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Pembrolizumab in combination with CAPOX and bevacizumab in patients with microsatellite stable (pMMR/MSS) metastatic colorectal cancer and a high immune infiltrate: a proof of concept study.

Preliminary results of FFCD 1703 POCHI trial

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Poitiers, Boulogne-Billancourt, Saint Malo, Dijon, Strasbourg, Marseille, Caen, Limoges, Quimper, Levallois-Perret, Perpignan, Caluire et Cuire, La Roche-sur-Yon, Rennes, Avignon, Nancy, Paris.

FFCD

PRODIGE
PARTENARIAT DE RECHERCHE EN ONCOLOGIE DIGESTIVE

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DECLARATION OF INTERESTS

David Tougeron reports:
Consultancy, advisory fees, honoraria from Servier, Pierre Fabre, Merck Serono, MSD, BMS, AZ, Roche, Sanofi, Takeda.
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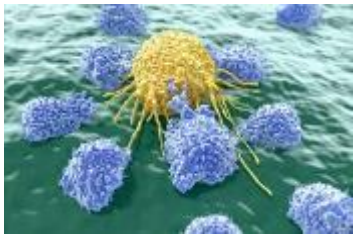
Background

- Immune checkpoint inhibitors (ICI) are currently considered ineffective in pMMR/MSS mCRC.
- Patients with high tumor infiltrating lymphocyte (TIL) accounted for ≈15% of mCRC.
- High TIL is associated with good prognostic.
- CRC with high immune score may benefit from anti-PD(L)1 therapies but there is no dedicated trial available up until now.
- In addition, immunogenic cell death induced by chemotherapy, such as oxaliplatin, and immunoregulation by anti-angiogenics, such as bevacizumab, can increase the efficacy of ICI.



Emile JF et al., Eur J Cancer 2017; Galon J et al., Science 2006
Antoniotti C, et al. Clin Cancer Res 2023.
Terme et al. Can Res 2013; Voron et al. J Exp Med 2015

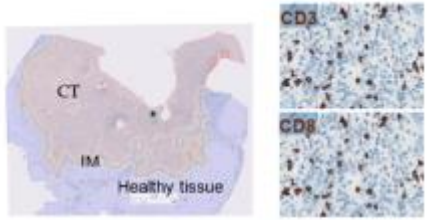
Background

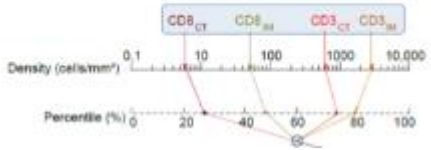
- Immunoscore©: Standardized and validated digital pathology-based immune score, based on CD3+ and CD8+ TIL in the center and periphery of the tumour.

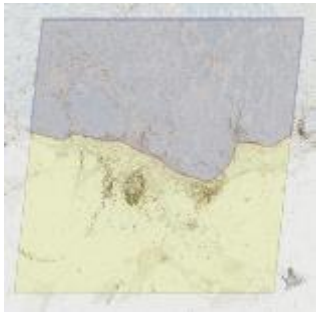
- TuLIS: Automated, validated and reproducible method for analysis of CD3+ TIL at invasion front.

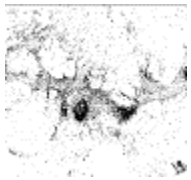
- TuLIS is validated in PETACC8 trial
- No score is validated to determine efficacy of ICI

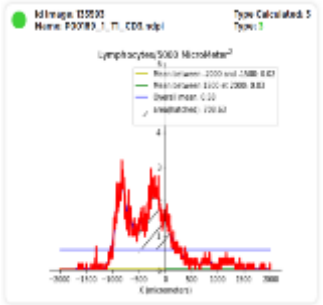
➔ **Use of 2 tests to determine patient eligibility**











Galon J et al., Science 2006;
Allard MA et al., Diagn Pathol 2012;
Emile JF et al., Eur J Cancer 2017

DESIGN

- **Single arm, open-label, multi-centre phase II study.**

- pMMR and MSS unresectable mCRC
- available primary tumour containing tumour-free margin
- At least one positive test (immunoscore/TuLIS)
- No prior treatment for metastatic disease

→

Every 3 weeks:
CAPOX (standard)
+ bevacizumab 7.5mg/kg
+ pembrolizumab 200 mg

Primary objective: Number of patients alive and without progression at 10 months based on RECIST 1.1 criteria evaluated by the investigator (PFS at 10 months, H0:50% and H1:70%, alpha 5% and power 85%).

55 patients to be enrolled.

RESULTS

- **Between April 2021 and August 2024, 196 patients were screened in 41 active centers.**
- **36 patients had at least one positive immune score (18%) but 30 analyzed (3 with non-inclusion criteria and 3 with no follow-up data)**
- **28 TuLIS positive, 8 immunoscore© positive (6 positives with both scores).**

	N=30 (%)
Median age	67 years
Men/Women	63%/37%
ECOG PS 0/1	87%/13%
Primary tumour site: right/left/rectum	**40%/50%/10%**
Metachronous/synchronous	**53%/47%**
RAS/BRAF-mutated tumor	63%/10%
Liver metastases	**50%**
Lung metastases	**33%**

RESULTS

- Median duration of treatment was 9.5 months (median cycle of treatment: 13.5, median oxaliplatin courses: 6.0, median pembrolizumab courses: 11.5)

- **At least one grade 3-4 treatment related adverse event was observed in 70% of patients.**
- No toxic death was observed.
- **Definitive stop of all drugs due treatment-related adverse events in 2 (7%) patients.**
- **Two patients stopped pembrolizumab due to toxicity.**

N(%)	Grade 3-4*
Patients with at least one grade 3-4 adverse event	**21 (70.0)**
Paresthesia	1 (3.3)
Adrenal Insuffiency	1 (3.3)
Diarrhoea	6 (20.0)
GGT increase	2 (6.7)
Neutrophil count decrease	3 (10.0)
Anorexia	2 (6.7)
Hyperglycemia	1 (3.3)
Fatigue	5 (16.7)

* only adverse events in 10% or more of treated patients were reported as well as immune-related adverse events

RESULTS

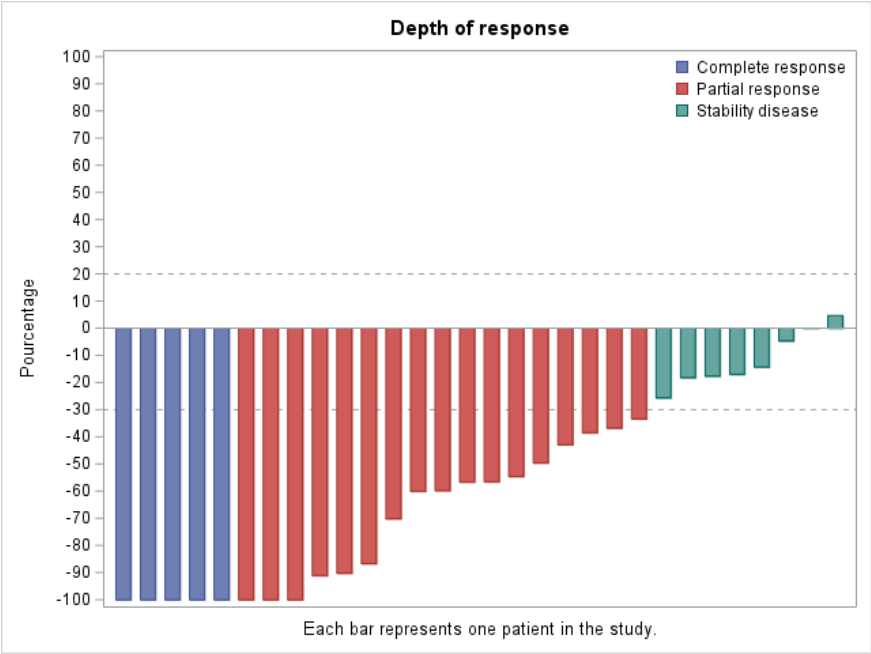
- **Median follow-up was 21 months (min 3.4 - max 33.9) (cut-off August 26, 2024).**

  - **ORR: 74%**
  - **DCR: 100%**

	N (%)
Complete response	**5 (17%)**
Partial response	**17 (57%)**
Stable disease	8 (27%)

- **Median DoR = 10 months**

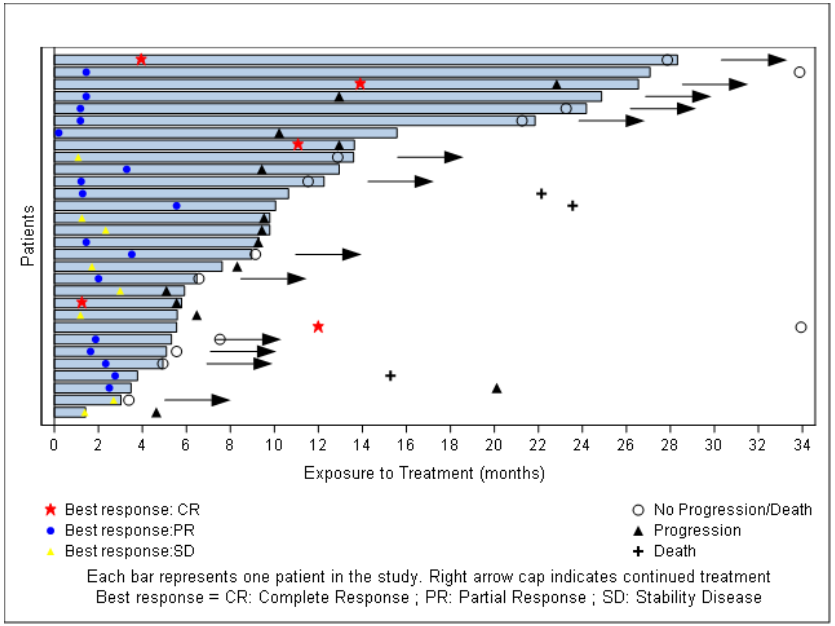
Waterfall plot of treatment response



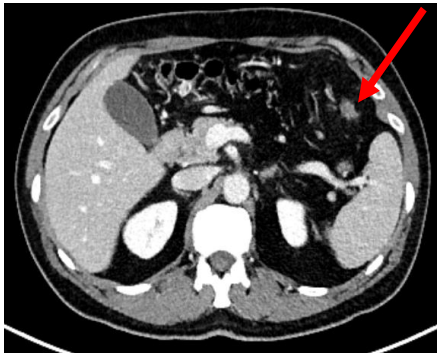
RESULTS

At cut-off date:

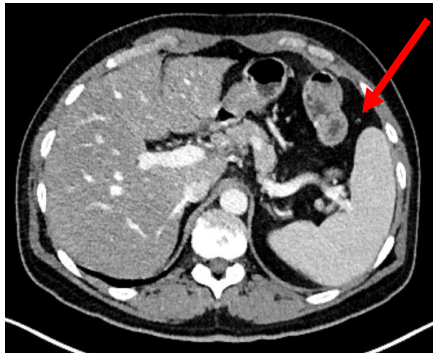
- **13 patients (43%) on treatment**
- **16 disease progression and 3 deaths**



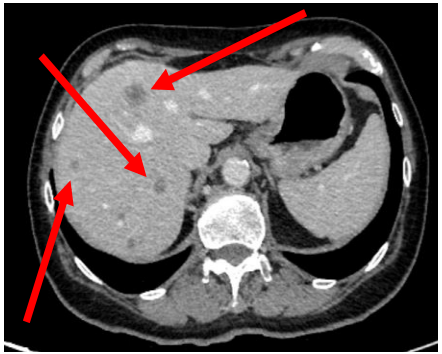
Baseline: May 2022



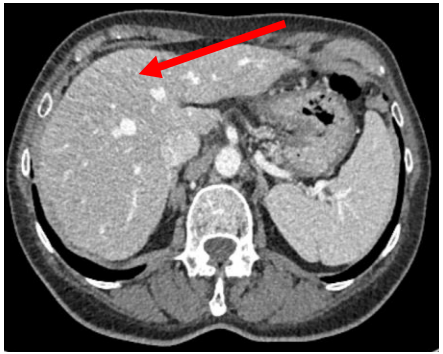
16 months: Septembre 2023



Baseline: July 2022

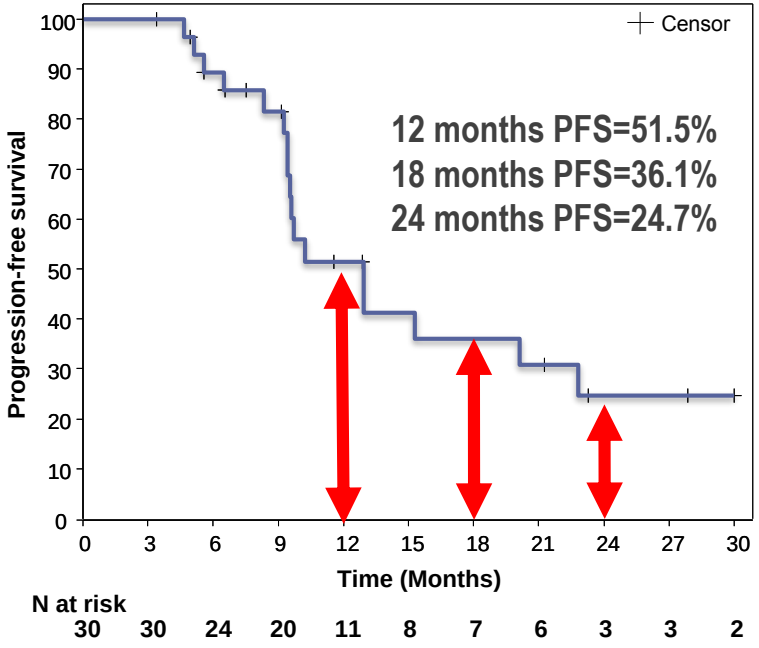


13 months: August 2023

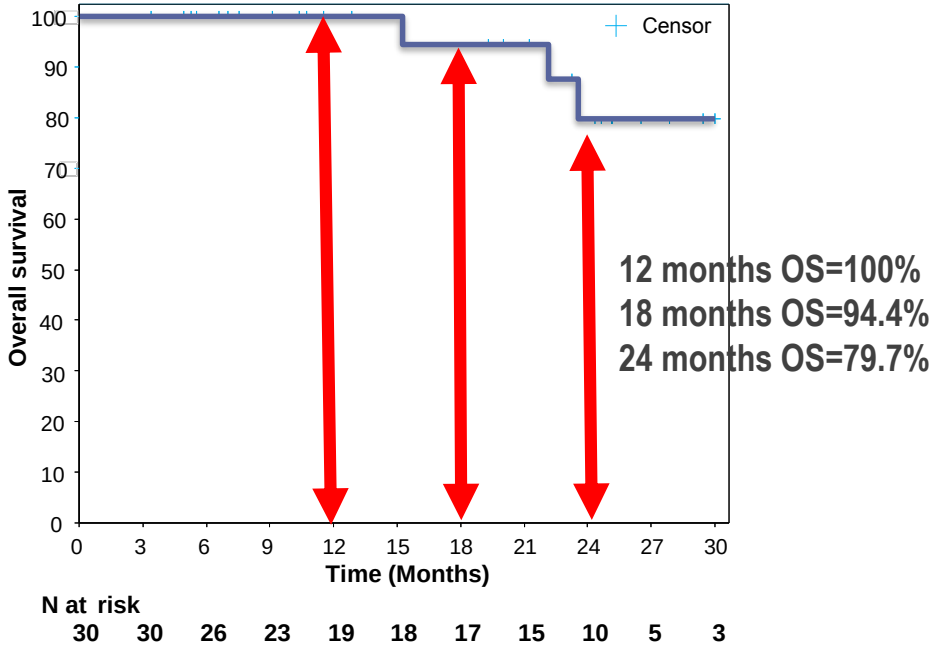


RESULTS

Progression-free survival

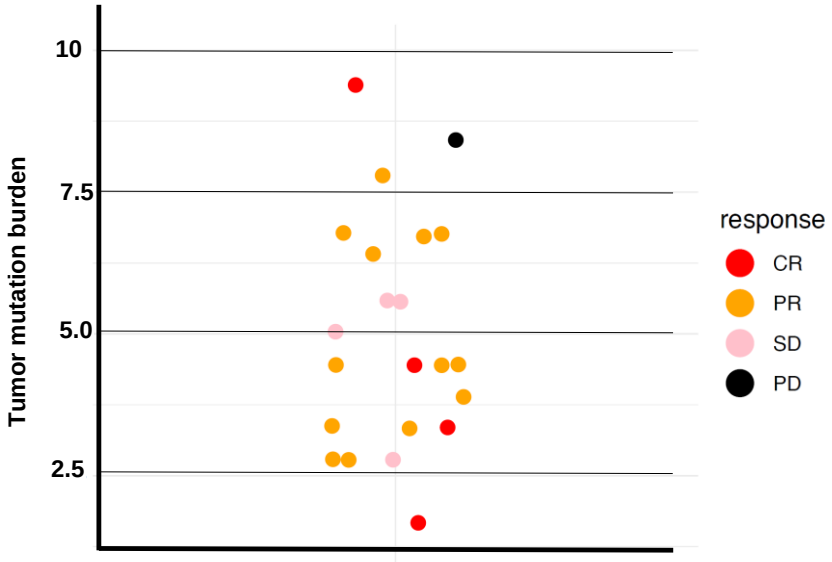


Overall survival



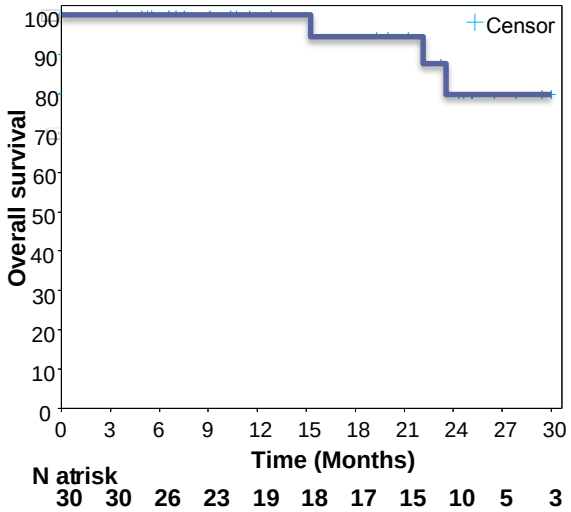
Biomarkers analyses

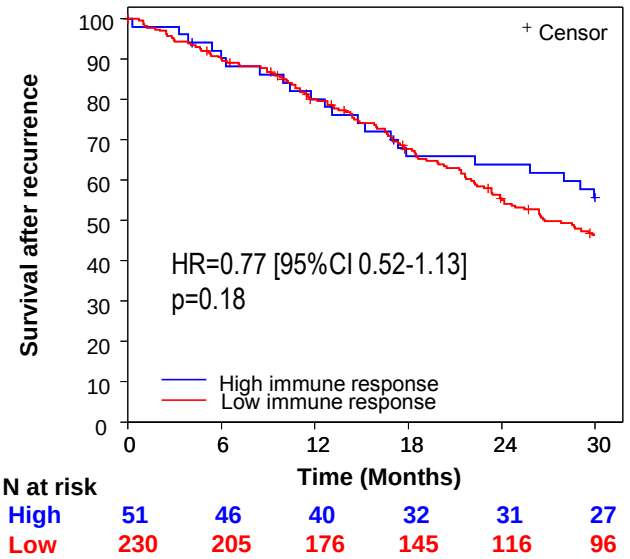
- All tumors were confirmed both pMMR and MSS (centralized).
- No tumor has *POLE* mutation or high TMB (n=22).
- No correlation was observed between TMB and response to treatment.



Biomarkers analyses

- In an external series we evaluated the prognostic value of TuLIS score.
- We have selected 281 patients from PETACC8 trial with a disease recurrence treated by standard chemotherapy +/- targeted therapy.
- No strong correlation was observed between TuLIS score and survival.





Emile JF et al.,
Eur J Cancer 2017

Discussion - Conclusion

- Good and expected safety profile of pembrolizumab plus CAPOX and bevacizumab.
- High efficacy of pembrolizumab combined to a standard therapeutic regimen in pMMR/MSS mCRC with high immune infiltrates with 17% of CR and 100% of DCR.
- Trial is still enrolling.
- Biomarker analyses are ongoing to identify predictors of complete response.
- The impressive response rate justify evaluation of the combination of IO and chemotherapy in a randomized phase III trial dedicated to pMMR/MSS mCRC patients with a high immune infiltrate.

We thank:
- Patients and their families
- All investigators
- FFCD as sponsor
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