- 26/11/2024

ctDNA monitoring

Circulating tumor DNA monitoring in patients with metastatic uveal melanoma treated with tebentafusp

Shufang RENAULT
Circulating tumor biomarkers laboratory (BTC Labo)

ENSEMBLE, PRENONS LE CANCER DE VITESSE

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Circulating tumor biomarkers laboratory

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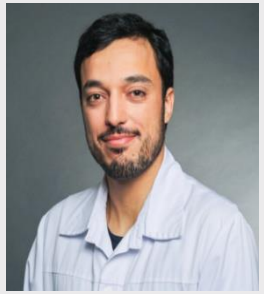

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Oncologist

Roberta Arpino
Visiting Ph.D student

Dr. Luc Cabel
Oncologist

Dr. Antoine Vasseur
Oncologist

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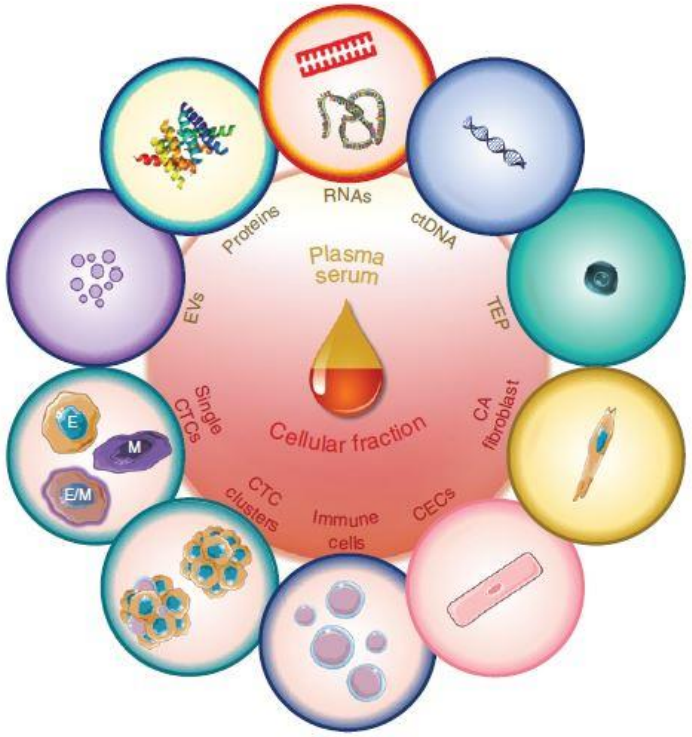
Circulating components



- Assessment of circulating components
  - Circulating tumor cells
  - Circulating tumor DNA
  - Proteins
  - Exosomes
  - miRNA and lncRNA
  - …

Catherine Alix-Panabières and Klaus Pantel; Cancer Discov 2021;11:858–73

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Clinical trial: STIC

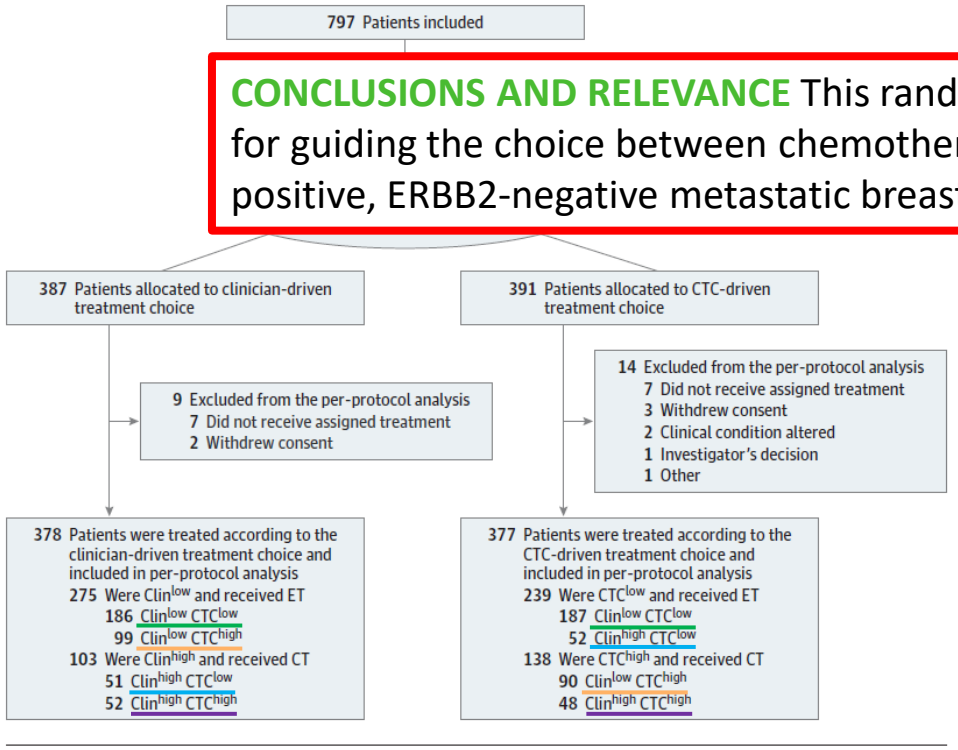
JAMA Oncology | Original Investigation

Efficacy of Circulating Tumor Cell Count–Driven vs Clinician-Driven First-line Therapy Choice in Hormone Receptor–Positive, ERBB2-Negative Metastatic Breast Cancer

The STIC CTC Randomized Clinical Trial

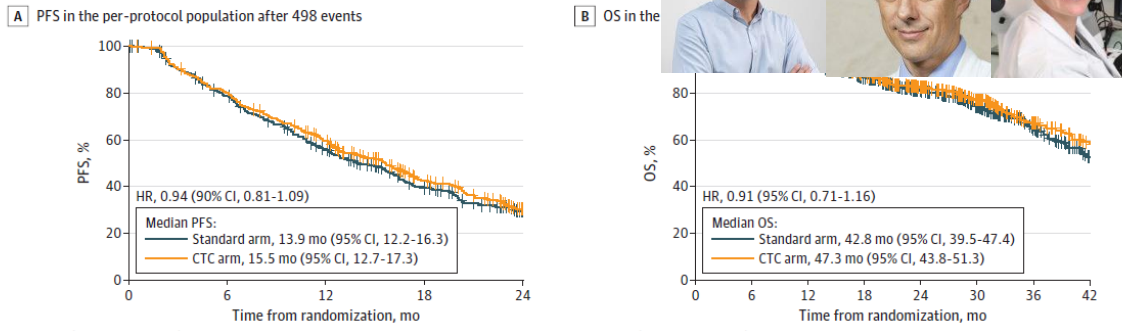
François-Clément Bidard, MD, PhD; William Jacot, MD, PhD; Nicolas Kiavue, MBBS; Sylvain Dureau, PharmD; Amir Kadi, PhD; Etienne Brain, MD, PhD; Thomas Bachelot, MD; Hugues Bourgeois, MD; Anthony Gonçalves, MD, PhD; Sylvain Ladoire, MD, PhD; Hervé Naman, MD; Florence Dalenc, MD, PhD; Joseph Gligorov, MD, PhD; Marc Espié, MD; George Emile, MD; Jean-Marc Ferrero, MD; Delphine Loirat, MD, PhD; Sophie Frank, MD; Luc Cabel, MD; Véronique Diéras, MD; Laure Cayrefourcq, MSc; Cécile Simondi, MSc; Frédérique Berger, MSc; Catherine Alix-Panabières, PhD; Jean-Yves Pierga, MD, PhD

Figure 1. Trial Profile



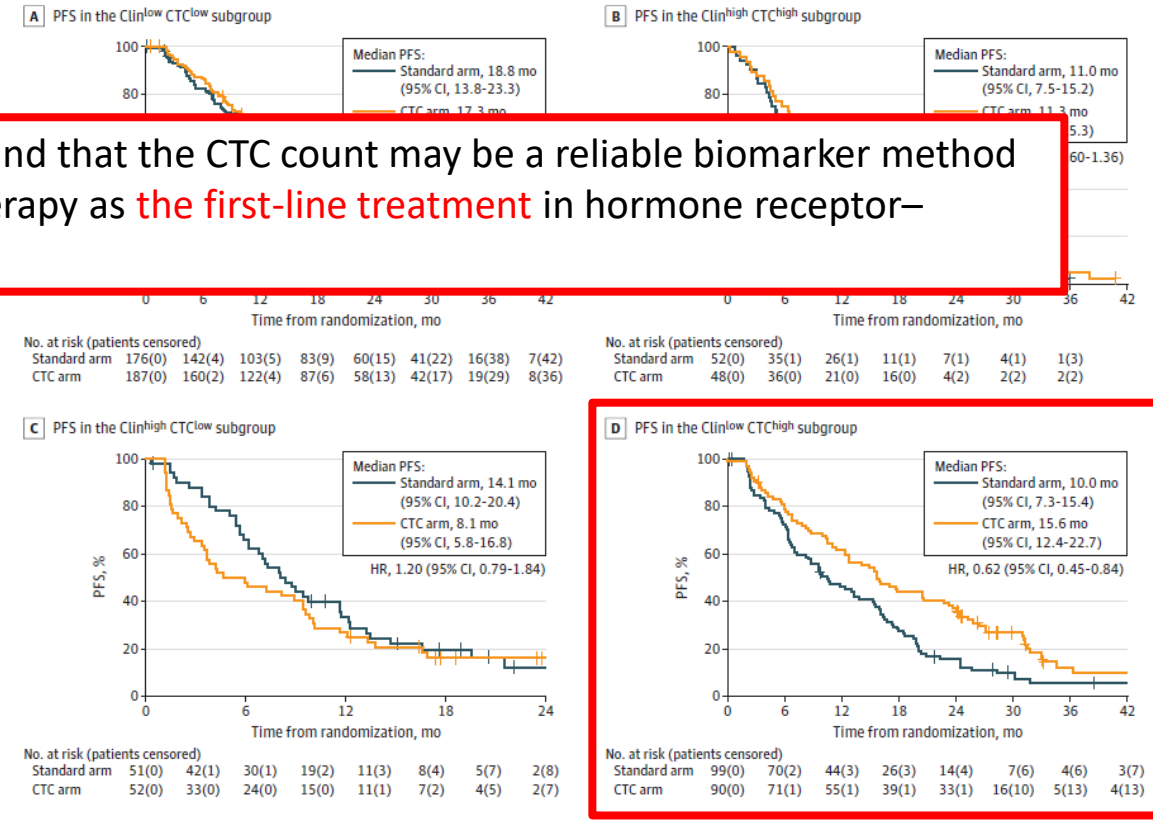
Clin^high indicates patients requiring chemotherapy according to the clinician-driven choice; Clin^low, patients requiring endocrine therapy (ET) according to the clinician-driven choice; CT, chemotherapy; CTC, circulating tumor cell; CTC^high, patients with ≥5 CTCs/7.5 mL; CTC^low, patients with <5 CTCs/7.5 mL.

Figure 2. Kaplan-Meier Curves of Progression-Free Survival (PFS) and Overall Survival (O



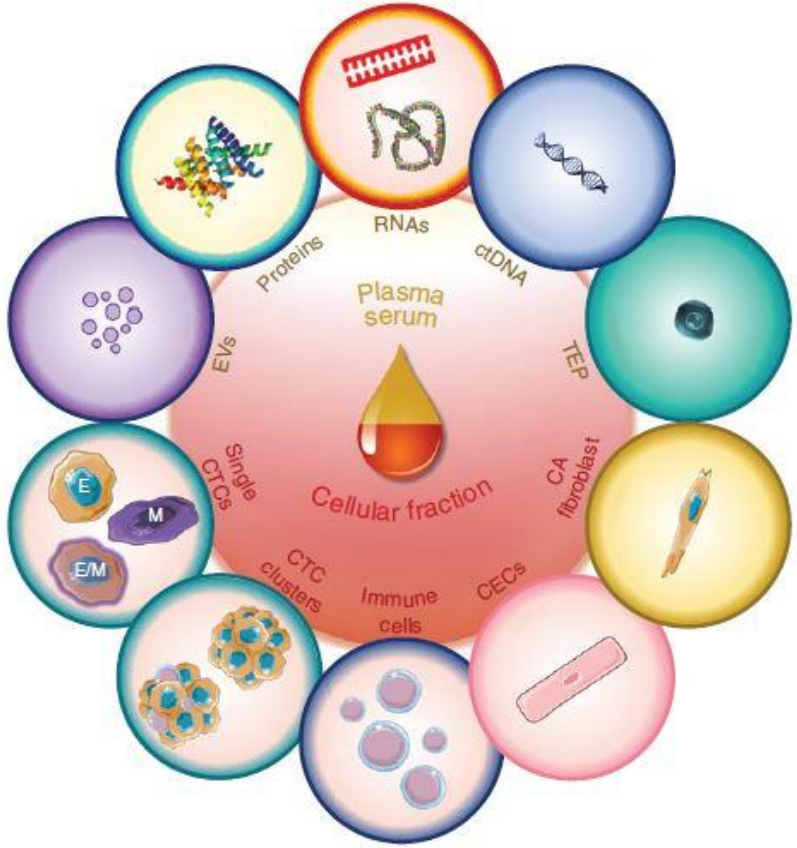
A, The PFS for each arm in the per-protocol population after 498 events had occurred; B, The OS for each arm in the per-protocol population when considering all events. CTC indicates circulating tumor cell; HR, hazard ratio.

Figure 3. Kaplan-Meier Curves of Progression-Free Survival (PFS) for Each Arm, When Considering All Events



CONCLUSIONS AND RELEVANCE This randomized clinical trial found that the CTC count may be a reliable biomarker method for guiding the choice between chemotherapy and endocrine therapy as the first-line treatment in hormone receptor–positive, ERBB2-negative metastatic breast cancer.

Circulating components



- Assessment of circulating components
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  - Proteins
  - Exosomes
  - miRNA and lncRNA
  - …

Catherine Alix-Panabières and Klaus Pantel; Cancer Discov 2021;11:858–73

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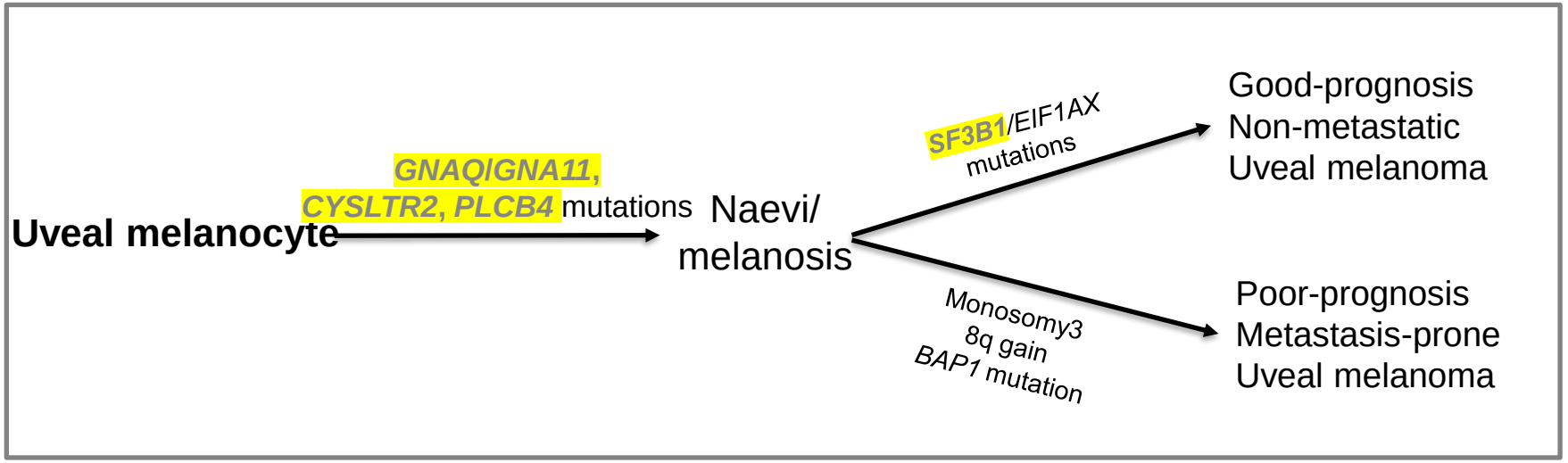
Different advantages and disavantages of using NGS and ddPCR to detect ctDNA

	Method	Detection sensitivity	Advantages	Disadvantages
Digital PCR	BEAMing dPCR	0.01%	1. ddPCR: ease to use 2. ddPCR: fast 3. No need of informatics expert support 4. Less expensive	1. Need to know the target in advance
	ddPCR	0.001%		
NGS	Safe-seq	0.1%	1. Capable of the detection of genetic or epigenetic changes without knowing the target in advance; ability of detecting new mutation	1. Take more time, slow 2. Expensive 3. Necessary of informatics expert support
	CAPP-seq	0.01%		
	iDES-CAPP-seq	0.001%		
	Bper	0.1%		

S.Renault et al, Expert Review of Molecular Diagnostics, 2017

UM: genetic profile



- 85% of UM have an activating hotspot mutation of *GNAQ* or *GNA11* genes
- GNAQ/GNA11 mutations are present in mutually exclusive manner

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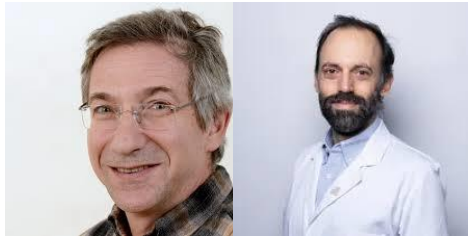
Circulating tumor DNA monitoring in patients with metastatic uveal melanoma treated with tebentafusp



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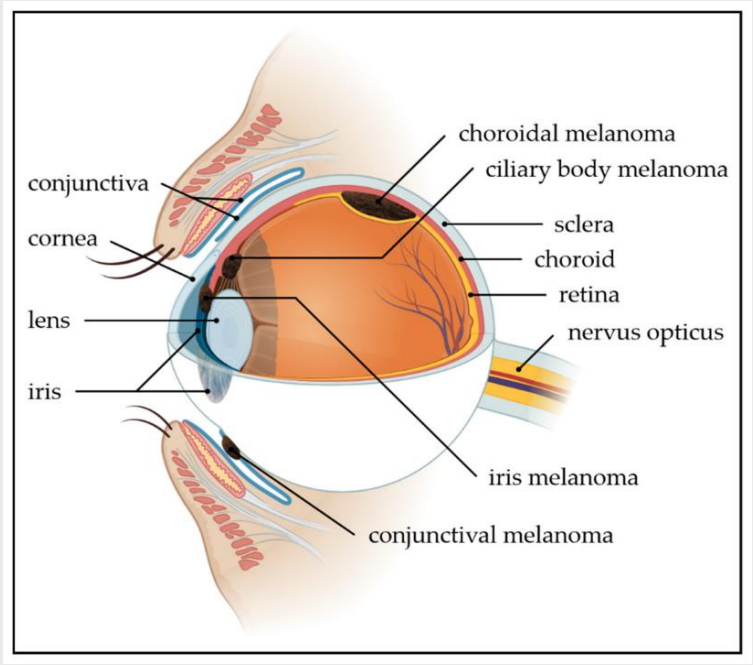
Uveal melanoma

- Uveal melanoma (UM) is the most common primary intraocular tumor in adults
- with an incidence of 2-8 new cases per million per year
- Arise from melanocytes of the choroid (90%), the iris (4%) and the ciliary body (6%)

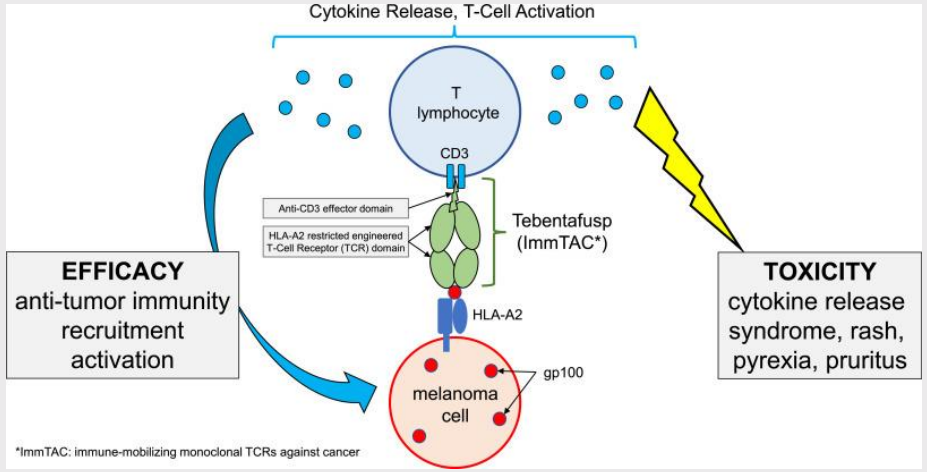


Uveal melanoma

- Metastatic disease eventually develops in approximately 30 to 50% of the patients, mainly in the liver with a median progression-free survival (PFS) and overall survival (OS) of ~3-4 months and ~10-16 months, respectively

- In case of liver metastases, no systemic therapy option had demonstrated an OS benefit until the recent approval of tebentafusp by FDA.

- In 2022, FDA approved the treatment of **tebentafusp** in unresectable or metastatic uveal melanoma in HLA-A*02:01-positive patients.



Tebentafusp is a bispecific protein consisting of an affinity-enhanced, HLA*A02:01-restricted, T-cell receptor specific for a gp100-derived peptide fused to an anti-CD3 single-chain variable fragment that can recruit and activate polyclonal T-cells

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Metastatic UM patients treated with tebentafups

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Overall Survival Benefit with Tebentafusp in Metastatic Uveal Melanoma

Paul Nathan, M.D., Ph.D., Jessica C. Hassel, M.D., Piotr Rutkowski, M.D., Ph.D., Jean-Francois Baurain, M.D., Ph.D., Marcus O. Butler, M.D., Max Schlaak, M.D., Ryan J. Sullivan, M.D., Sebastian Ochsenreither, M.D., Reinhard Dummer, M.D., John M. Kirkwood, M.D., Anthony M. Joshua, M.D., Ph.D., Joseph J. Sacco, M.D., Ph.D., Alexander N. Shoushtari, M.D., Marlana Orloff, M.D., Josep M. Piulats, M.D., Ph.D., Mohammed Milhem, M.D., April K.S. Salama, M.D., Brendan Curti, M.D., Lev Demidov, M.D., Lauris Gastaud, M.D., Cornelia Mauch, M.D., Ph.D., Melinda Yushak, M.D., M.P.H., Richard D. Carvajal, M.D., Omid Hamid, M.D., Shaad E. Abdullah, M.D., Chris Holland, M.S., Howard Goodall, M.D., and Sophie Piperno-Neumann, M.D., for the IMCgp100-202 Investigators*

N Engl J Med 2021;385:1196-206.

METHODS

- open-label, phase 3 trial, randomly assigned previously untreated HLA-A* 02:01–positive patients with metastatic uveal melanoma in a 2:1 ratio to receive tebentafusp (tebentafusp group, N= 252) or the investigator's choice of therapy with single agent pembrolizumab, ipilimumab, or dacarbazine (control group, N=126), stratified according to the lactate dehydrogenase level. The primary end point was overall survival.

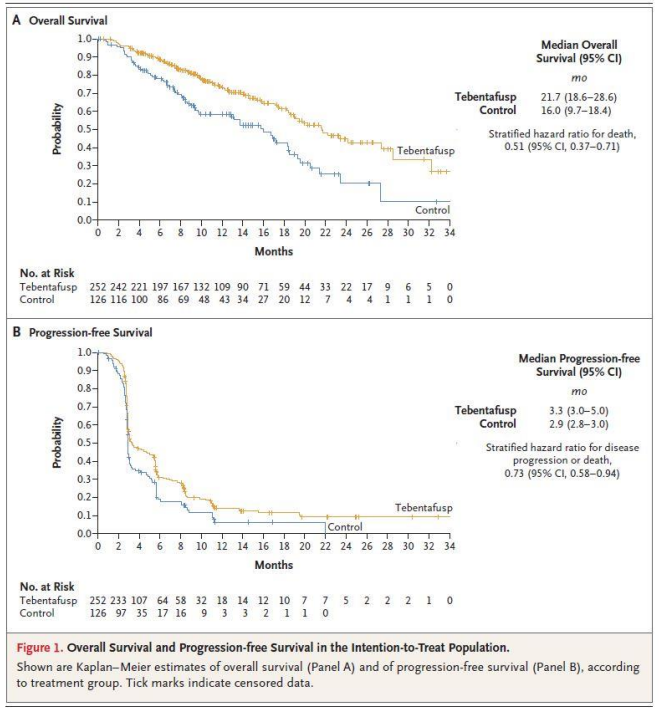
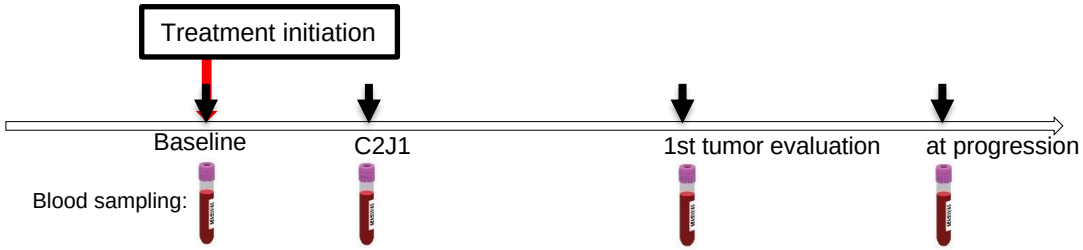


Figure 1. **Overall Survival and Progression-free Survival in the Intention-to-Treat Population.**
Shown are Kaplan–Meier estimates of overall survival (Panel A) and of progression-free survival (Panel B), according to treatment group. Tick marks indicate censored data.

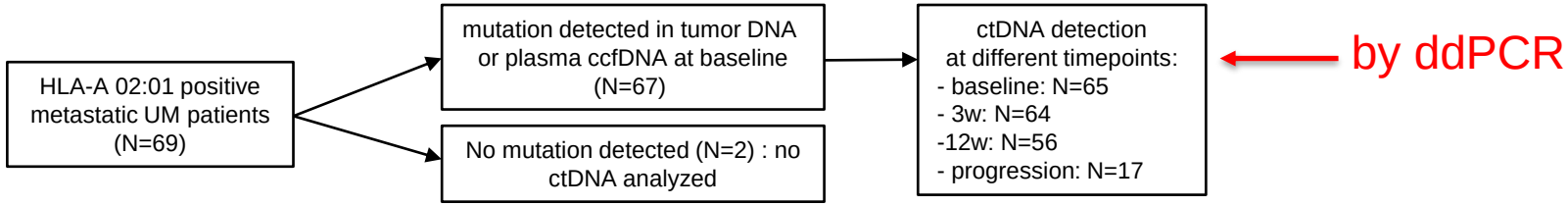
- Although tebentafusp showed an OS benefit in IMCgp100-202, the randomized phase 3 trial (NCT03070392), its efficacy in the real-world setting remains elusive.
- Importantly, tumor responses according to RECIST criteria were observed in only a fraction of patients (~11%) and discrepancies between radiographic response and OS were reported.
- Therefore, easily accessible, sensitive and specific methods allowing a better monitoring of individuals with metastatic UM (MUM) treated with tebentafusp in real-life are needed.

ctDNA in mUM patients treated with tebentafups

A.



B.



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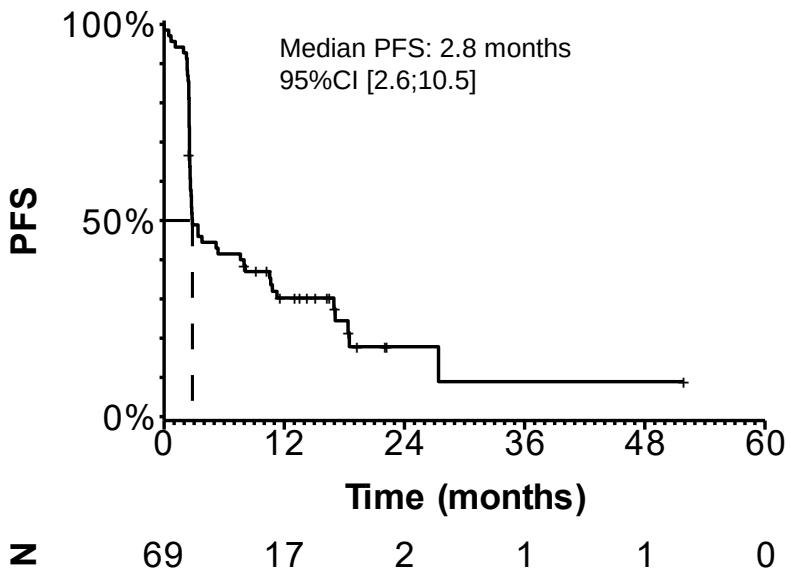
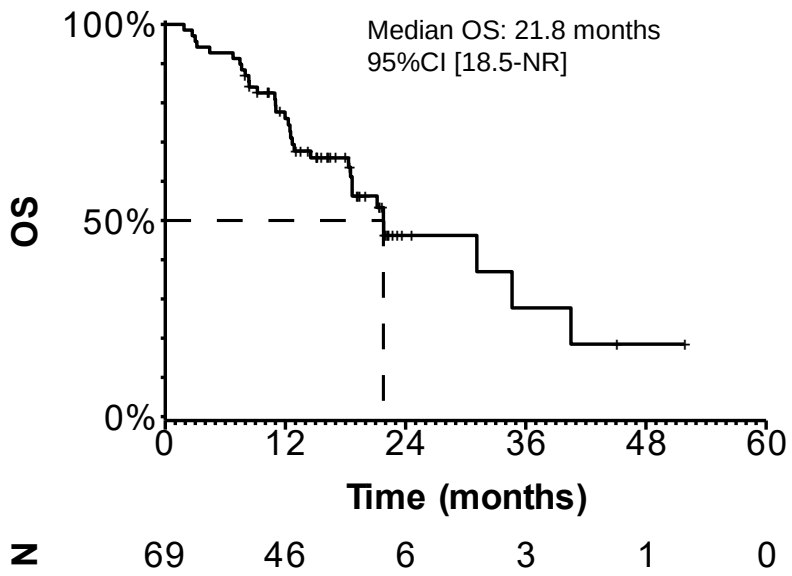
Patients' outcomes: progression-free survival (PFS) and overall survival (OS)

- The objective response rate (ORR) was 10% (n = 7/68), all being partial responses (PR)





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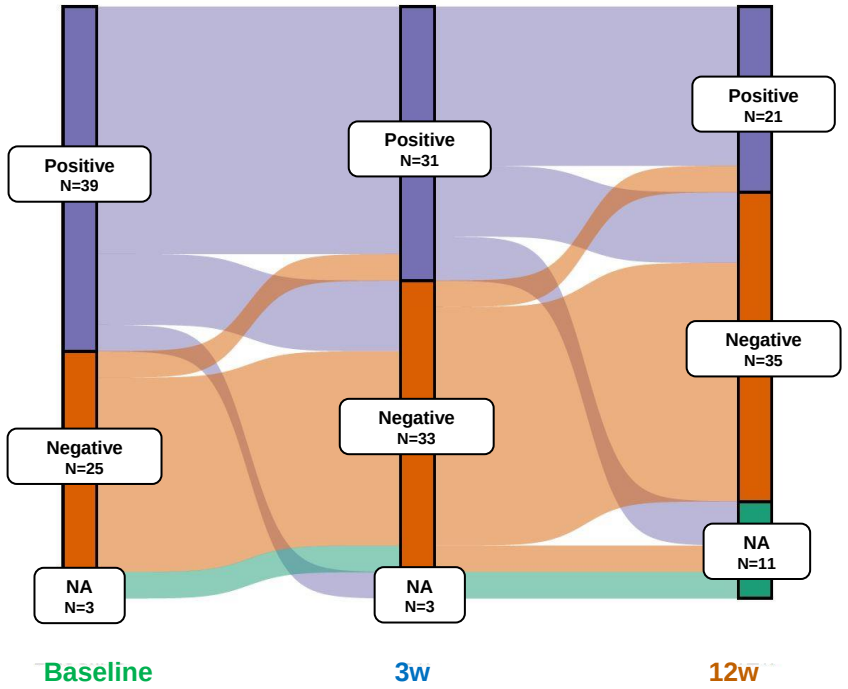
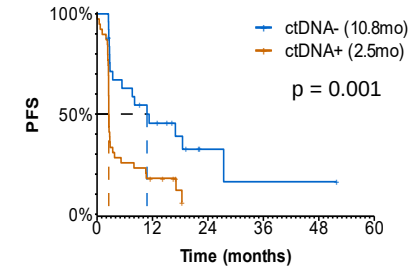
Prognostic value of ctDNA detection at baseline, 3w and 12w

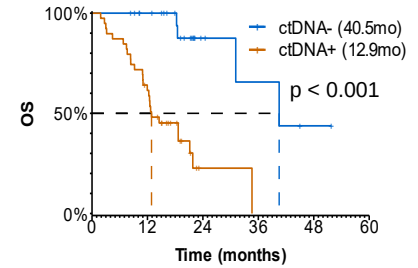
A.



B. baseline

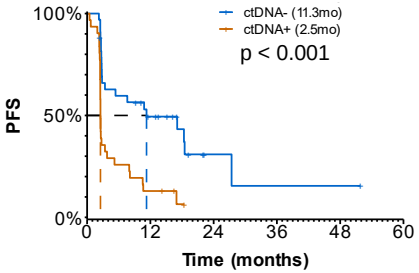


No. at risk: 25 10 2 1 1 0 / 39 6 0 0 0 0

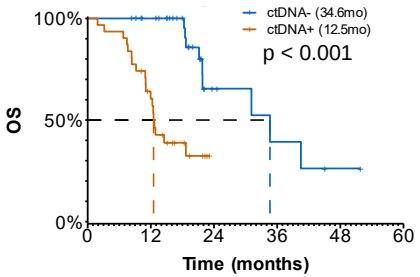


No. at risk: 25 21 5 3 1 0 / 39 23 1 0 0 0

C. 3w

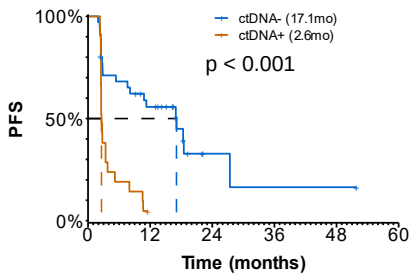


N: 33 13 2 1 1 0 / 31 4 0 0 0 0

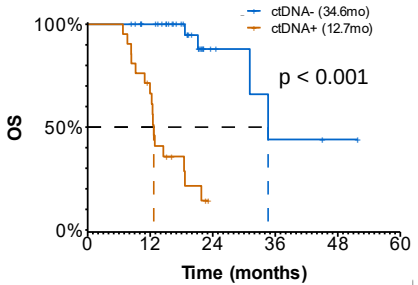


N: 33 29 6 3 1 0 / 31 17 0 0 0 0

D. 12w



N: 35 17 2 1 1 0 / 21 0 0 0 0 0



N: 35 30 5 2 1 0 / 21 13 0 0 0 0

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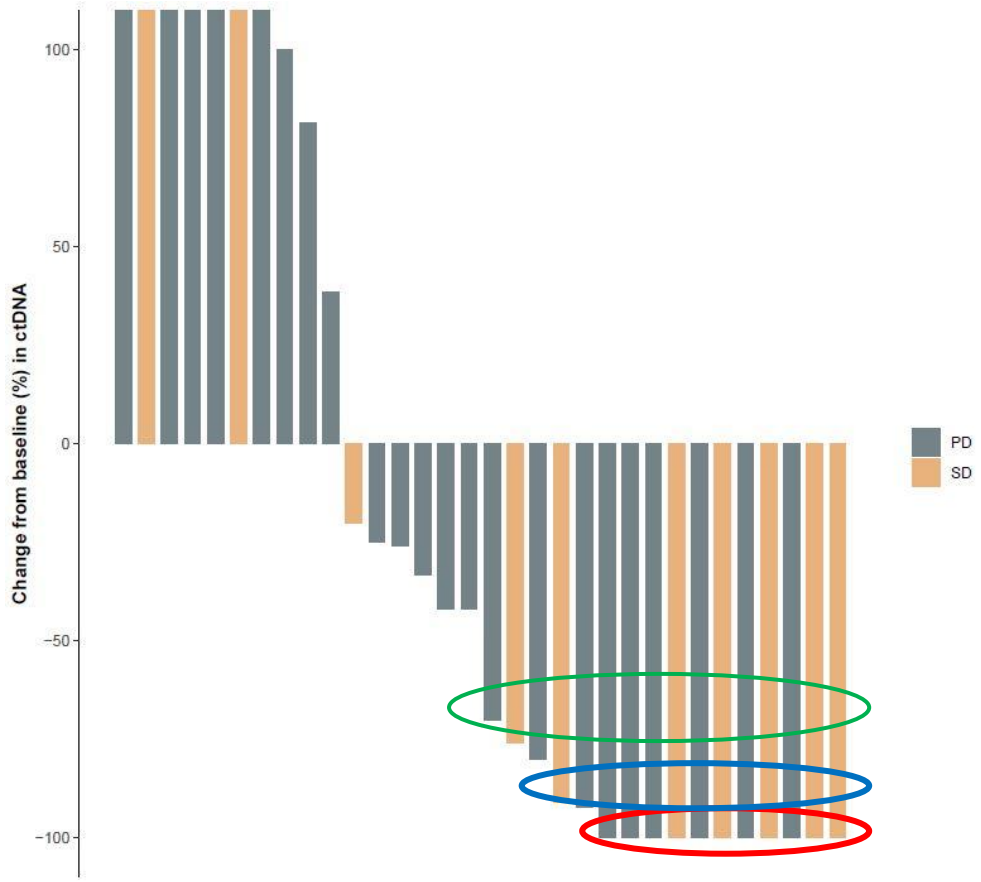
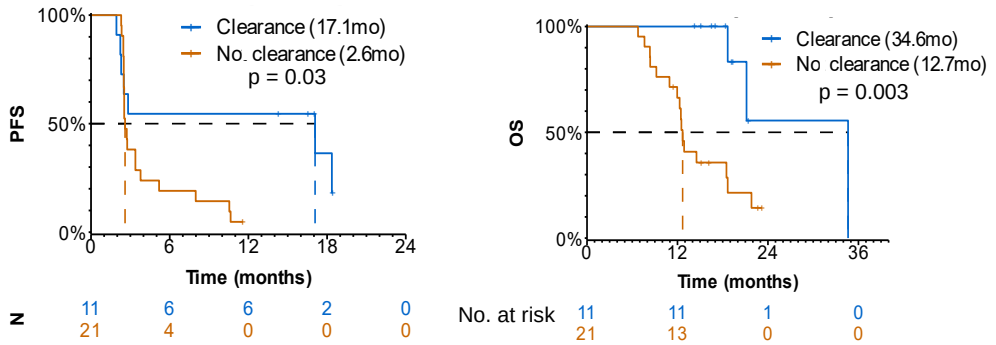
Predictive value of ctDNA variations on tebentafusp (baseline and 12w)

A.



ctDNA variation at 12w according to tumor response at first assessment

B.



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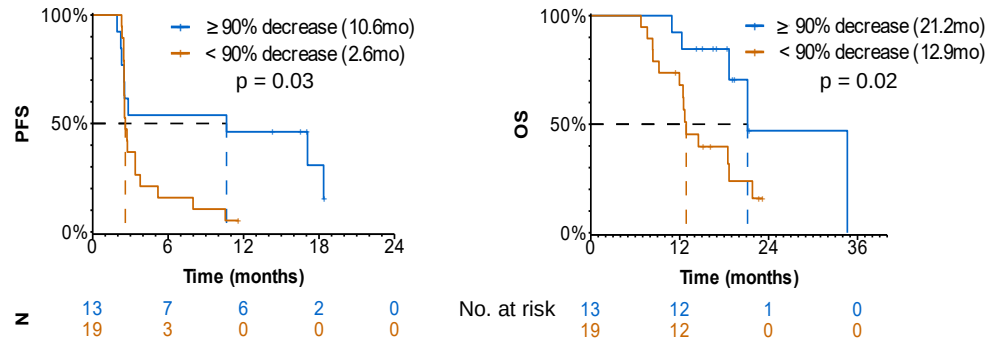
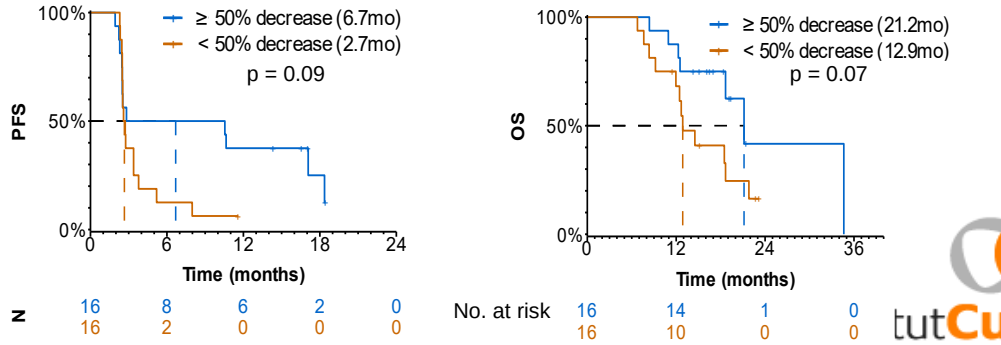


D.



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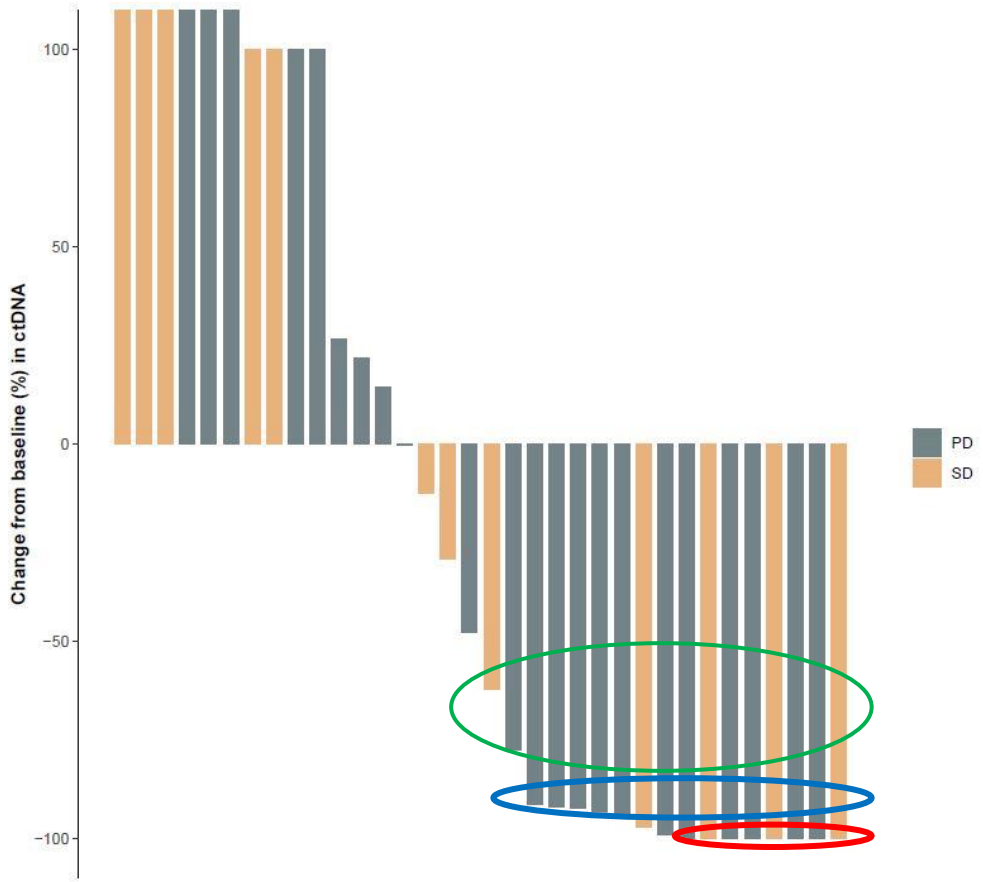
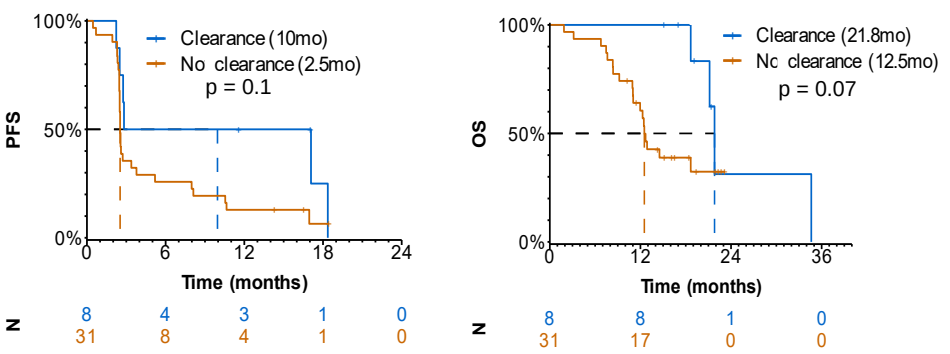
Predictive value of ctDNA variations on tebentafusp (baseline and 3w)

A.



ctDNA variation at 3w according to tumor response at first assessment

B.



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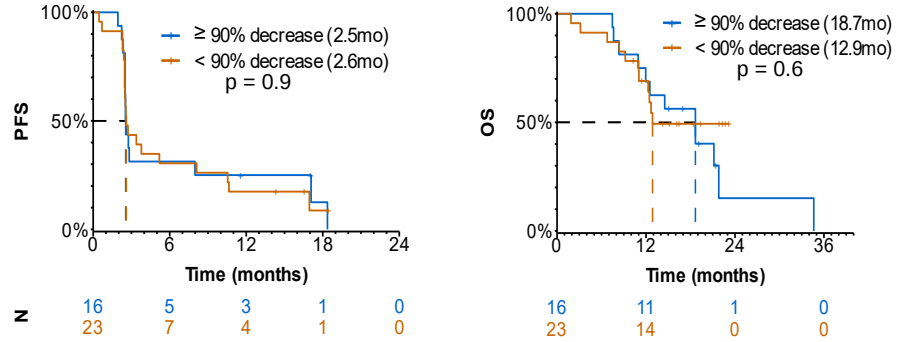

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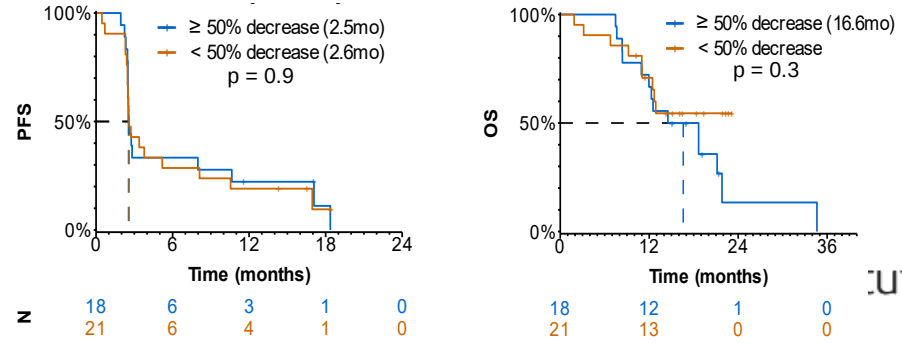

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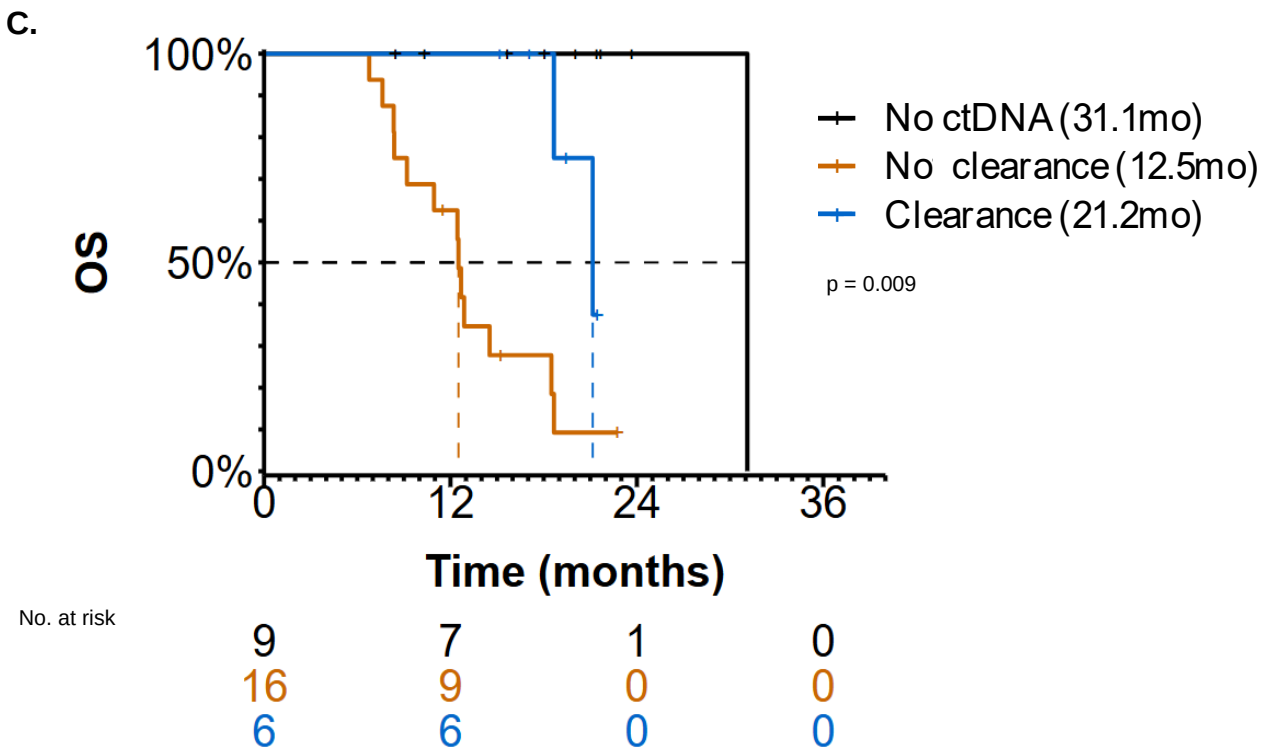
Predictive value of ctDNA variations on tebentafusp in patients with progressive disease

discrepancies between radiographic response and OS



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Article

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Prospective assessment of circulating tumor DNA in patients with metastatic uveal melanoma treated with tebentafusp

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Check for updates

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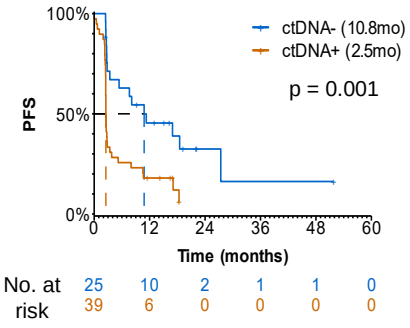
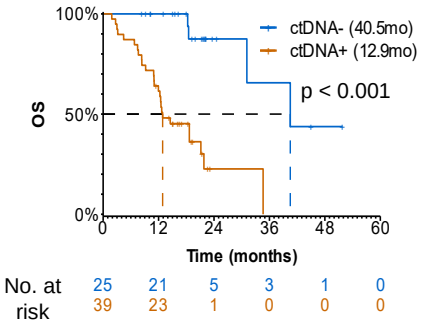
A. Prognostic value of ctDNA detection at baseline

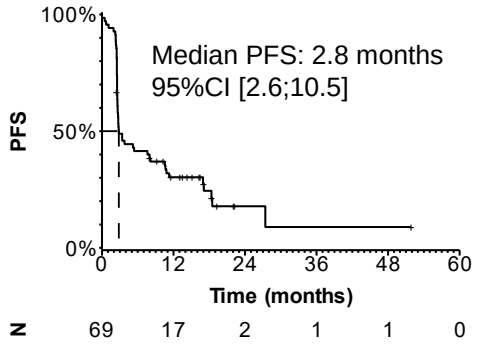


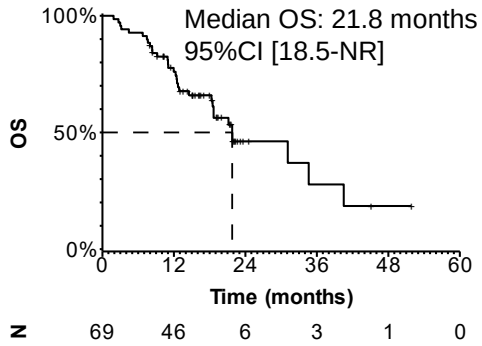


B. Predictive value of ctDNA variations on tebentafusp

In conclusion, our data

- showed that in a real-world setting, tebentafusp had similar treatment efficacy to what was observed in previous clinical trials.
- demonstrated that ddPCR-based ctDNA monitoring could serve as a practical and cost-effective approach, directly applicable in routine clinical practice.





IMCgp100-202 phase 3 trial using ***multiplex PCR based NGS***

Jean-Francois Baurain, M.D., Ph.D., Marcus O. Butler, M.D., Max Schlaak, M.D., Ryan J. Sullivan, M.D., Sebastian Ochsenreither, M.D., Reinhard Dummer, M.D., John M. Kirkwood, M.D., Anthony M. Joshua, M.D., Ph.D., Joseph J. Sacco, M.D., Ph.D., Alexander N. Shoushtari, M.D., Marlana Orloff, M.D., Josep M. Piulats, M.D., Ph.D., Mohammed Milhem, M.D., April K.S. Salama, M.D., Brendan Curti, M.D., Lev Demidov, M.D., Lauris Gastaud, M.D., Cornelia Mauch, M.D., Ph.D., Melinda Yushak, M.D., M.P.H., Richard D. Carvajal, M.D., Omid Hamid, M.D., Shaad E. Abdullah, M.D., Chris Holland, M.S., Howard Goodall, M.D., and Sophie Piperno-Neumann, M.D., for the IMCgp100-202 Investigators*

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6 6 0 0

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ARTICLE OPEN

Fulvestrant and everolimus efficacy after CDK4/6 inhibitor: a prospective study with circulating tumor DNA analysis

Antoine Vasseur[1,2], Luc Cabel[1], Caroline Hego[2], Wissam Takka[2], Olfa Trabelsi Grati[3], Benjamin Renouf[4], Florence Lerebours[1], Delphine Loirat[1], Etienne Brain[1], Paul Cottu[1], Marie-Paule Sablin[1], Jean-Yves Pierga[1,5], Céline Callens[3], Shufang Renault[2,7]✉ and François-Clément Bidard[1,2,6,7]✉

 Oncogene

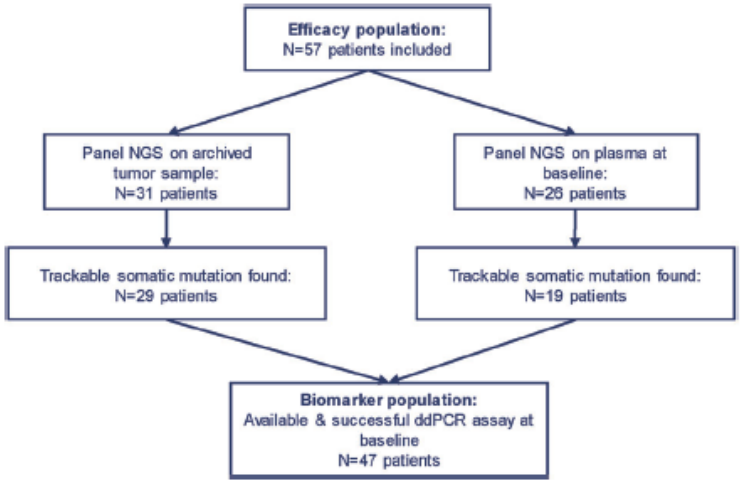

Fig. 1 Workflow of the study. ER+: estrogen receptor positive; mBC: metastatic breast cancer; NGS: next-sequencing generation; ddPCR: droplet digital PCR.

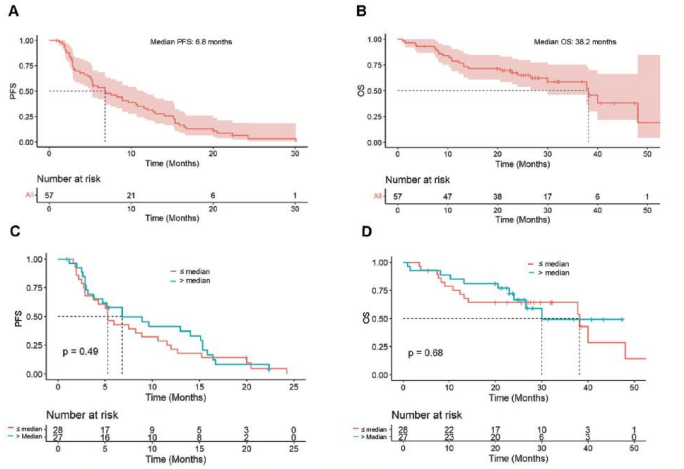

Fig. 2 Progression-free survival and overall survival in patients treated with everolimus and fulvestrant. In the whole population (**A**, **B**) and according to previous palbociclib treatment duration (above or under/equal to median PFS (**C**, **D**)). PFS progression-free survival, OS overall survival.

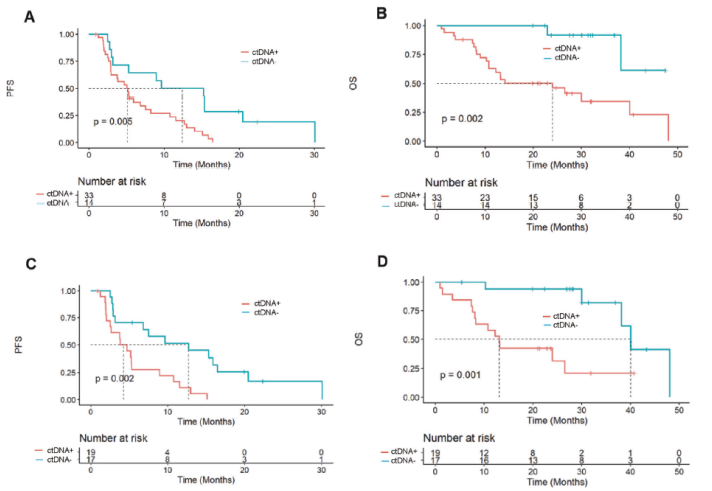

Fig. 4 Prognostic value of ctDNA detection at different time points. Progression-free survival and overall survival according to ctDNA detection at baseline (**A**, **B**) and 3 weeks (**C**, **D**). PFS progression-free survival, OS overall survival.

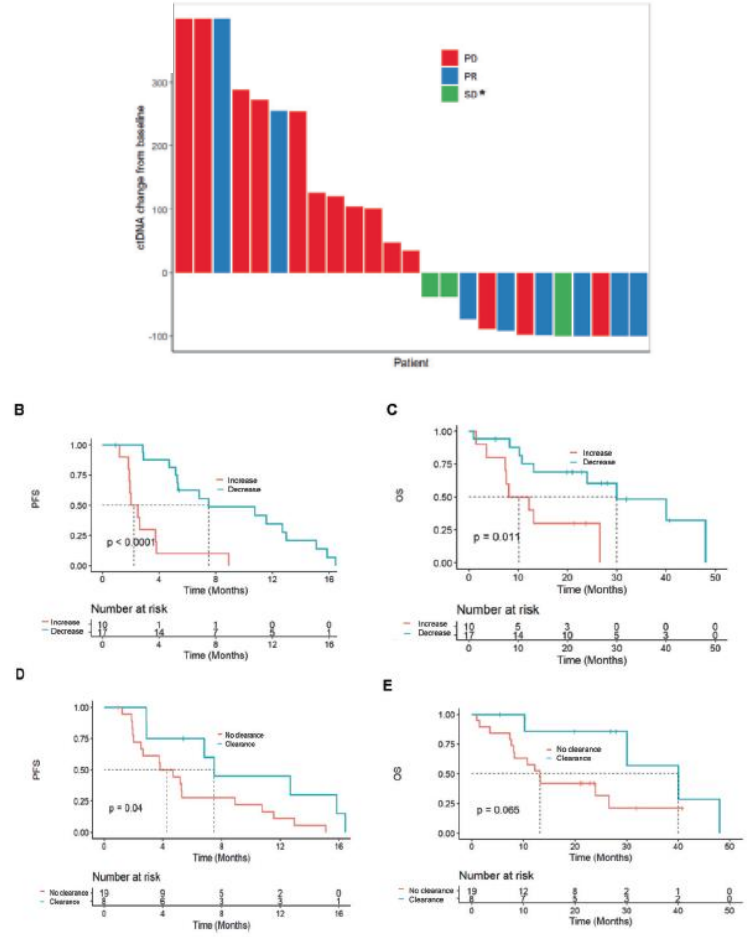

Fig. 5 Tumor response and prognostic value of early ctDNA variations. Tumor response according to ctDNA change from baseline (A).*SD ≥ 6 months. Progression-free survival and overall survival according to early ctDNA variation (B, C) and ctDNA clearance (D, E). PDprogressive disease, PR partial response, SD stable disease, PFS progression-free survival; OS: overall survival.

ARTICLE

Microsatellite instability detection in breast cancer using drop-off droplet digital PCR

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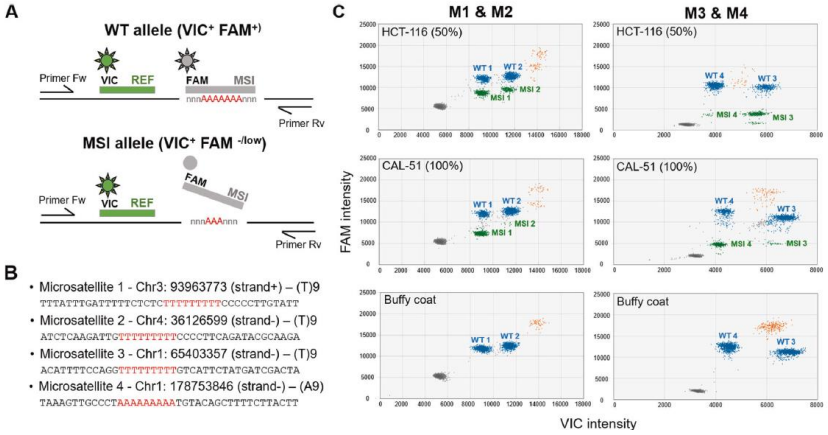
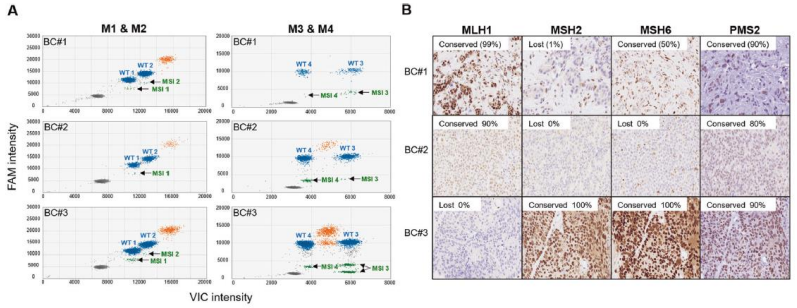
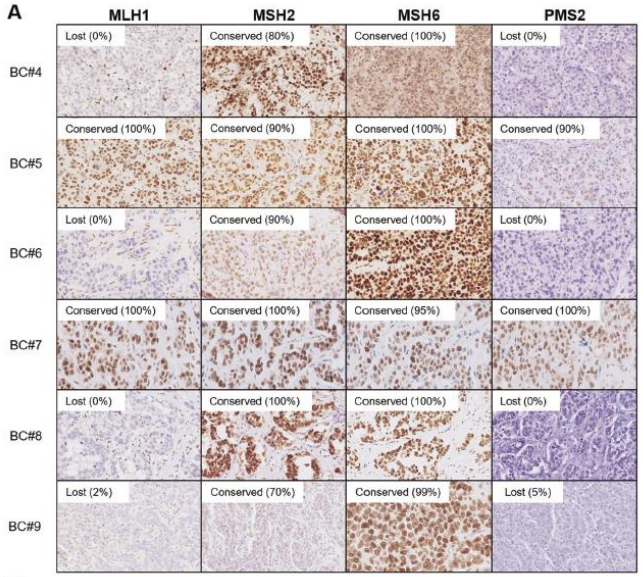




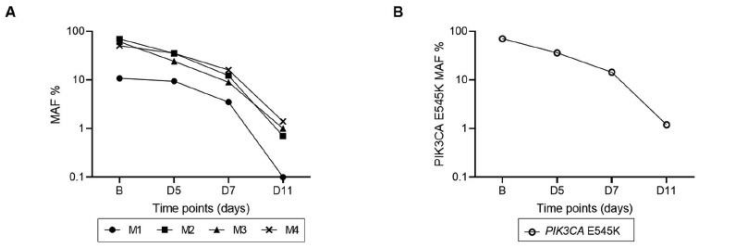
C

BC samples	ddPCR	MMR IHC	NGS			MLH1 methylation	Pentaplex PCR
			MSI status	MMR gene alteration	TMB (variants/Mb)		
BC#1	MSI-H M3, M4	Loss of MSH2	MSI-H	Pathogenic mutation in MSH2 and LOH	49.8	Not analyzed	MSS
BC#2	MSI-H M3, M4	Loss of MSH2 & MSH6	MSI-H	Pathogenic mutation in MSH2 and LOH	34	Not analyzed	MSI-H
BC#3	MSI-H M1, M3, M4	Loss of MLH1	MSI-H	Not detected	10.9	MLH1 methylation	MSI-H

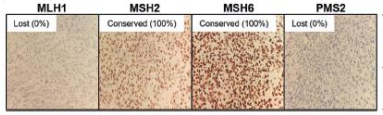


B

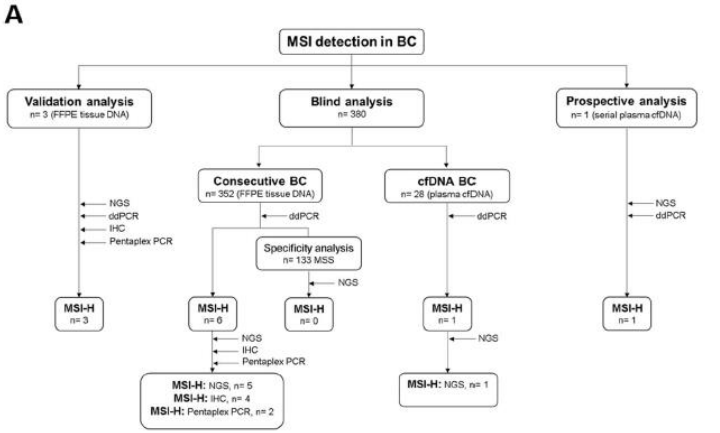
BC samples	ddPCR	MMR IHC	NGS			MLH1 methylation	Pentaplex PCR
			MSI status	MMR gene alteration	TMB (variants/MB)		
BC#4	MSI-H M1, M2, M3	Loss of MLH1 & PMS2	MSI-H	MLH1 homozygous deletion	22.7	Not analyzed	MSS
BC#5	MSI-H M1, M2	No loss	MSS	Not detected	2	Not analyzed	MSS
BC#6	MSI-H M1, M3	Loss of MLH1 & PMS2	MSI-H	Not detected	13.9	MLH1 methylation	MSS
BC#7	MSI-H M1, M2, M3, M4	No loss	MSI-H	MSH2 homozygous deletion	8	Not analyzed	MSS
BC#8	MSI-H M1, M3, M4	Loss of MLH1 & PMS2	MSI-H	Not detected	12	MLH1 methylation	MSI-H
BC#9	MSI-H M1, M3, M4	Loss of MLH1 & PMS2	MSI-H	MSH3 frameshift indel MLH3 frameshift indel MSH3 in-frame indel	15	No MLH1 methylation	MSI-H



C



BC sample	ddPCR	MMR IHC	NGS			Pentaplex PCR
			MSI status	MMR gene alteration	TMB (variants/Mb)	
P#29	MSI-H M1, M2, M3, M4	Loss of MLH1 & PMS2	MSI-H	MLH1 homozygous deletion	15.9	MSI-H



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