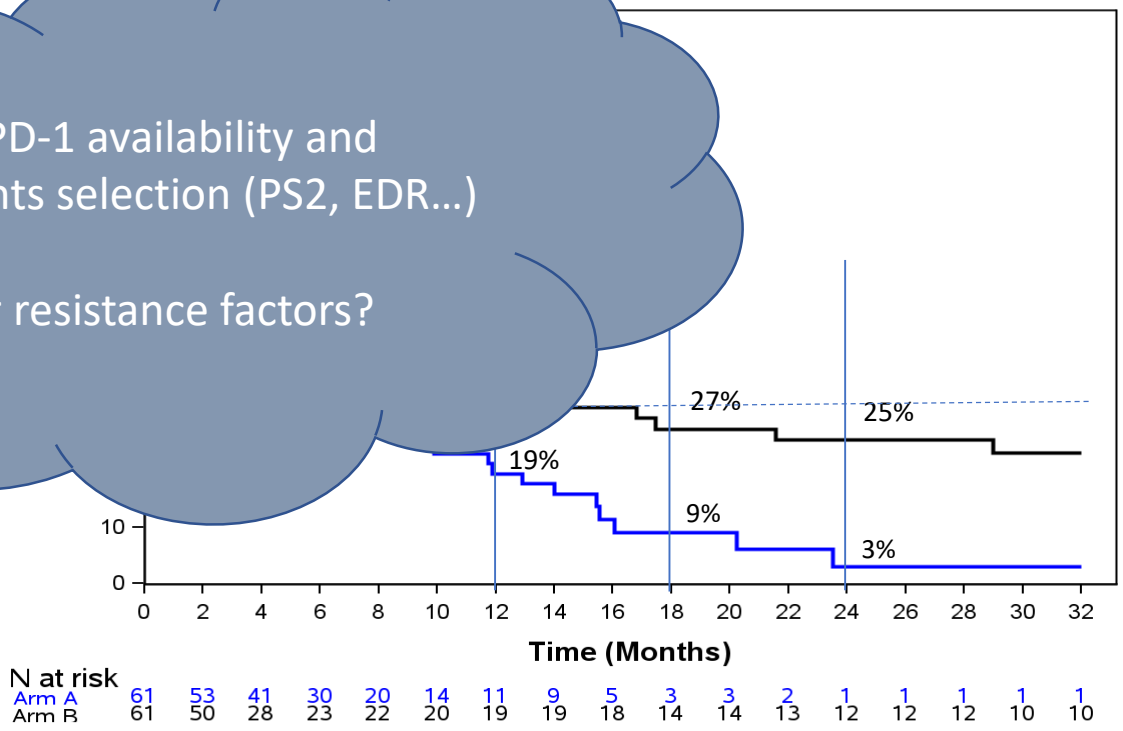
Discussion

KEYNOTE 177



- Anti-PD-1 availability and Patients selection (PS2, EDR…)
- Other resistance factors?

PRODIGE 54-SAMCO



Summary

- The study met its primary endpoint on PFS
- Avelumab performed better than 2nd line historical treatments
- ORR and DCR were similar between treatment arms but disease control was maintained over 18 months with avelumab in the vast majority of patients
- The use of avelumab led to lower rates of G3/4 AEs
- Resistance to ICI is a not rare in MSI/dMMR mCRC and has to be investigated further

Conclusions

The SAMCO-PRODIGE 54 randomized phase II study:

- **Shows the efficacy and safety of avelumab in 2nd line treatment for dMMR/MSI mCRC**
- **Confirm in this randomized phase II that the use of anti-PD(L)1 remains relevant beyond 1st line not pre-treated with an immune check point inhibitor**
- **Indirectly suggests that dMMR/MSI mCRC should be treated as soon as possible with an ICI**
- **overall survival, quality of life & biomarkers analysis (tumour, blood and stools) from the SAMCO-PRODIGE 54 will be analysed and presented in future meetings in order to identify predictors of response/resistance**

Acknowledgments

- Patients and their families
- David Tougeron, Marie Moreau, Jérémie Bez, Emilie Barbier, Karine le Malicot, Cécile Girault, Thierry André and Pierre Laurent-Puig
- The FFCD as sponsor of the trial and PRODIGE intergroup
- All participating investigators across the country
- Merck Serono for partially supporting the study

Thank you for your attention