ELBS

Uveal Melanoma
- Perspectives/challenges in metastatic disease -

Jessica C. Hassel

Section of DermatoOncology

Department of Dermatology and National Centre for Tumor Diseases (NCT)

University Hospital Heidelberg

NCT
NATIONALES CENTRUM FÜR TUMORERKRANKUNGEN HEIDELBERG

getragen von:
Deutsches Krebsforschungszentrum
Universitätsklinikum Heidelberg
Thoraxklinik-Heidelberg
Deutsche Krebshilfe

Potential Conflicts of Interest

Scientific support:

BMS, Sanofi, Sunpharma

Talks:

Almirall, Amgen, BMS, GSK, Immunocore, MSD, Novartis, Pfizer, Pierre Fabre, Roche, Sanofi, Sunpharma

Advisory Boards:

GSK, MSD, Pierre Fabre, Sunpharma

NCT

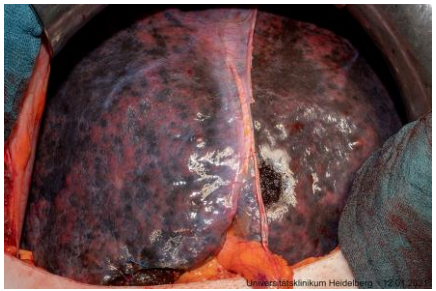
Treatment options in metastasized Uveal Melanoma

Clinical trial?

Liver-directed therapy

- Chemosaturation (PHP)
- Chemoperfusion (HAI)
- TACE
- SIRT
- Resection?

OS benefit?



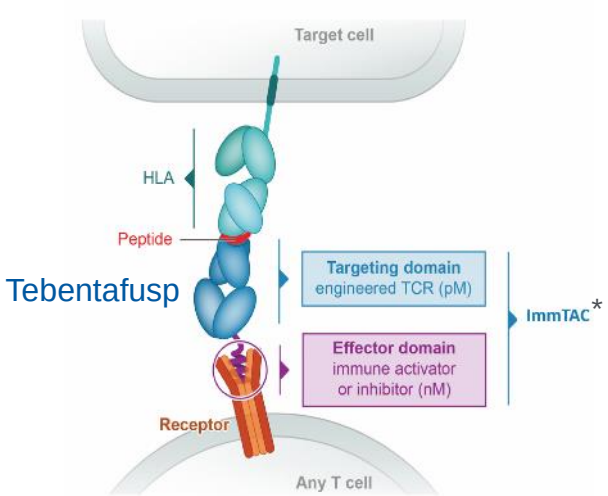
Systemic herapy

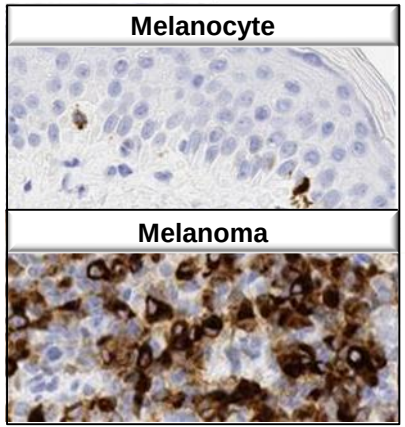
- ImmTAC: Tebentafusp
- Immune checkpoint blocker
- Chemotherapy
- Targeted?

√ OS benefit!

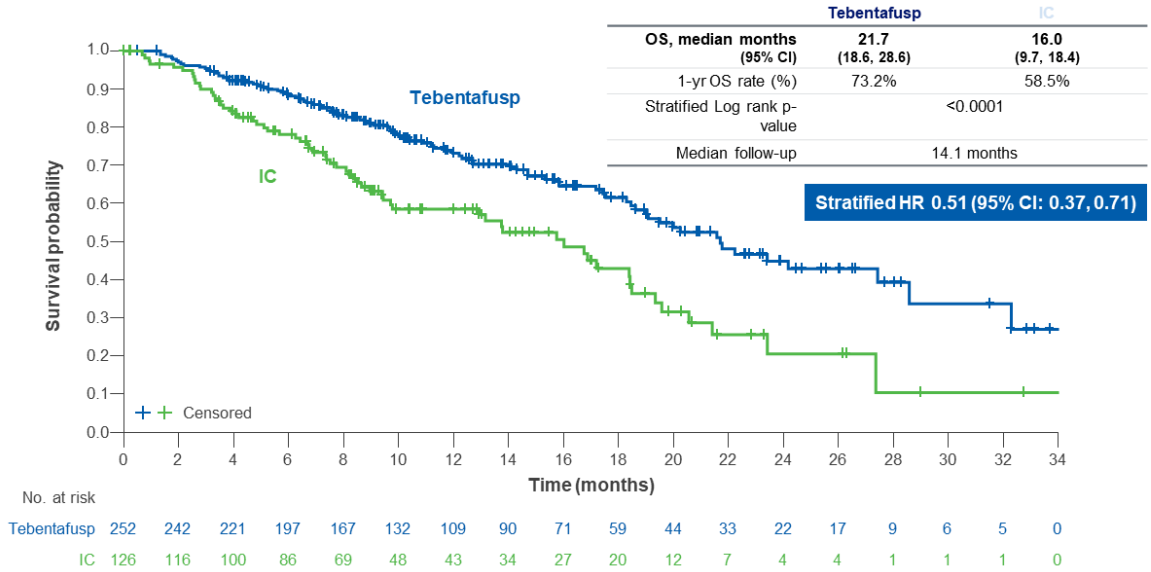
NCT

Tebentafusp





Phase 3: IMCgp100-202

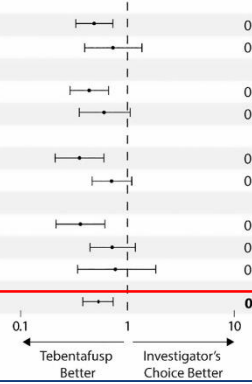


Nathan, Hassel et al, NEJM 2021

*Immune mobilising monoclonal T-cell receptors Against Cancer

Who benefits most?

Subgroup	Tebentafusp No. of Patients	Tebentafusp No. (%) of Death	Investigator's Choice No. of Patients	Investigator's Choice No. (%) of Death	Hazard Ratio (95% CI)
Region					
North America	86	28 (33)	52	24 (46)	0.52 (0.30-0.91)
Non-North America	166	59 (36)	74	39 (53)	0.49 (0.33-0.74)
Investigator's Choice					
Pembrolizumab	199	65 (33)	103	49 (48)	0.51 (0.35-0.75)
Ipilimumab	40	16 (40)	16	7 (44)	0.89 (0.38-2.31)
Dacarbazine	13	6 (46)	7	7 (100)	0.29 (0.09-0.86)
Gender					
Male	128	48 (38)	62	35 (57)	0.48 (0.31-0.75)
Female	124	39 (32)	64	28 (44)	0.57 (0.35-0.94)
Age					
<65 yr	130	41 (32)	61	29 (48)	0.48 (0.30-0.79)
≥65 yr	122	46 (38)	65	34 (52)	0.58 (0.38-0.92)
ECOG status					
0	192	59 (31)	85	42 (49)	0.48 (0.33-0.72)
1	49	24 (49)	31	18 (58)	0.72 (0.39-1.36)
Baseline alkaline phosphatase					
≤ ULN	198	49 (25)	102	43 (42)	0.44 (0.29-0.66)
> ULN	53	37 (70)	24	20 (83)	0.60 (0.35-1.05)
Lactate dehydrogenase					
≤ ULN	162	28 (17)	80	29 (36)	0.35 (0.21-0.60)
> ULN	90	59 (66)	46	34 (74)	0.70 (0.46-1.09)
Largest metastatic lesion					
M1a (≤3.0 cm)	139	29 (21)	70	28 (40)	0.36 (0.21-0.61)
M1b (3.1-8.0 cm)	92	43 (47)	46	26 (57)	0.71 (0.44-1.17)
M1c (≥8.1 cm)	21	15 (71)	10	9 (90)	0.76 (0.34-1.82)
ITT population	**252**	**87 (35)**	**126**	**63 (50)**	**0.51 (0.37-0.71)**



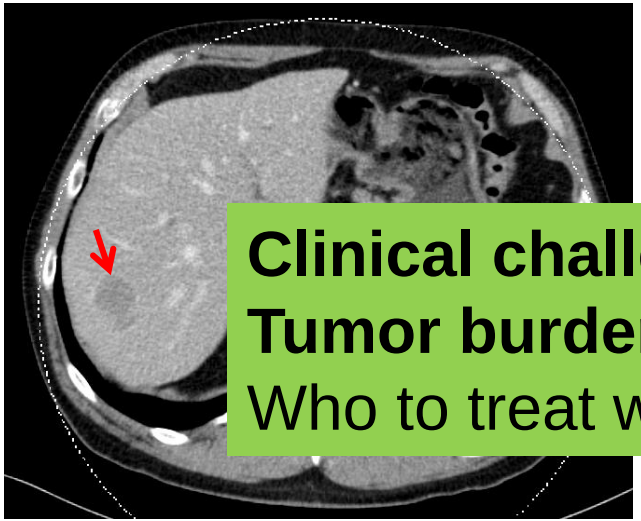
Uveal melanoma patients with:

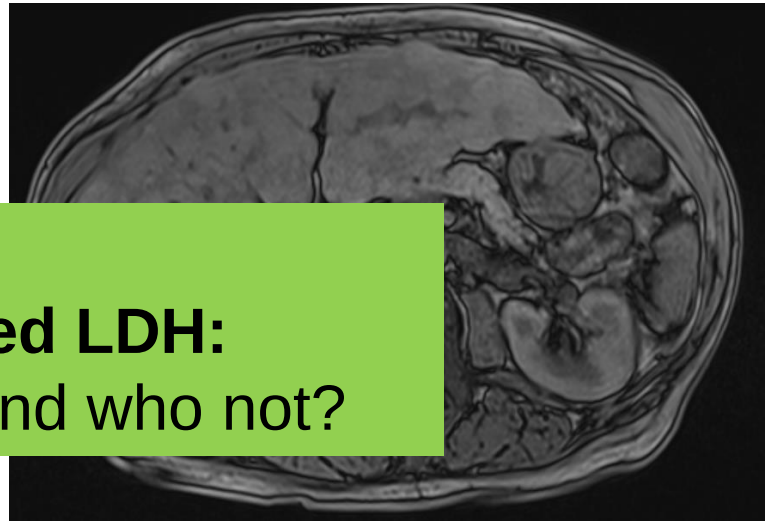
- ECOG 0
- Normal LDH
- M1a stage

➔ Low tumor burden!

Nathan et al. NEJM 2021, Figure S2.

Who to treat with tebentafusp





Clinical challenge:
Tumor burden - Elevated LDH:
Who to treat with Tebe and who not?

- Low tumor burden
- Normal LDH at inclusion
- Low dynamic of disease
- firstline

> 3 years with Tebe

- High tumor burden
- High LDH at inclusion
- High dynamic of disease
- ≥ 2ndline

died 4 months after Tebe initiation

Low response rate with Tebentafusp

ORR and DCR by investigator assessment

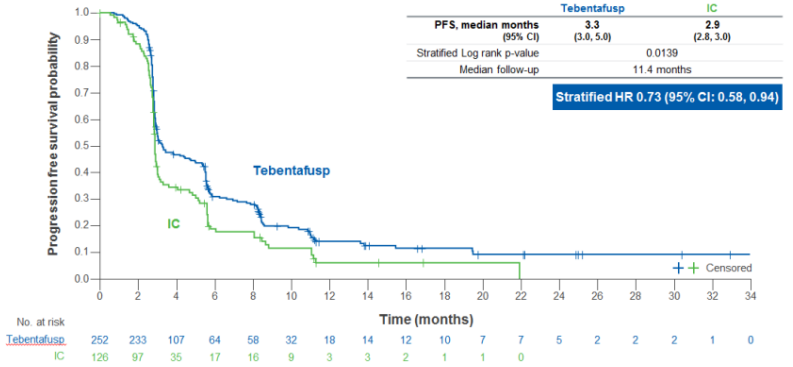
American Association for Cancer Research FINDING CURES TOGETHER

Best response to systemic therapy	Tebentafusp (n=252) n (%)	IC (n=126) n (%)
ORR*	23 (9)	6 (5)
CR	1 (0.4)	0
PR	22 (9)	6 (5)
SD	92 (37)	28 (22)
PD	131 (52)	78 (62)
Non-evaluable/not applicable	6 (2)	10 (8)
DCR ≥12 wks†	115 (46)	34 (27)

†Defined as CR, PR or SD for ≥12 weeks.
CR, complete response; DCR, disease control rate; PD, progressive disease; PR, partial response; SD, stable disease.

Progression free survival

American Association for Cancer Research FINDING CURES TOGETHER

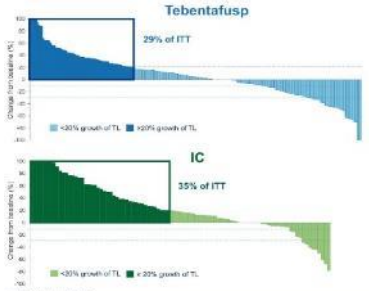


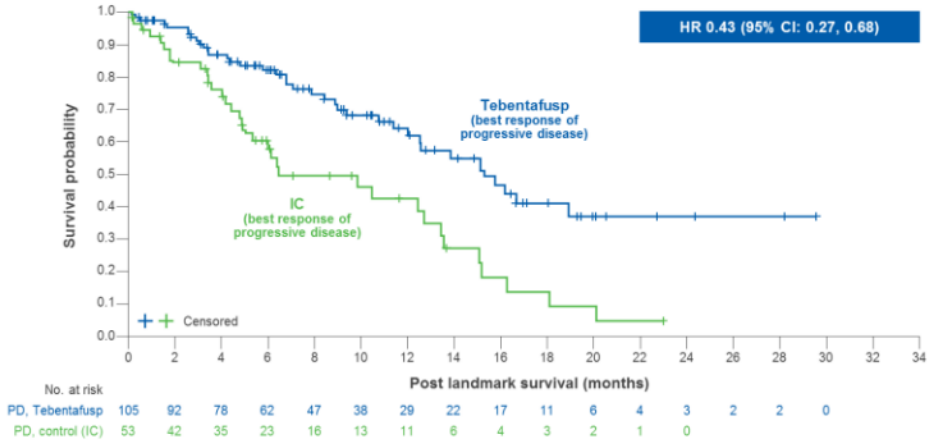
AACR ANNUAL MEETING 2021: APRIL 10-15, 2021 AND MAY 17-21, 2021

NCT

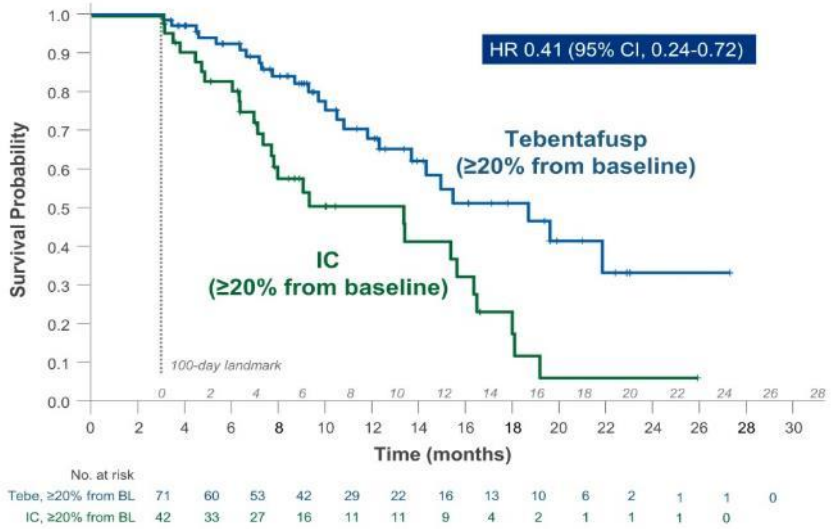
Overall survival in patients with PD as best response

TBP in 53% Tebe and 17% Pembro patients





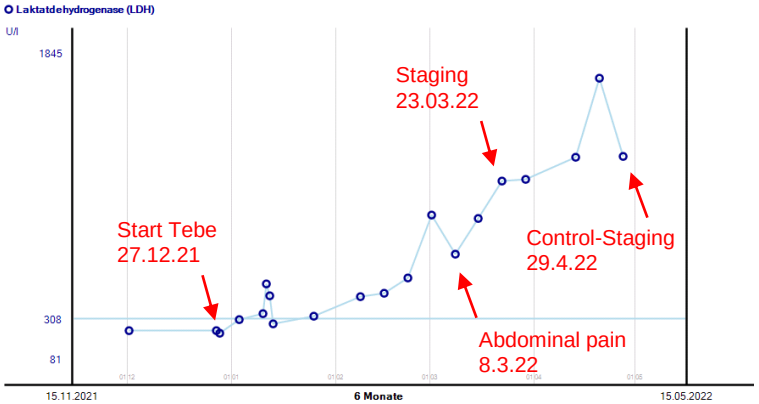
Nathan, Hassel et al, NEJM 2021



Joshua et al, #9509, ASCO 2021

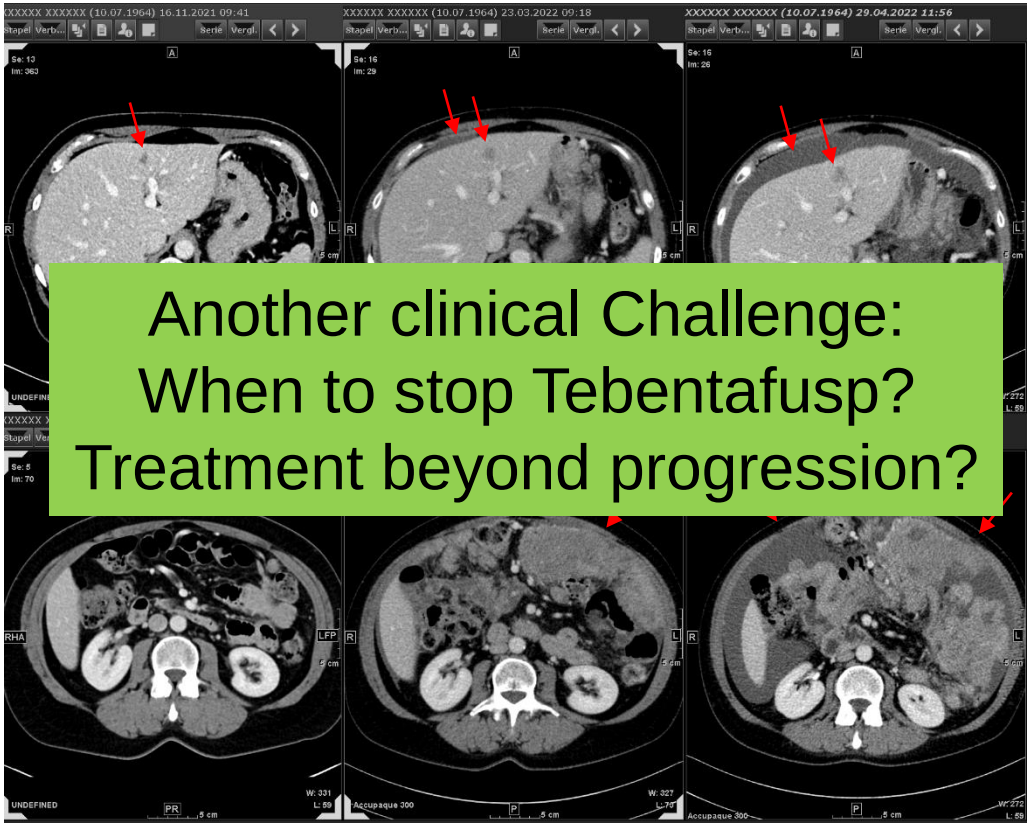
NCT

Clinical Case: 57yo female



- Start Tebe after 3x PHP
- Constantly rising LDH
- Good clinical condition
- Staging: stable liver mets, increasing peritoneal mets

16.11.21, LDH 243U/l 23.3.22, LDH 1100U/l 29.4.22, LDH 1200U/l



Another clinical Challenge:
When to stop Tebentafusp?
Treatment beyond progression?

Liquid biopsy?

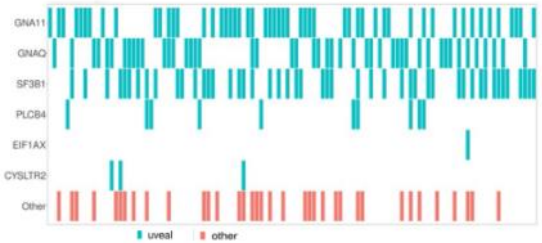
IMC-100-102

Eligibility

- Metastatic UM
- HLA-A*02:01 positive
- ≥1 prior therapy in metastatic setting
- Measurable disease

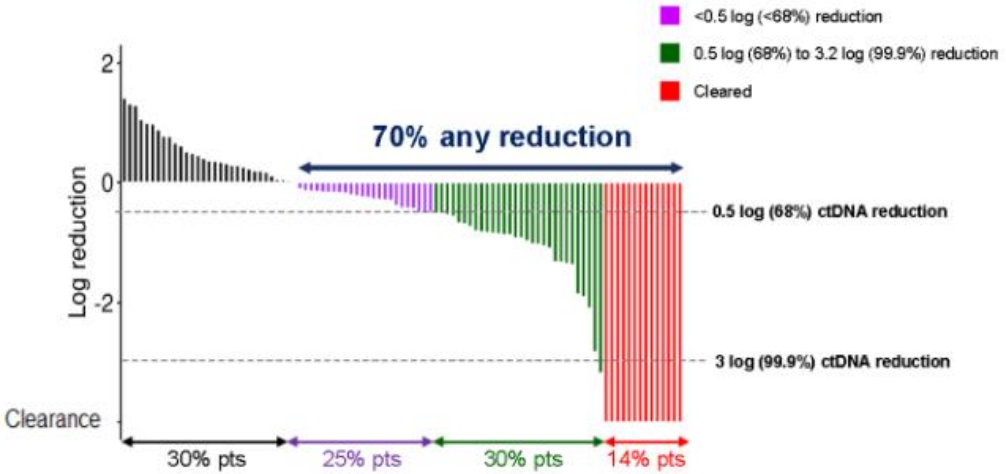
Treatment Regimen

Almost all evaluable patients had mutations in known UM oncogenes



New custom panel to detect melanoma ctDNA using multiplex PCR followed by next gen sequencing, including UM specific: GNAQ, GNA11, SF3B1, PLCB4, CYSLTR2, EIF1AX

1. Yanchoan M, et al. *NEJM* 2017; 377(25): 2500–2501.

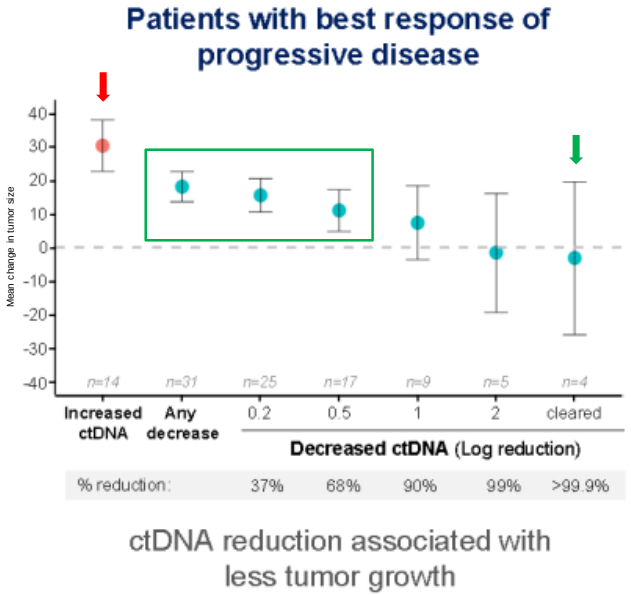


2021 ESMO congress

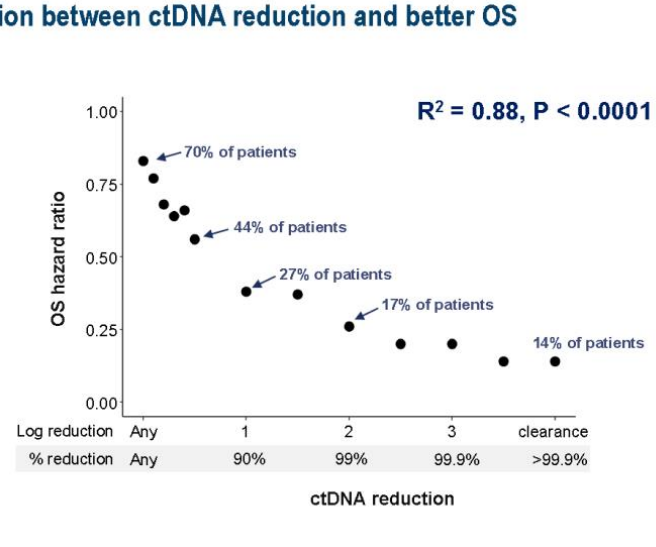
Shoushtari et al, #3600, ESMO 2021

NCT

ctDNA better than RECIST?



ctDNA reduction associated with less tumor growth

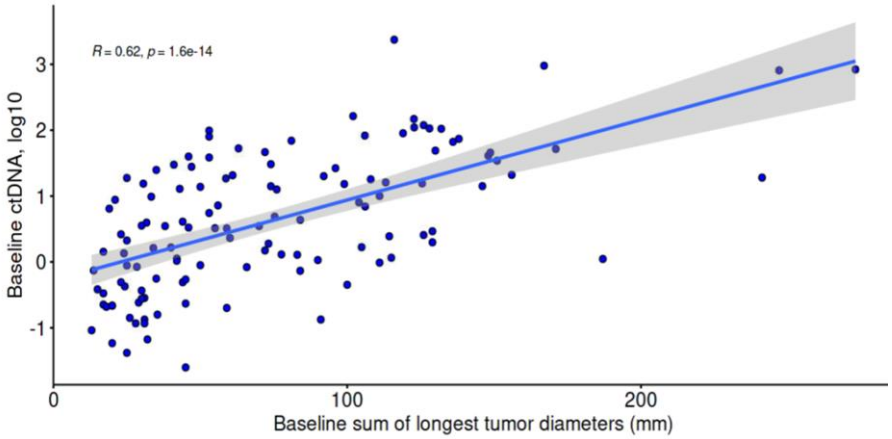


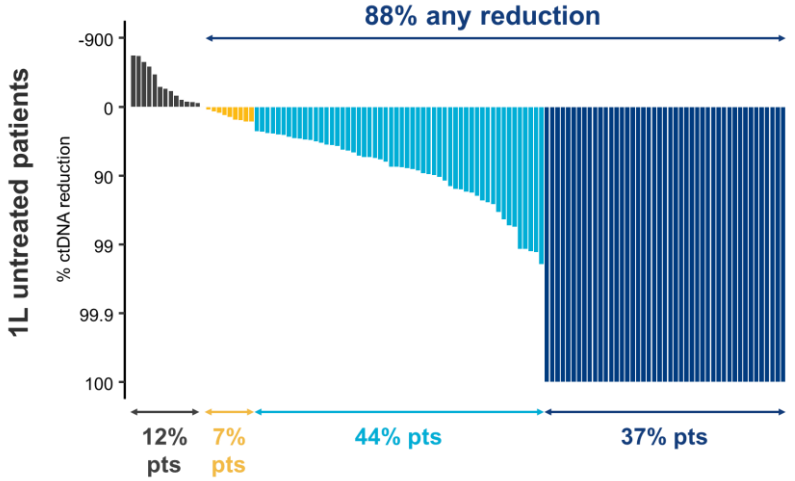
2021 ESMO congress

Shoushtari et al, #3600, ESMO 2021

NCT

Similar results from phase 3 firstline trial

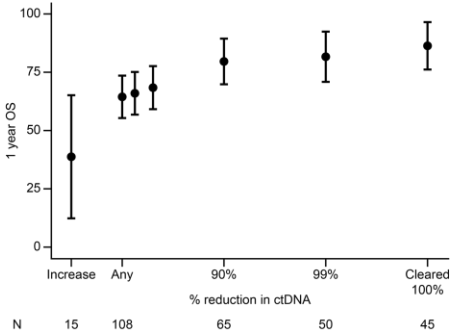


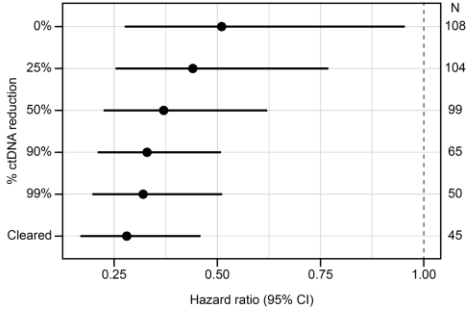


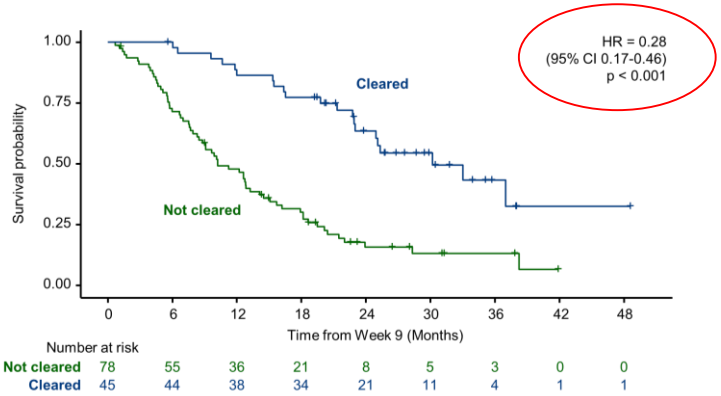
ctDNA levels at baseline correlated with tumor burden

Sullivan et al, #1035, AACR 2023

Clearance of ctDNA correlated with OS



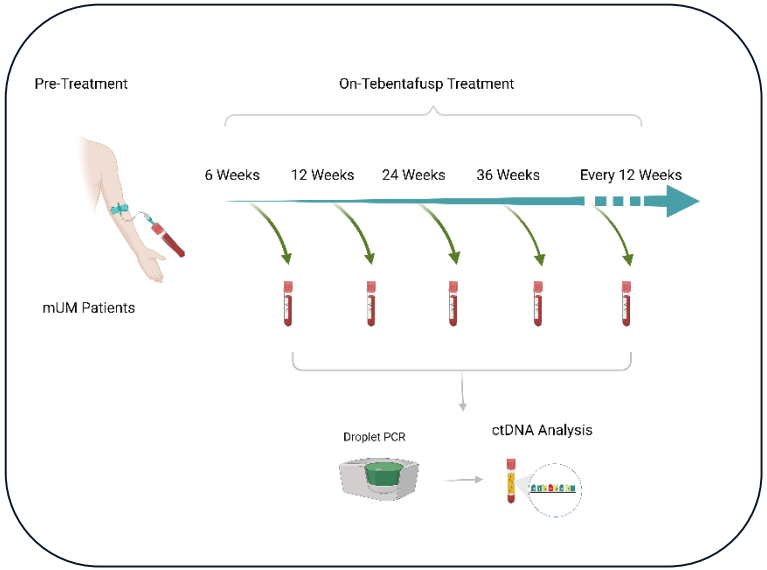




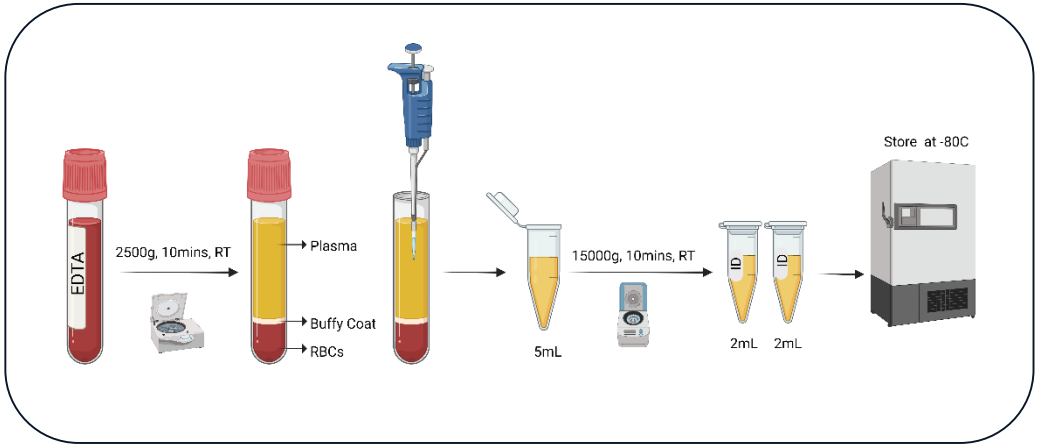
Sullivan et al, #1035, AACR 2023

Monitoring ctDNA in mUM Patients Under Tebentafusp

Sample Collection Time Points



Blood Processing for Plasma ctDNA Analysis



oncobit

NCT

Conclusions

- Liver-directed therapies without proven OS benefit
- Tebentafusp as first systemic agent with proven OS benefit
- Patients with low tumor burden (ECOG 0, normal LDH, M1a stage) benefit more
- However, also patients with high tumor burden benefit compared to IC
- Difficult clinical decision who not to treat with Tebe if HLA-0201+
- Chemosaturation to cut-down liver tumor burden?
- Difficult clinical decision who not to treat beyond progression (LDH? Liquid biopsy?)
- How to get liquid biopsy into clinical routine?

NCT

IMMUNOCORE

DECOG comittee
„Uveal melanoma“

Thank you!

Guy Ungerechts

Team Section DermatOncology

ctDNA and minimal residual disease in UM

Professor Paul Nathan

Consultant Medical Oncologist

Mount Vernon Cancer Centre

Honorary Professor of Oncology UCL

Honorary Consultant Medical Oncologist UCLH

UK

Mount Vernon Cancer Centre

CONFLICT OF INTEREST STATEMENT

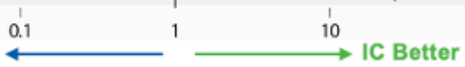
In the past two years I have received funding for advisory boards and/or speakers bureau from the following sources:

- AZ
- BMS
- Esai
- Ideaya
- Immunocore
- Ipsen
- Medicenna
- MSD
- Merck
- Novartis
- Pfizer
- 4SC

Mount Vernon Cancer Centre

IMCgp100-202 Pre-planned subset analysis

Subgroup	Tebentafusp No. of Patients	Tebentafusp No. (%) of Death	IC No. of Patients	IC No. (%) of Death	Hazard Ratio (95% CI)
Region					
North America	86	28 (33)	52	24 (46)	0.52 (0.30-0.91)
Non-North America	166	59 (36)	74	39 (53)	0.49 (0.33-0.74)
Investigator's Choice					
Pembrolizumab	199	65 (33)	103	49 (48)	0.51 (0.35-0.75)
Ipilimumab	40	16 (40)	16	7 (44)	0.89 (0.38-2.31)
Dacarbazine	13	6 (46)	7	7 (100)	0.29 (0.09-0.86)
Gender					
Male	128	48 (38)	62	35 (57)	0.48 (0.31-0.75)
Female	124	39 (32)	64	28 (44)	0.57 (0.35-0.94)
Age					
<65 yr	130	41 (32)	61	29 (48)	0.48 (0.30-0.79)
≥65 yr	122	46 (38)	65	34 (52)	0.58 (0.38-0.92)
ECOG status					
0	192	59 (31)	85	42 (49)	0.48 (0.33-0.72)
1	49	24 (49)	31	18 (58)	0.72 (0.39-1.36)
Baseline alkaline phosphatase					
≤ ULN	198	49 (25)	102	43 (42)	0.44 (0.29-0.66)
> ULN	53	37 (70)	24	20 (83)	0.60 (0.35-1.05)
Lactate dehydrogenase					
≤ ULN	162	28 (17)	80	29 (36)	0.35 (0.21-0.60)
> ULN	90	59 (66)	46	34 (74)	0.70 (0.46-1.09)
Largest metastatic lesion					
M1a (≤3.0 cm)	139	29 (21)	70	28 (40)	0.36 (0.21-0.61)
M1b (3.1-8.0 cm)	92	43 (47)	46	26 (57)	0.71 (0.44-1.17)
M1c (≥8.1 cm)	21	15 (71)	10	9 (90)	0.76 (0.34-1.82)
ITT population	**252**	**87 (35)**	**126**	**63 (50)**	**0.51 (0.37-0.71)**



Mount Vernon Cancer Centre

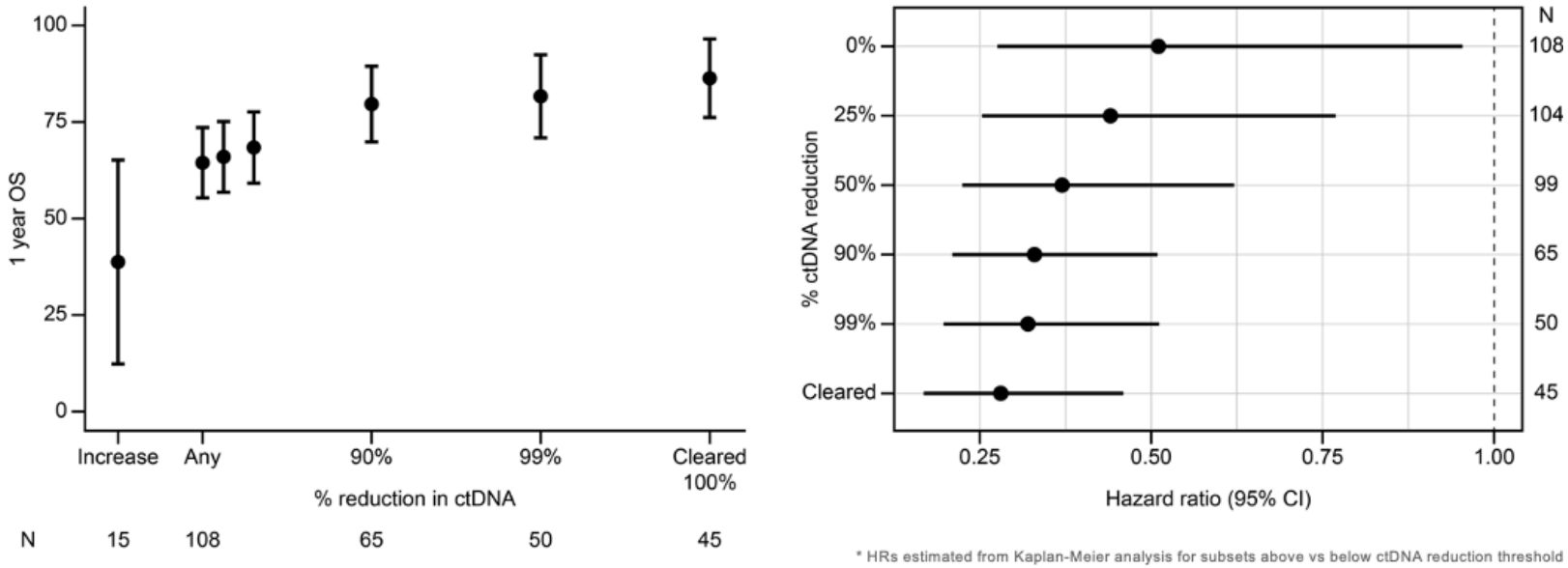
Nathan et al, N Engl J Med 2021;385:1196-206

Early ctDNA reduction is associated with better overall survival in the Phase 3 trial of tebentafusp in previously untreated metastatic uveal melanoma

Ryan Sullivan[1], Laura Collins[2], Manuel Rodrigues[3], Paul Nathan[4], Jessica C. Hassel[5], Reinhard Dummer[6], John M. Kirkwood[7], Piotr Rutkowski[8], Jean-Francois Baurain[9], Marcus O. Butler[10], Max Schlaak[11], Sebastian Ochsenreither[12], Shaad E. Abdullah[13], Chris Holland[13], Koustubh Ranade[13], Alexander N. Shoushtari[14]

[1]Massachusetts General Hospital, Boston, MA, USA; [2]Immunocore, Abingdon-on-Thames, UK; [3]Institut Curie, Paris, France; [4]Mount Vernon Cancer Centre – East and North Herts NHS Trust, Northwood, UK; [5]University Hospital Heidelberg, Heidelberg, Germany; [6]University of Zurich Hospital, Zürich, Switzerland; [7]University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [8]Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [9]Institut Roi Albert II Cliniques Universitaires St-Luc, Université catholique de Louvain, Brussels, Belgium; [10]Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada; [11]Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [12]Cancer Center, and Dept. of Hematology, Oncology and Tumor Immunology, Campus Benjamin Franklin, Charité - Universitätsmedizin Berlin; [13]Immunocore, Rockville, MD, USA; [14]Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Figure 4. Deeper reductions in ctDNA were associated with progressively longer OS



* HRs estimated from Kaplan-Meier analysis for subsets above vs below ctDNA reduction threshold

- Lower baseline ctDNA levels were associated with longer overall survival (< median levels HR 0.43 (95% C.I. 0.28-0.67))
- 79/202 (39%) patients with undetectable ctDNA at baseline had 1-year OS of 90%
- 123/202 (61%) patients with detectable ctDNA at baseline had 1-year OS of 62%
- 15/123 (12%) patients without any reduction in ctDNA on tebentafusp had 1-year OS of 43%

Mount Vernon Cancer Centre

Sullivan et al AACR 2023

TebeMRD

Full title: A Phase II Non-Randomized, Open-label, Multi-centre Study of the Safety and Efficacy of Tebentafusp in Melanoma with Molecular Relapsed Disease

Short title: Tebentafusp in MRD Melanoma

CI Prof Mark Middleton

Trial Management Group:

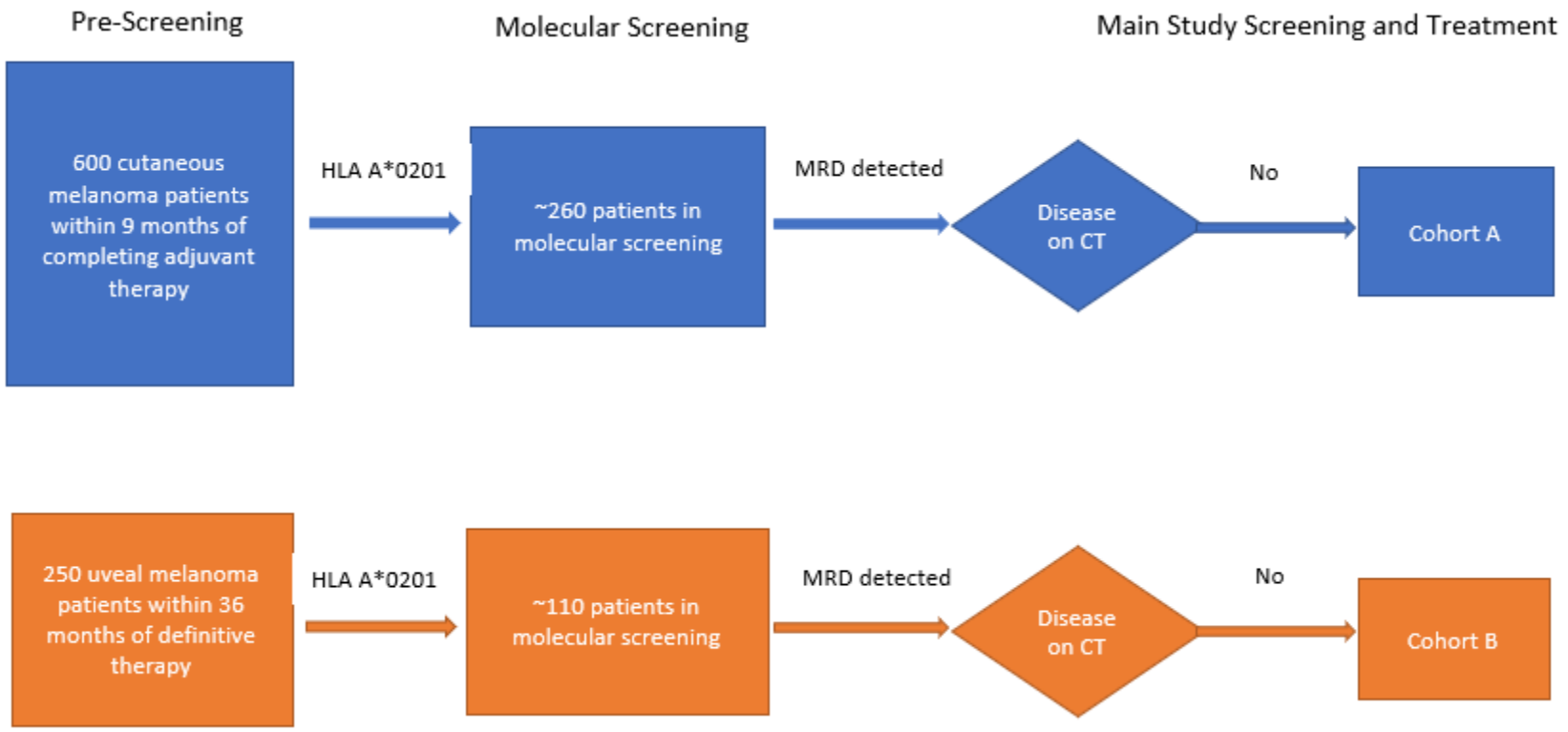
Prof. Paul Nathan, Dr. Joe Sacco

TebeMRD

- Cutaneous and Uveal Cohorts
- HLA A2.01
- Following treatment of high risk disease with curative intent
- 850 patients screened – 3/12ly ctDNA for 1 year
- 50 patients with detected ctDNA Rx with tebentafusp for up to 6/12

Mount Vernon Cancer Centre

Trial Design – TebeMRD



Mount Vernon Cancer Centre

TebeMRD

- Primary endpoint
  - Molecular response rate – defined as pMR & cMR
- Secondary endpoints
  - Efficacy – RFS at 12 months, duration of MR, OS
  - Safety & tolerability
  - Molecular relapse rate – baseline, 6/12 & 12/12

Mount Vernon Cancer Centre

Summary

- Strong evidence that fall in ctDNA correlates with OS benefit from tebentafusp. Likely superior to radiological endpoints.
- 40% of patients with radiological evidence of disease on 1st line phase III study were ctDNA –ve.
- TebeMRD investigates whether treatment with tebentafusp at the point of ctDNA molecularly defined relapse is associated with greater benefit

Mount Vernon Cancer Centre

Department of Dermatology and Venereology
University Skin Cancer Center

1st ELBS Clinical WG Uveal Melanoma Meeting 2023

Uveal Melanoma: Biology and genetics

Christoffer Gebhardt| 26th September 2023

Zertifiziertes Hautkrebszentrum

Fleur Hiege-Centrum für Hautkrebsforschung

Hubertus Wald Tumorzentrum
Universitäres Cancer Center Hamburg
Ein Kompetenznetzwerk des UKE

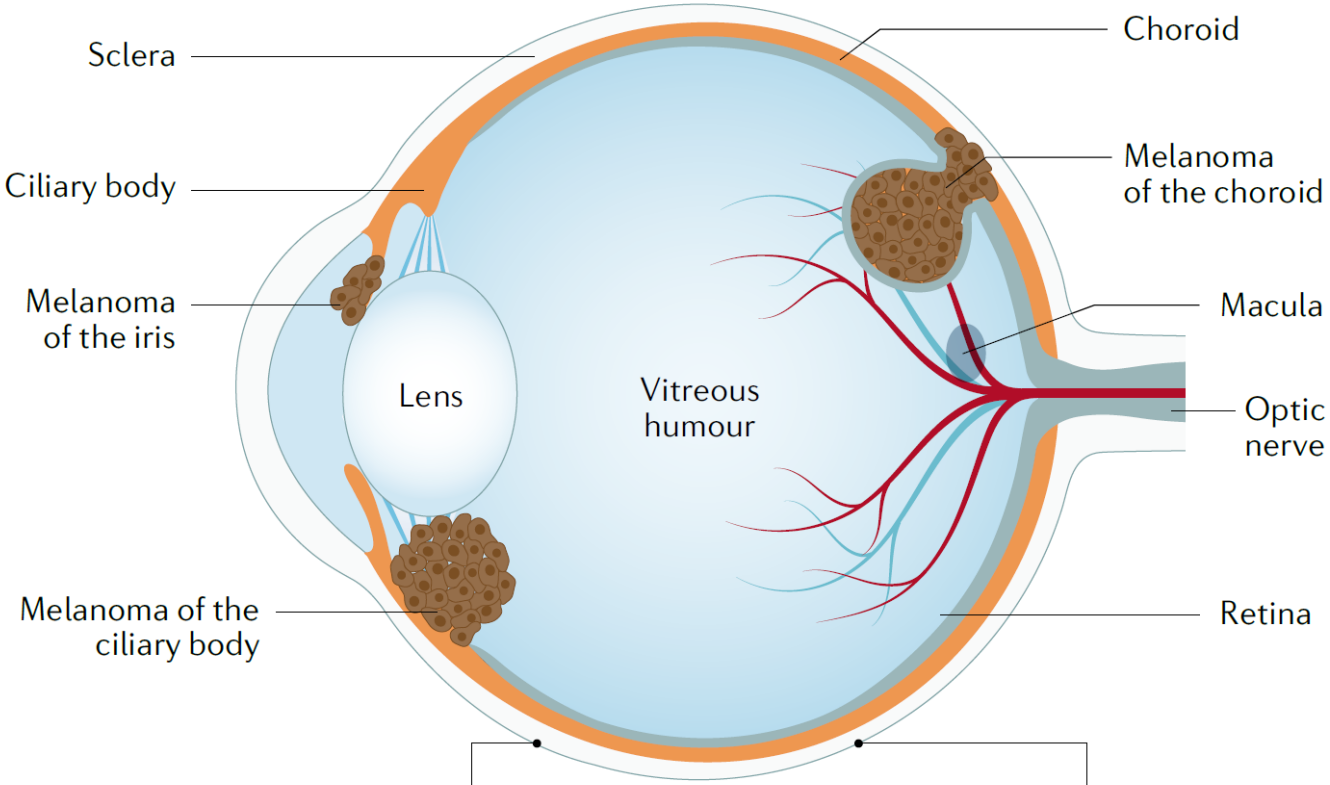
Conflict of Interest/Disclosures

Advisory Roles for, and Honoraria as well as Travel Expenses by the following Companies:

Almirall
Amgen
Beiersdorf
BioNTech
Bristol-Myers Squibb
GlaxoSmithKline
Immunocore
Janssen
MSD Sharp & Dohme
Novartis
Pierre-Fabre
Roche
Sanofi Genzyme
Sciomics
SUN Pharma
Sysmex/Inostix

Co-Founder of Dermagnostix and Dermagnostix R&D

Uveal Melanoma



Risk factors for developing UM

- Age 50–70 years
- Fair skin colour
- Many skin naevi
- Sensitivity to sunburn
- Northern European ancestry
- Light iris colour (blue or grey)
- Congenital ocular melanocytosis
- Melanocytoma
- Family member with cutaneous melanoma
- Family member with uveal melanoma
- Germline mutation in *BAP1*, *MLH1* or *PALB2*

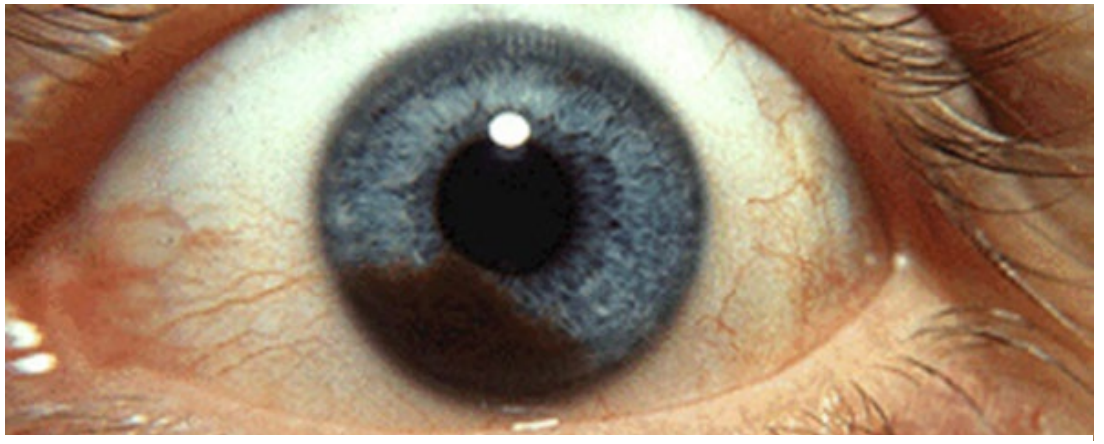
Symptoms of UM

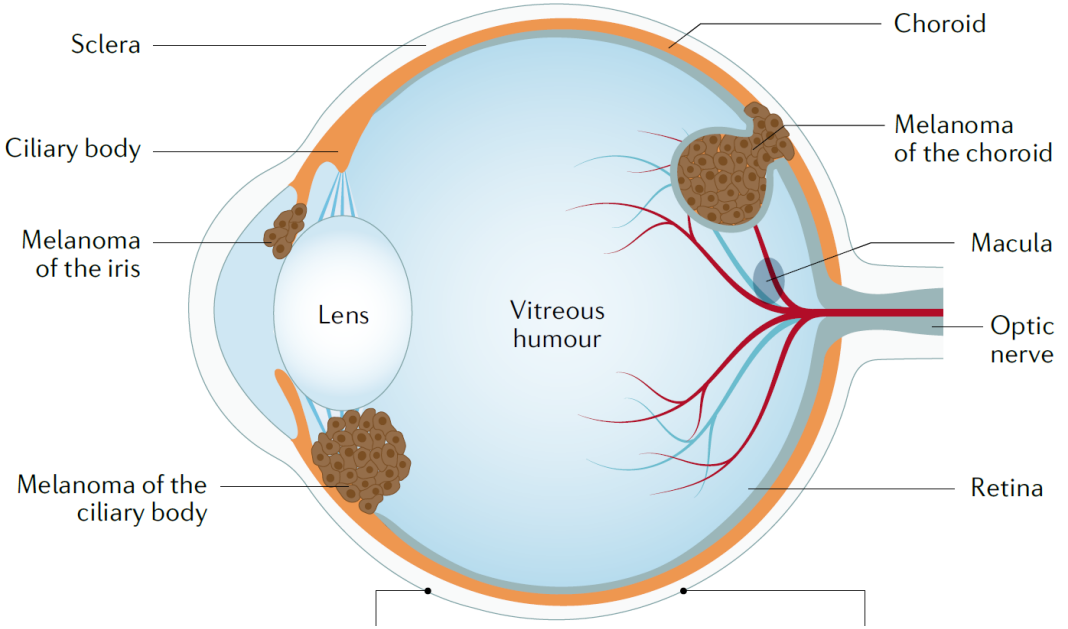
- Blurred or distorted vision
- Visual field loss
- Flashes of light
- Change in iris colour

Jager et al. 2020 Nature Reviews Disease Primers; Shain et al. 2019 Nat Genet

Uveal Melanoma

- UM arises in the uveal tract:[1,2]
  - Choroid (85–90%), ciliary body (5–8%) and iris (3–5%)
- The eye is an immune-privileged area, which affects how the immune system interacts with UM[3]
- **UM** can be considered an immunologically **'cold' tumor**, with a low response rate to treatment with ICIs[4]
  - Characterized by point mutations in the G-protein α-subunit coded for by the *GNAQ* and *GNA11* genes[5]
  - *GNAQ/GNA11* mutations have been found in 83–96% of patients[5-8]
- **CM**, in contrast, has many of the hallmarks of a **'hot' tumor** with a high mutational burden and response to ICIs[4]
  - CM has a different mutational profile versus UM, with mutations commonly seen in *BRAF, RAS* and *NF1*[9]

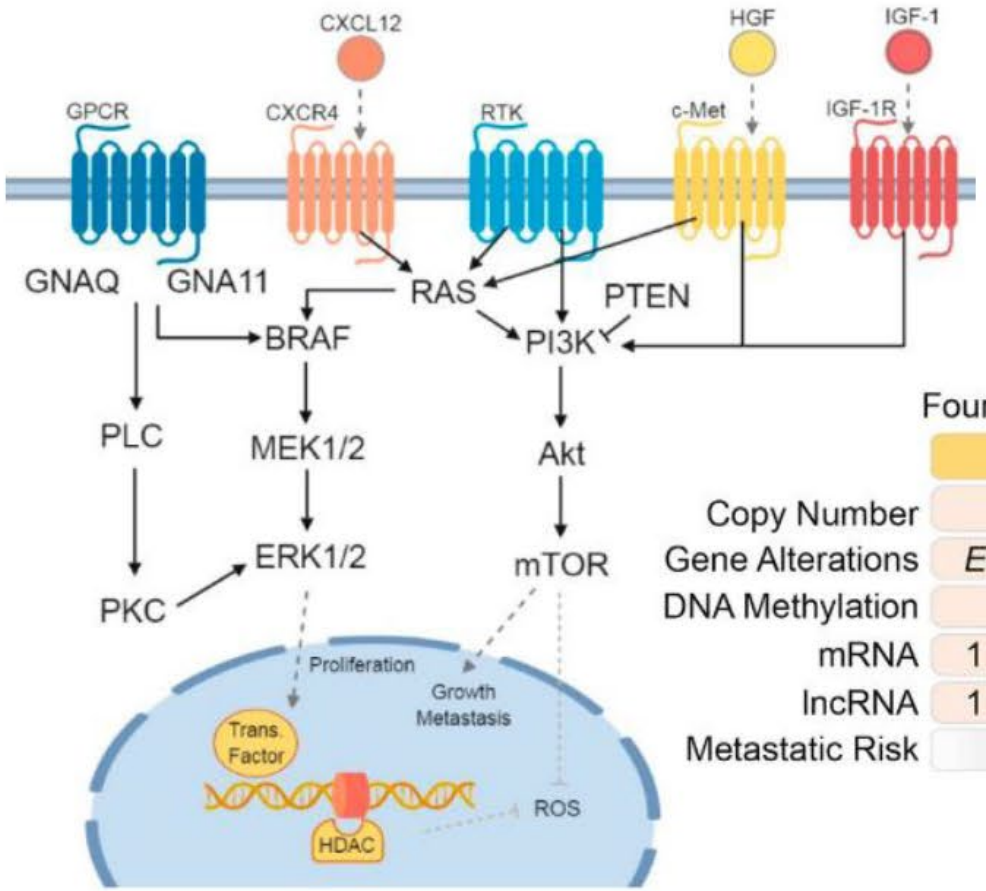


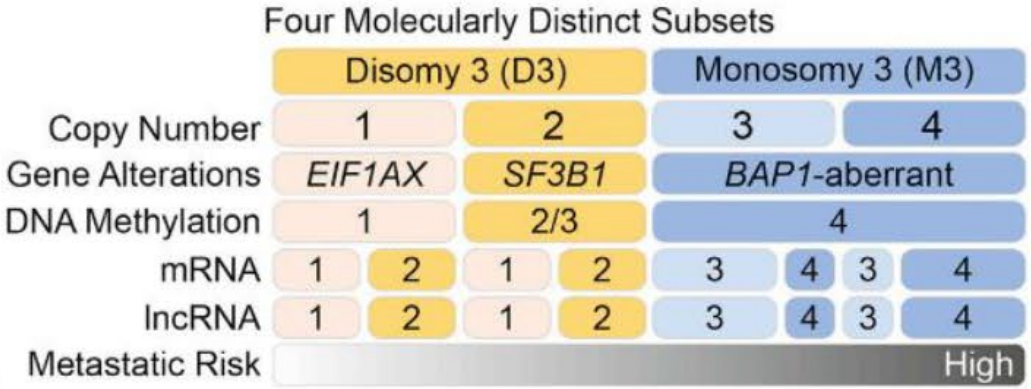


CM: cutaneous melanoma; ICI: immune checkpoint inhibitor; UM: uveal melanoma.

1. Nathan P, et al. *Eur J Cancer* 2015;51:2404–12; 2. Krantz BA, et al. *Clin Ophthalmol* 2017;11:279–89; 3. Niederkorn JY. *Front Immunol* 2012;3:148; 4. Damato BE, et al. *Cancers (Basel)* 2019;11:971; 5. Field MG, et al. *Clin Cancer Res* 2016;22:1234–42; 6. Van Raamsdonk CD, et al. *N Engl J Med* 2010;363:2191–9; 7. Piperno-Neumann S, et al. *J Clin Oncol* 2014;32(Suppl.): Abstract 9043; 8. Griewank KG, et al. *Mod Pathol* 2014;27:175–83; 9. Cancer Genome Atlas Network. *Cell* 2015;161:1681–96; 10. Kumar PJ, Clark ML. *Clinical Medicine*. Elsevier, 2012.

Uveal Melanoma has a different tumor biology than cutaneous melanoma





Van der Kooji et al, Cancers 2019; Robertson et al, Cancer Cell 2017

Uveal Melanoma has a different tumor biology than cutaneous melanoma

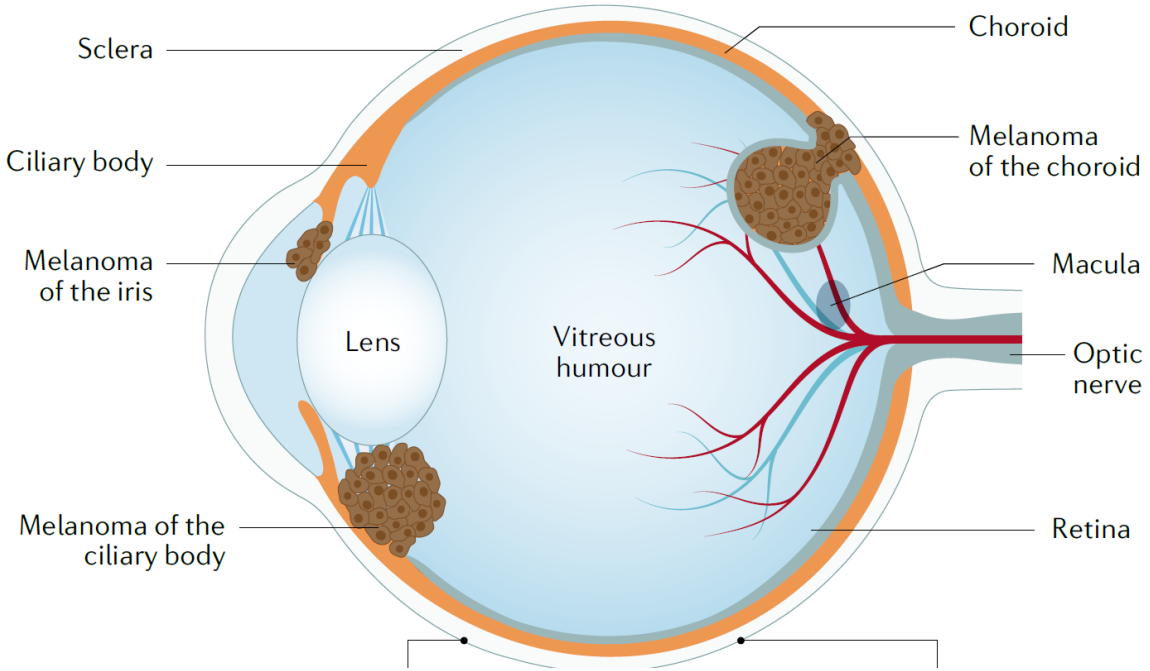
	UM	CM
Incidence	8,000 new cases worldwide/year[1]	230,000 new cases worldwide/year[1]
UV radiation-driven mutation	None[1]	Yes[1]
Familial inheritance	1–2%[1]	~10%[1]
Metastatic pattern	• Up to 50% develop metastases following successful treatment of the primary tumor[1,2] • Predominantly liver[1,4] • Hematogenous dissemination[1,4]	• 15.5% develop metastases[3] • Most common sites (in order): lungs, liver, bones, brain[1,3,4] • Lymphatic and hematogenous spread[1,4]
Immunogenicity	• Similar extent of immune cell infiltration in metastatic sites[5] • Higher ratio in UM of: exhausted CD8+ T cells to cytotoxic T cells, to CD8+ T cells, and to Th1 cells[5] • Lower infiltration of PD-1-positive lymphocytes in UM metastatic sites[6] • Lower levels of PD-L1 in UM metastatic sites[5,6]	
Genetic burden	Low genetic mutational burden[1,4]	High genetic mutational burden[1,4]
Associated genes	Distribution:[4,7–9] BRAF: 0% KIT: 0% GNAQ: ~63% GNA11: ~33% PLCB4:~2.5% CYSLTR2:~4% BAP1: ~60% SF3B1 ~25% EIF1AX: ~15%	Distribution:[4,7,10,11] *BRAF*: ~36% *KIT*: ~1.7% *GNAQ*: ~1.4% *GNA11*: ~1.3% *NRAS*: ~12% *NF1*: ~14% *CDKN2A*
Prognosis	Patients with metastases (mostly liver)[12] have: • Median survival of 3–30 months[12-15] • 1-year survival rate of ~29–83%[12,15] • 5-year survival rate of <20%[14]	Patients with advanced/metastatic CM have: • Median survival of 4–>60 months[16-20] • 1-year survival rate of 36–81%[16,21,22] • 5-year survival rate of 10–70%[17-20,22]
Responsiveness to immunotherapy	Low response rates to immunotherapy[1,4,13,23]	Higher response to ICIs (anti-CTLA4, anti-PD-1, anti-PD-L1) than UM, especially to ICI combination (up to 58% ORR)[1,24]
Targeted therapies	None[1,25]	Anti-BRAF, anti-MEK[1]

CTLA4: cytotoxic T-lymphocyte antigen 4; ICIs, immune checkpoint inhibitors; ORR, overall response rate; PD-1: programmed death-1; PD-L1: programmed death-ligand 1; UV: ultraviolet.

1. Pandiani C, et al. *Genes Dev* 2017;31:724–43; 2. Dogrusöz M, Jager MJ. *Asia-Pac J Ophthalmol* 2017;6:186–96; 3. Zbytek B, et al. *Expert Rev Dermatol* 2008;3:569–85; 4. Rodrigues M, et al. *Cancers (Basel)* 2019;11(7):1032; 5. Hoefsmit EP, et al. *J Immunother Cancer* 2020;8:e001501; 6. Qin Y, et al. *Oncoimmunol* 2017;6:e1321187; 7. Beadling C, et al. Clin *Cancer Res* 2008;14:6821–8; 8. Piperno-Neumann S, et al. *J Clin Oncol* 2014;32(Suppl.): Abstract 9043; 9. Robertson AG, et al. *Cancer Cell* 2018;33:151; 10. Akbani R, et al. *Cell* 2015;161:1681–96; 10. Shaughnessy M, et al. *J Transl Genet Genom* 2018;2:14; 12. Khoja L, et al. *Ann Oncol* 2019;30:1370–80; 13. Schank TE et al. *Cancers (Basel)* 2019;11:1048; 14. NCCN Guidelines, Version 3.2020 (Jan 15 2021), Uveal Melanoma. Available at: https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/uveal.pdf. Last accessed February 2021; 15. Rantala ES, et al. *Melanoma Res* 2019;29:561–8; 16. Larkin J, et al. *J Clin Oncol* 2018;36:383–90; 17. Larkin J, et al. *N Engl J Med* 2019;381:1535–46; 18. Robert C, et al. *Lancet Oncol* 2019;20:1239–51; 19. Robert C, et al. *J Clin Oncol* 2020;38:3937–46; 20. NCCN guidelines Version 2.2021 (Feb 19 2021), Melanoma: Cutaneous. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf. Last accessed April 2021 ; 21. Lebbé C, et al. *J Clin Oncol* 2019;37:867–76; 22. Wang Y, et al. *Medicine* 2021;100:4; 23. Pelster MS, et al. *J Clin Oncol* 2021;39:599–607; 24. Leonardi GC, et al. *Int J Oncol* 2020;57:609-18; 25. Croce M et al. *Cancers (Basel)* 2019;11:846.

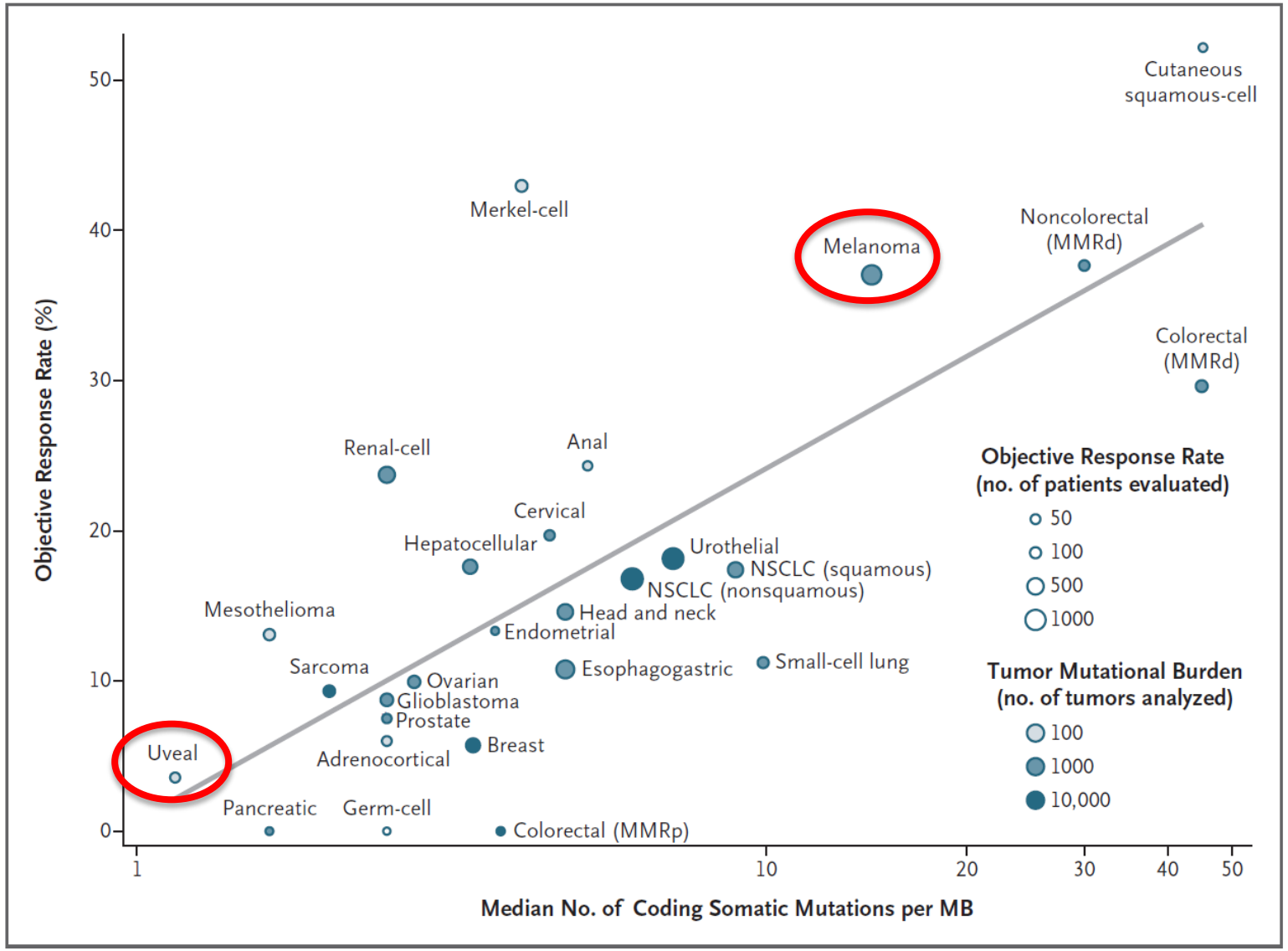
Uveal Melanoma: Treatment resistance in mUM

- **(Liver-)metastasis Resection**
- **Liver-directed therapy** (chemosaturation/ -perfusion, SIRT, TACE)**:** limited RCT data, efficacy difficult to interpret
- **Targted therapy:** no druggable targets, low efficacy (sorafenib, selumetinib)
- **Systemic chemotherapy:** low efficacy (mono-/polychemotherapy)
- **Systemic Immunotherapy:** ORR up to 17%, 12mo OS: 52% (NIVO+IPI), PD-1 shows similar efficacy



Jager et al., Nat Dis Primer 2020
Piulats, et al. *J Clin Oncol* 2021
Rantala, et al. *Melanoma Res* 2019
Khoja, et al. *Ann Oncol* 2019

Tumor mutational burden predicts response to ICB



UM has one of the lowest TMB of all tumor types, which likely explains the poor observed activity of CPIs in UM relative to their benefit in CM

Yarchoan, 2017 New Engl J Med

Molecular prognostic testing to predict metastatic disease and stratify risk

- Identifying a high-risk mUM patient means they can be more aggressively monitored and treated[1–3]
- Significant heterogeneity exists in metastatic risk profiling for melanoma[1–3]
- Clinical, histopathologic and genetic variables can be assessed, often in combination.[3,4] Most common approaches include:

PRAME: An antigen recognized by cytolytic T lymphocytes and an independent prognostic UM biomarker. PRAME mRNA expression analysis identifies increased metastatic risk in patients with Stage I or disomy 3 tumors[1,5]

DecisionDx™ – Melanoma (Castle Biosciences): A genetic expression profiling tool to analyze 31 genes within Stage I or II melanoma tumors to assess metastatic risk[2,5]

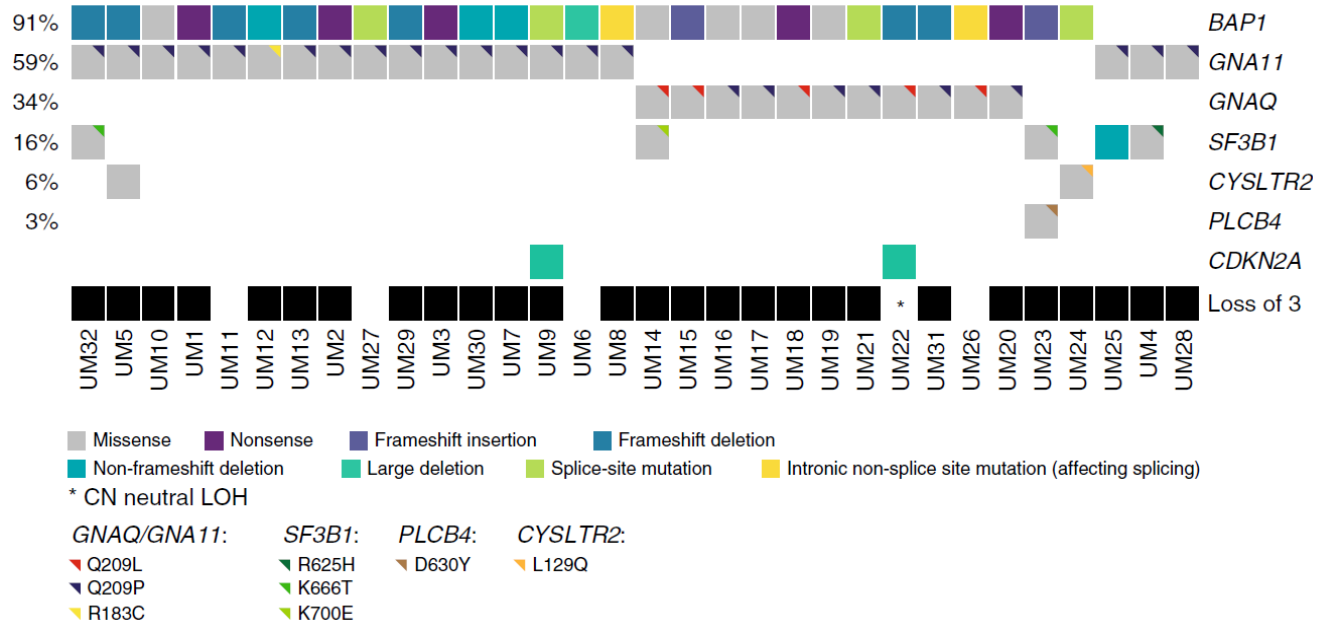
LUMPO system (Liverpool Ocular Oncology Centre): Combines clinical, histologic and genetic data to enhance reliability of prediction of metastatic disease, while minimizing bias from missing data and competing risks. This system also estimates survival time[3]

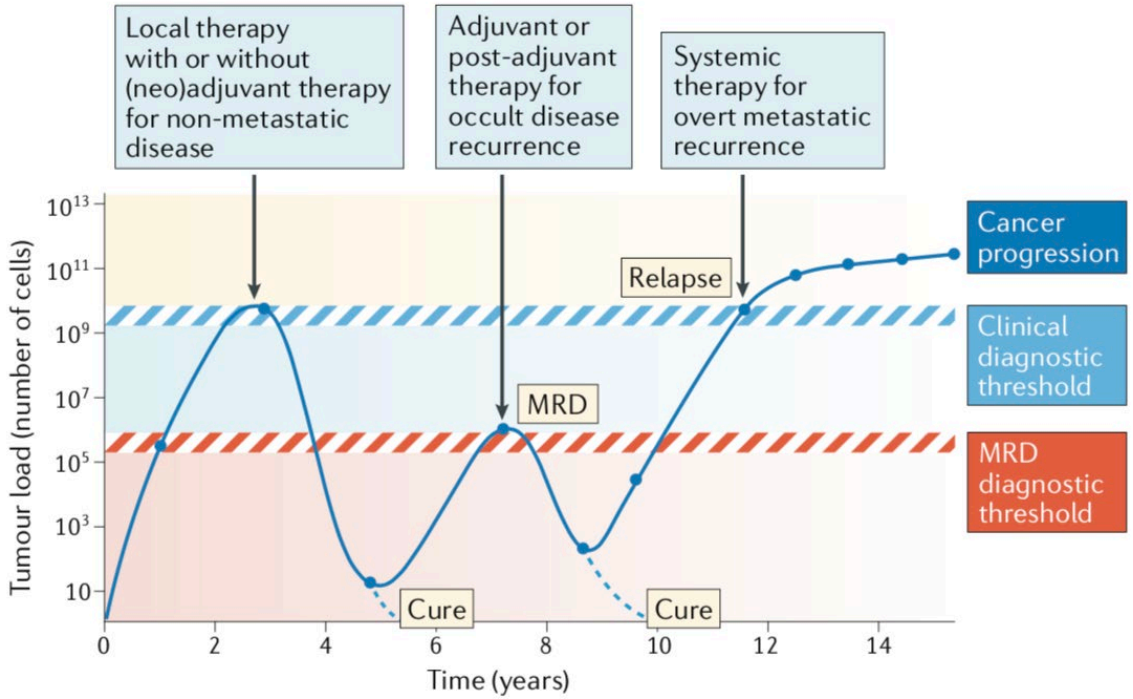
LUMPO: Liverpool Uveal Melanoma Prognosticator Online; PRAME: preferentially expressed antigen in melanoma; mRNA: messenger ribonucleic acid; mUM: metastatic uveal melanoma.

1. Field MG, et al. *Cancer Res* 2016;22:1234–42; 2. Cook RW, et al. *Diagn Pathol* 2018;13:13; 3. DeParis SW, et al. *Invest Ophthalmol Vis Sci* 2016;57:6116–22; 4. Carvajal RD, et al. *Br J Ophthalmol* 2017;101:38–44; 5. Krantz BA, et al. *Clin Ophthalmol* 2017;11:279–89.

Therapy monitoring using Liquid Biopsy (ctDNA) in Uveal Melanoma

Driver mutations in UM



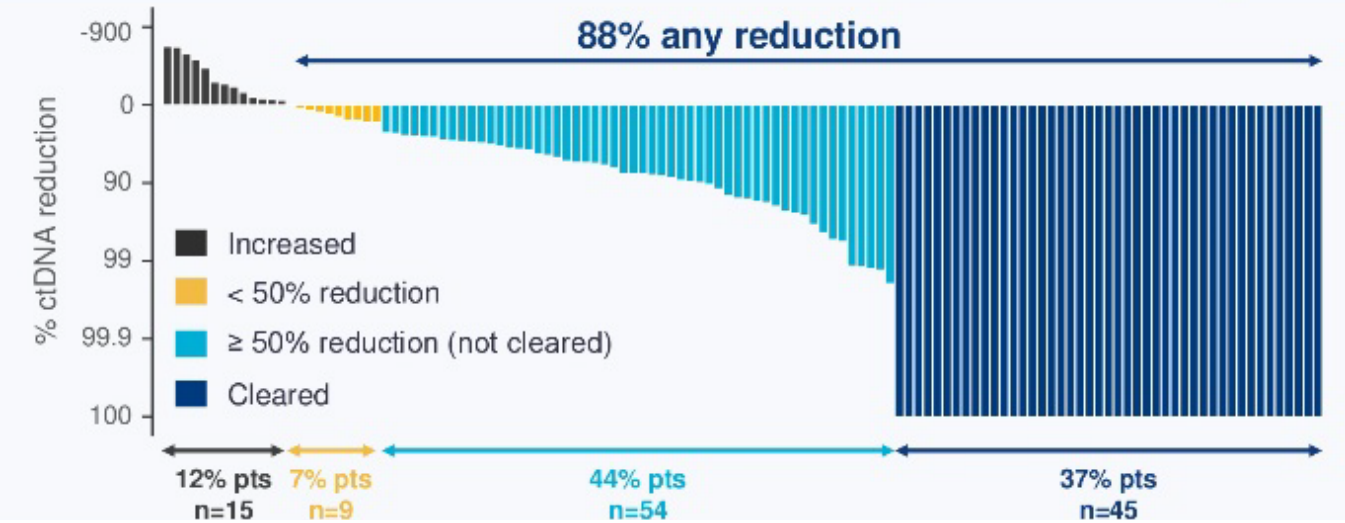


Karlsson et al. Nature Comm. 2020

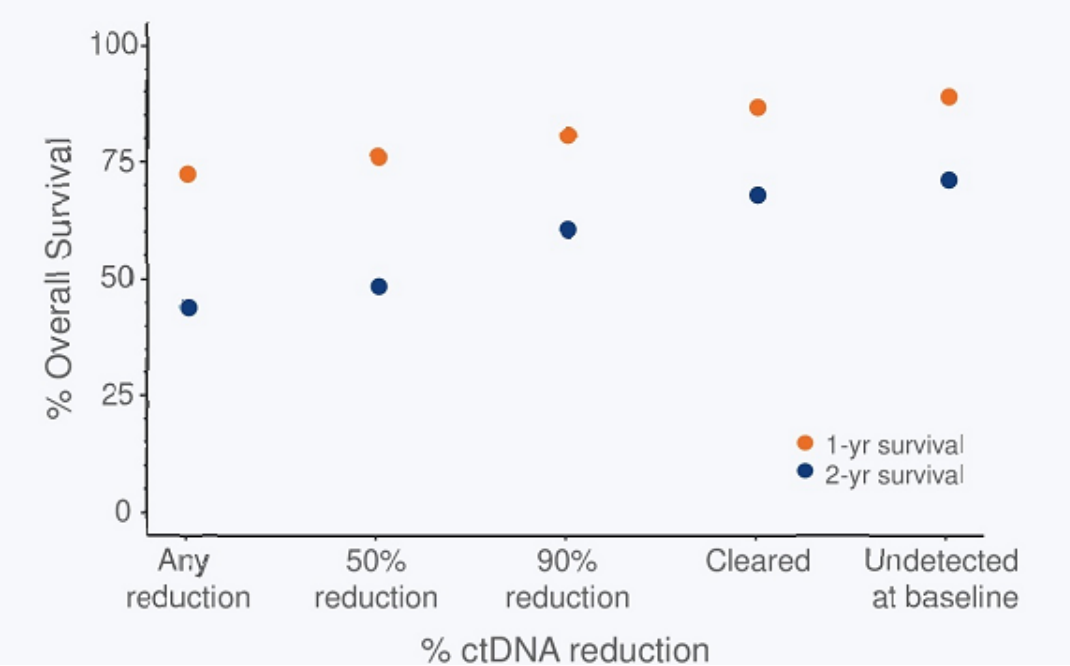
Pantel & Alix-Panabières Nat Rev Clin Oncol 2019

ctDNA dynamics as predictive marker for OS under tebentafusp

ctDNA reduction (baseline – week 9) in 88% of all tebentafusp-treated patients

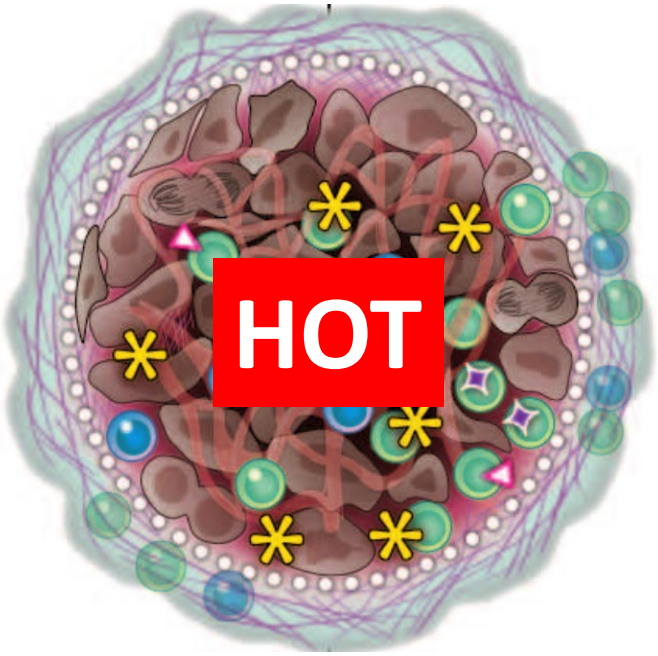


Deep ctDNA reduction (baseline – week 9) correlates with prolonged OS

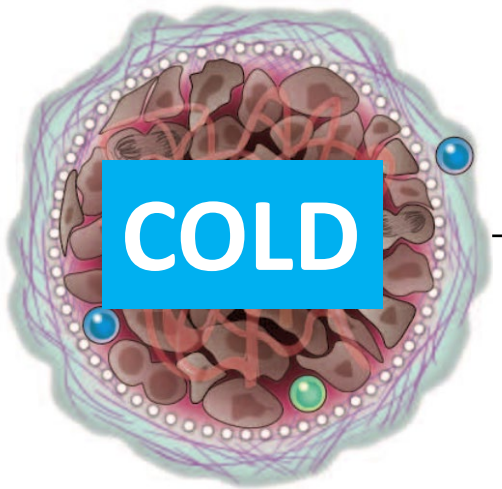


Feng et al, ASCO 2023 #9589

Overcoming resistance to immuno-therapy



Immunogenic Tumor

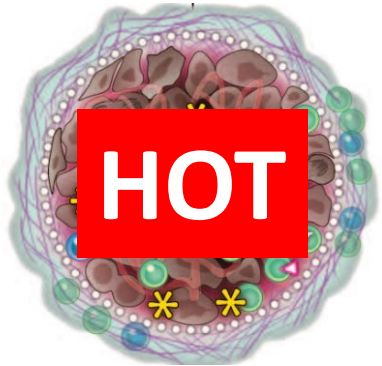


Non-immunogenic Tumor

combination

sequence

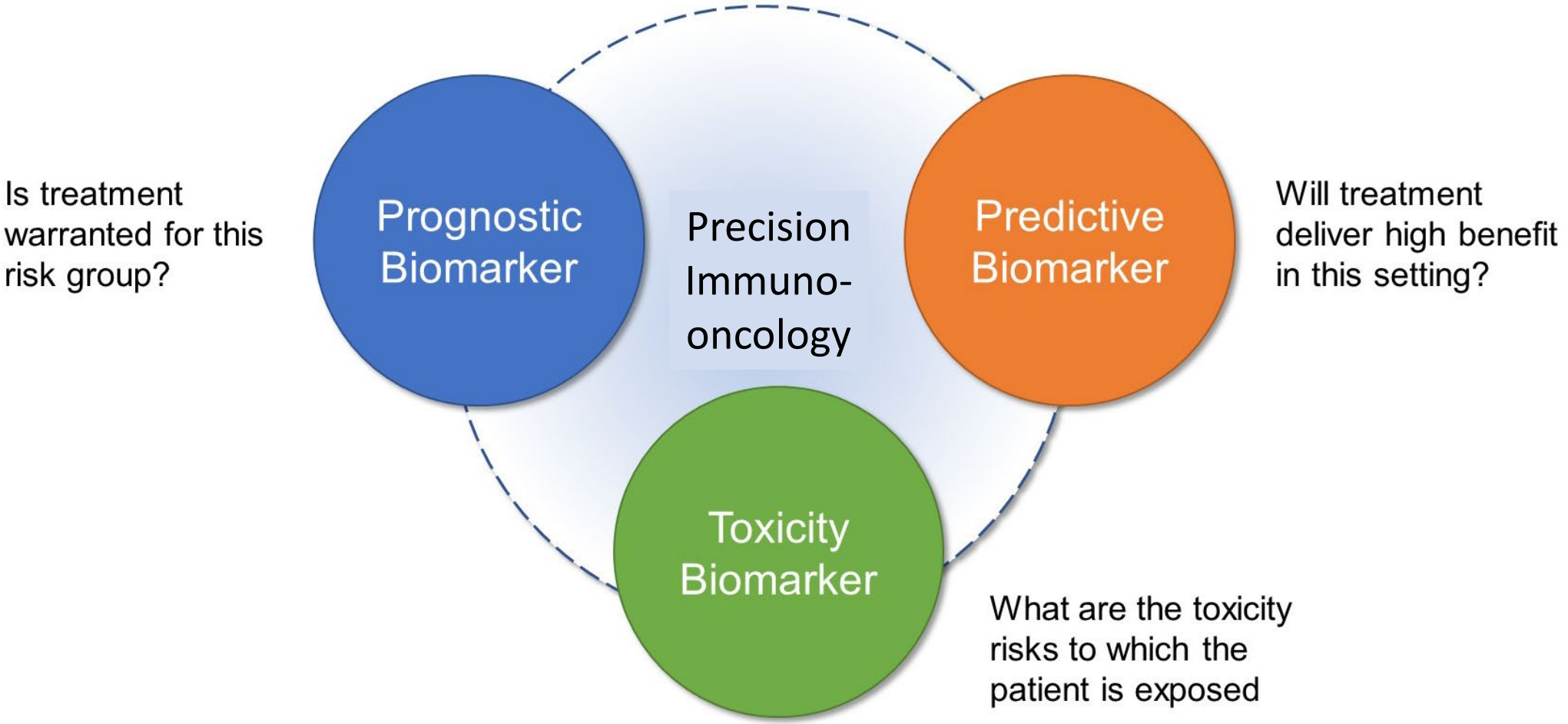
- Radiation
- Targeted Tx
- Chemo Tx
- Checkpoint-Inhibitors
- Bispecific Antibodies
- Cellular Therapies
- Immunomodulation Tx
- Intratumoral Tx
- Tumor Vaccination



Immuno-therapy

Modified from Sharma & Allison, Science 2015

Towards precision Immuno-oncology in mUM



Trial designs using ctDNA levels for therapeutic decisions

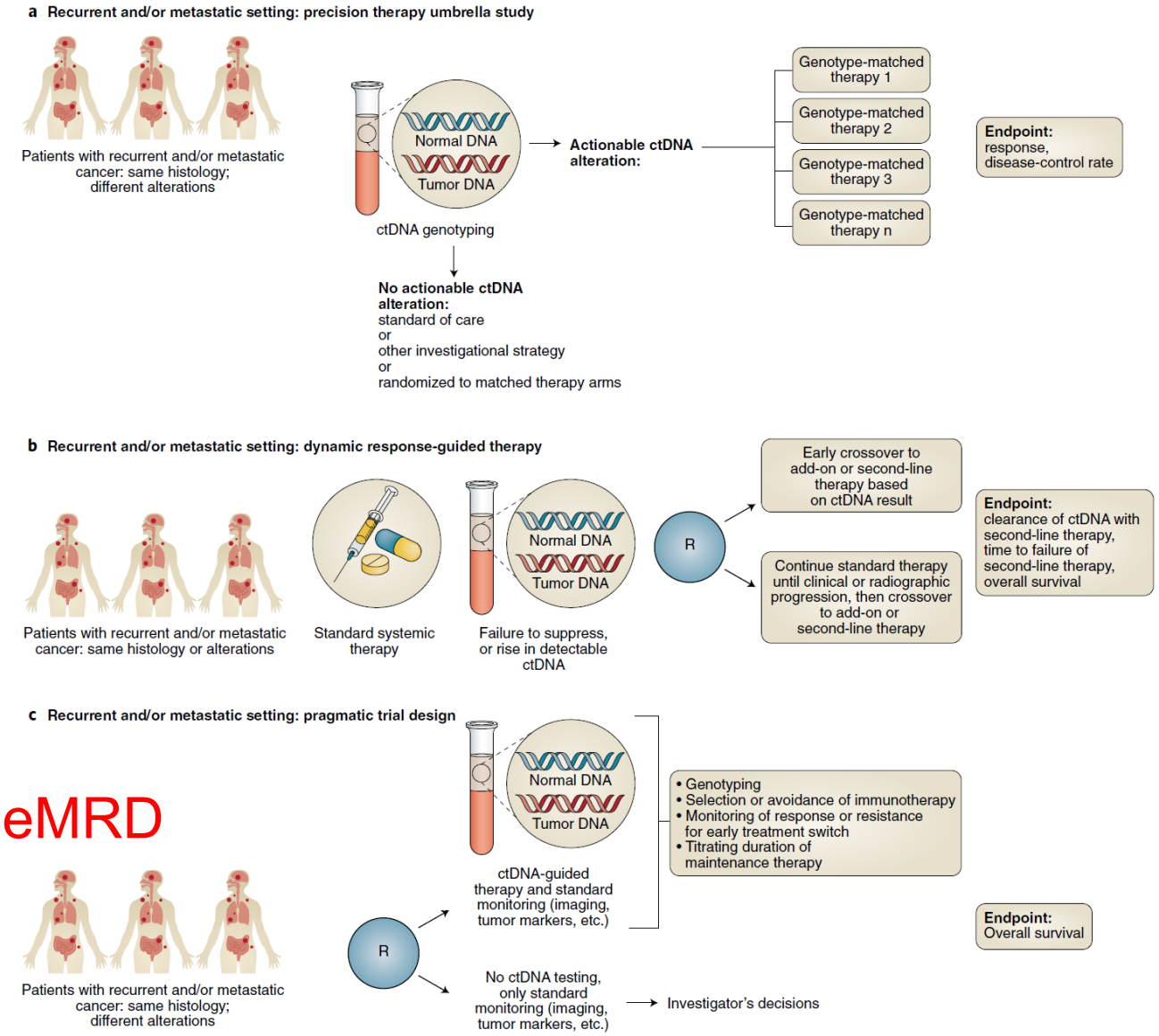
Prognosis
Identifying patients at risk of metastasis

Early Detection of Metastasis/MRD
Follow Up

Therapy selection
Prediction of resistance
1L: Tebe OR IPI/NIVO

Therapy monitoring
Treatment beyond progression?
Identifying resistance

TebeMRD



Cescon et al., 2020 Nature Cancer

Department of Dermatology and Venereology
University Skin Cancer Center

Thank you for your attention!

Fleur Hiege Centrum
für Hautkrebsforschung

Zertifiziertes Hautkrebszentrum

ctDNA @Curie

Manuel Rodrigues, MD PhD
Shufang Renault, PhD
Marc-Henri Stern, MD PhD

Institut Curie
Paris

- ~320 new primary tumor patients
- ~70 new metastatic patients per year
- 108 patients treated with tebentafusp (early access)

ENSEMBLE, PRENONS LE
CANCER DE VITESSE

institut Curie

Proof of concept study: ctDNA & liver surgery (« ctDNA R0 » cohort)

53 patients
2-y trial
longitudinal ctDNA assessment for monitoring patients undergoing liver surgery.

ddPCR

GNAQ Q209P / Q209L / Q209R
GNA11 Q209L
GNAQ R183Q
GNA11 R183C

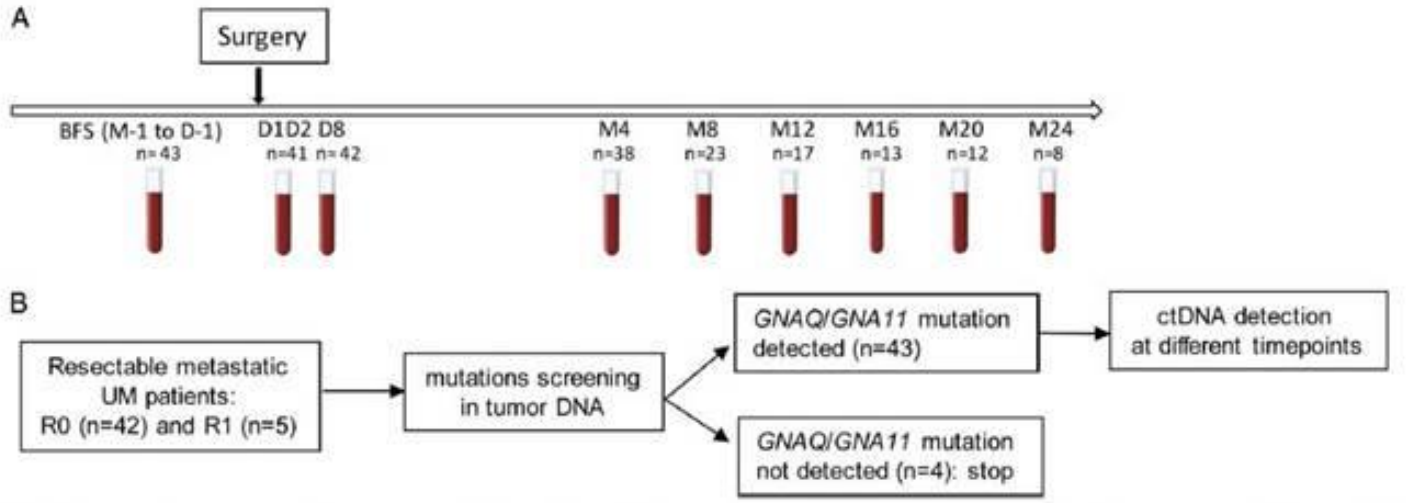
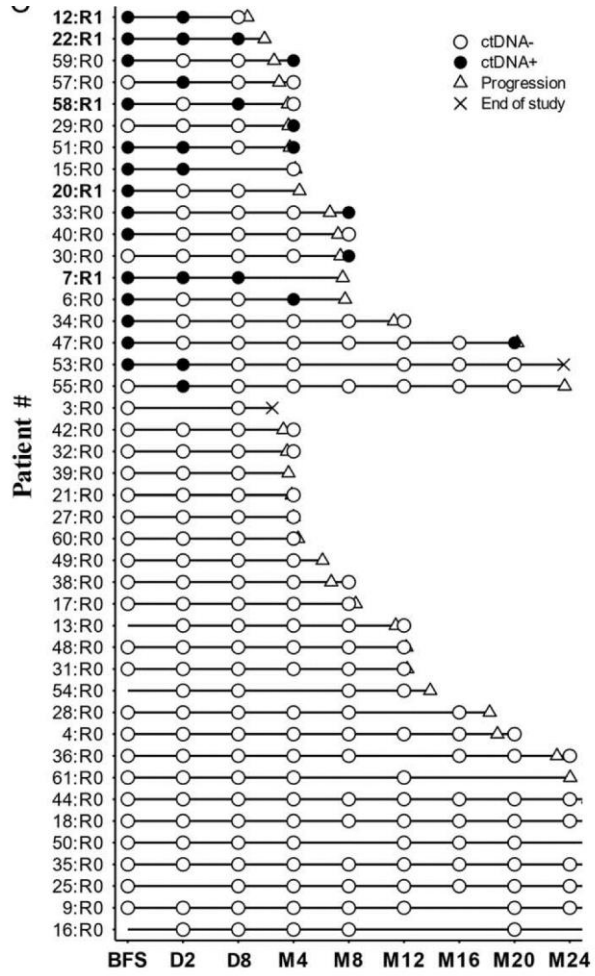


FIGURE 1. Blood sampling (A) and workflow of the study (B). BFS indicates before surgery; R0, microscopically complete resection; R1, microscopically incomplete resection.

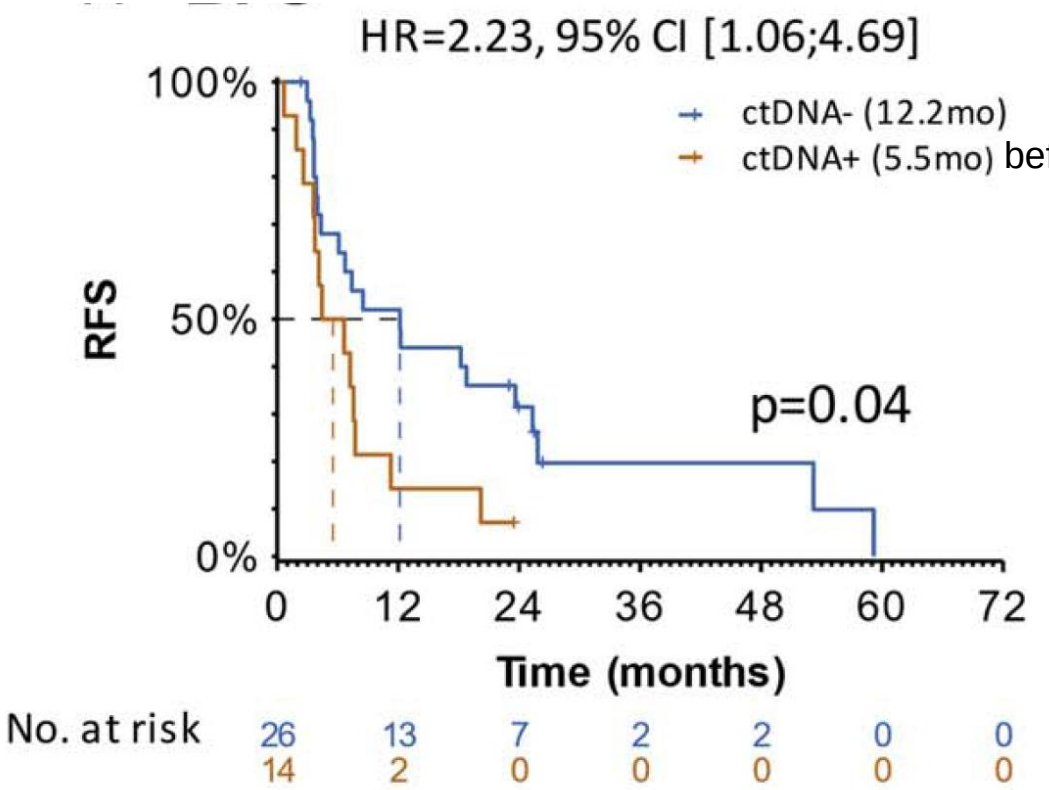


Pascale Mariani
Shufang Renault
Aurore Rampanou
Marc-Henri Stern

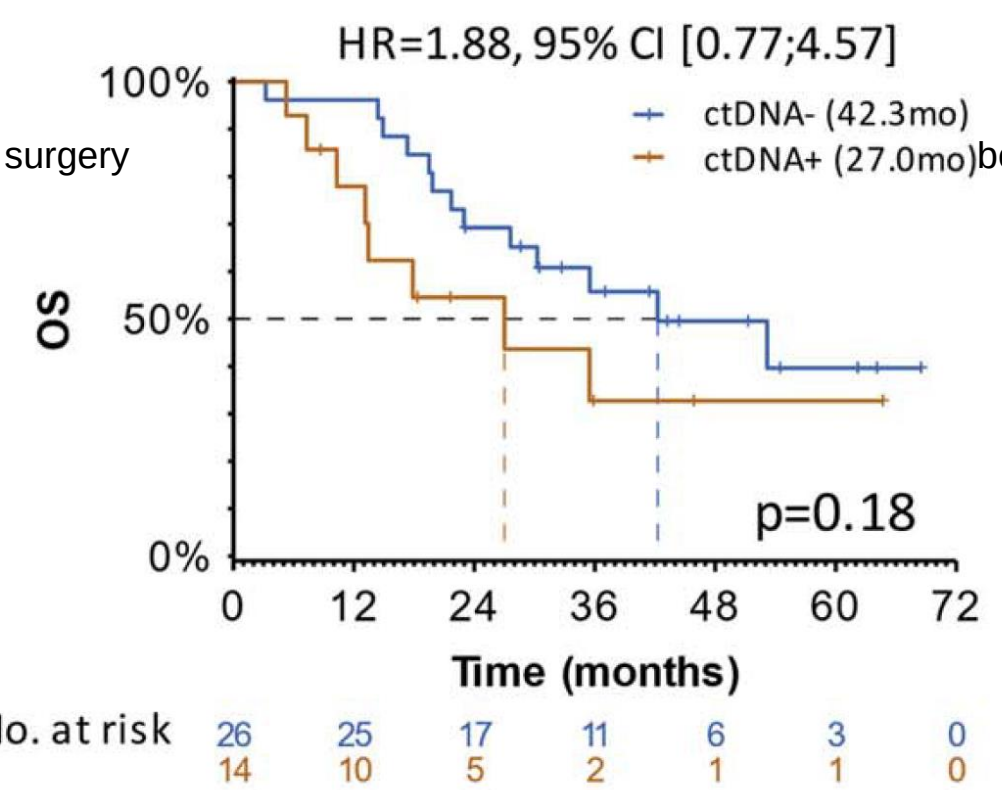
Mariani et al. Annals of Surgery 2023

institutCurie

Proof of concept study: ctDNA & liver surgery (« ctDNA R0 » cohort)



before surgery



before surgery

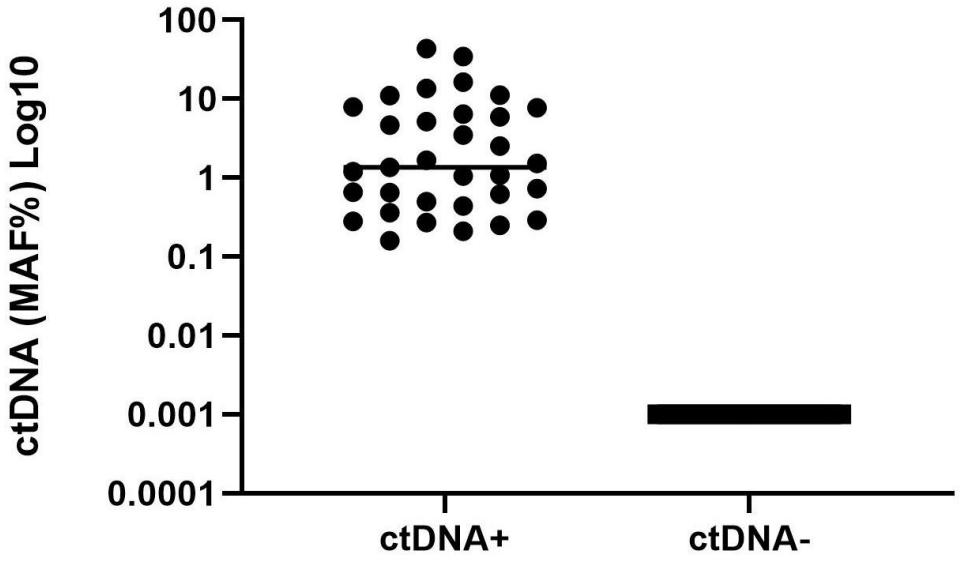
→ Now in routine to select patients for liver surgery

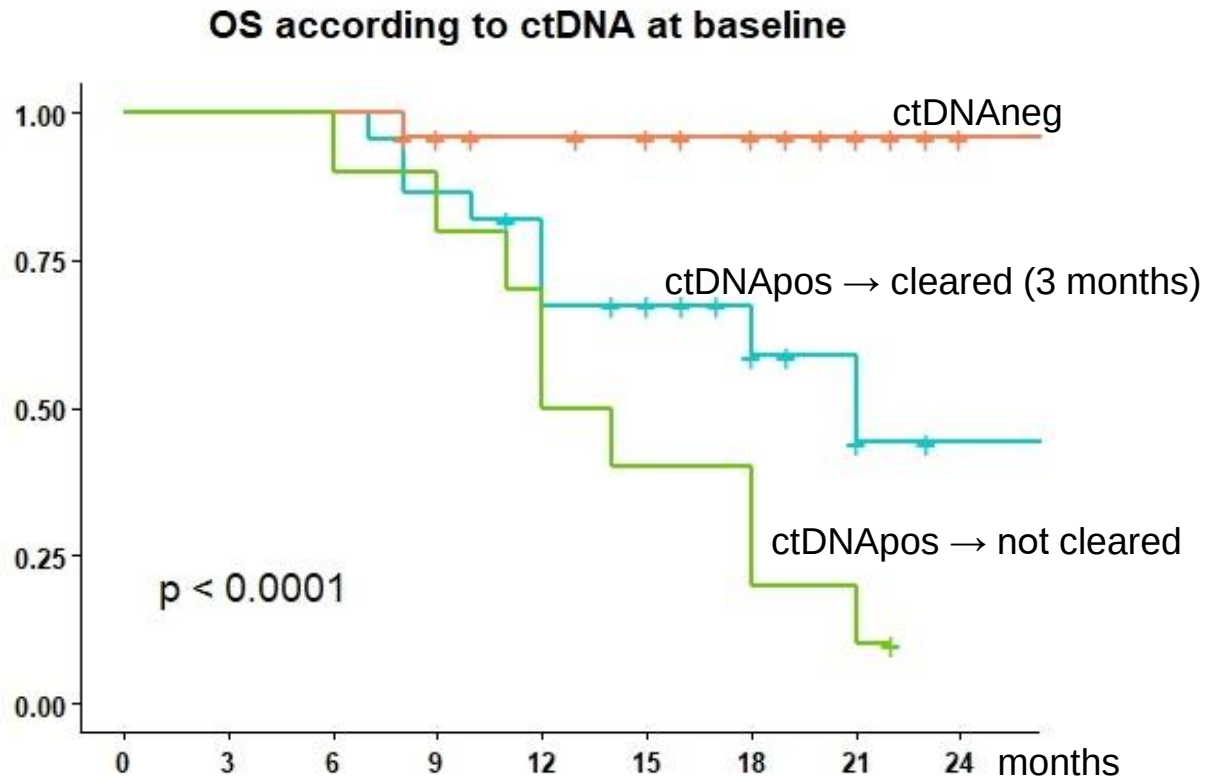
Mariani et al. Annals of Surgery 2023

institutCurie

Proof of concept study: ctDNA & tebentafusp (« ALCINA » cohort)

63 pts treated with tebentafusphad mUM with *GNAQ/GNA11* mutations
“real-life” study → smaller metastases (not RECIST)
Pts with detectable **ctDNA at baseline = 62% pts**



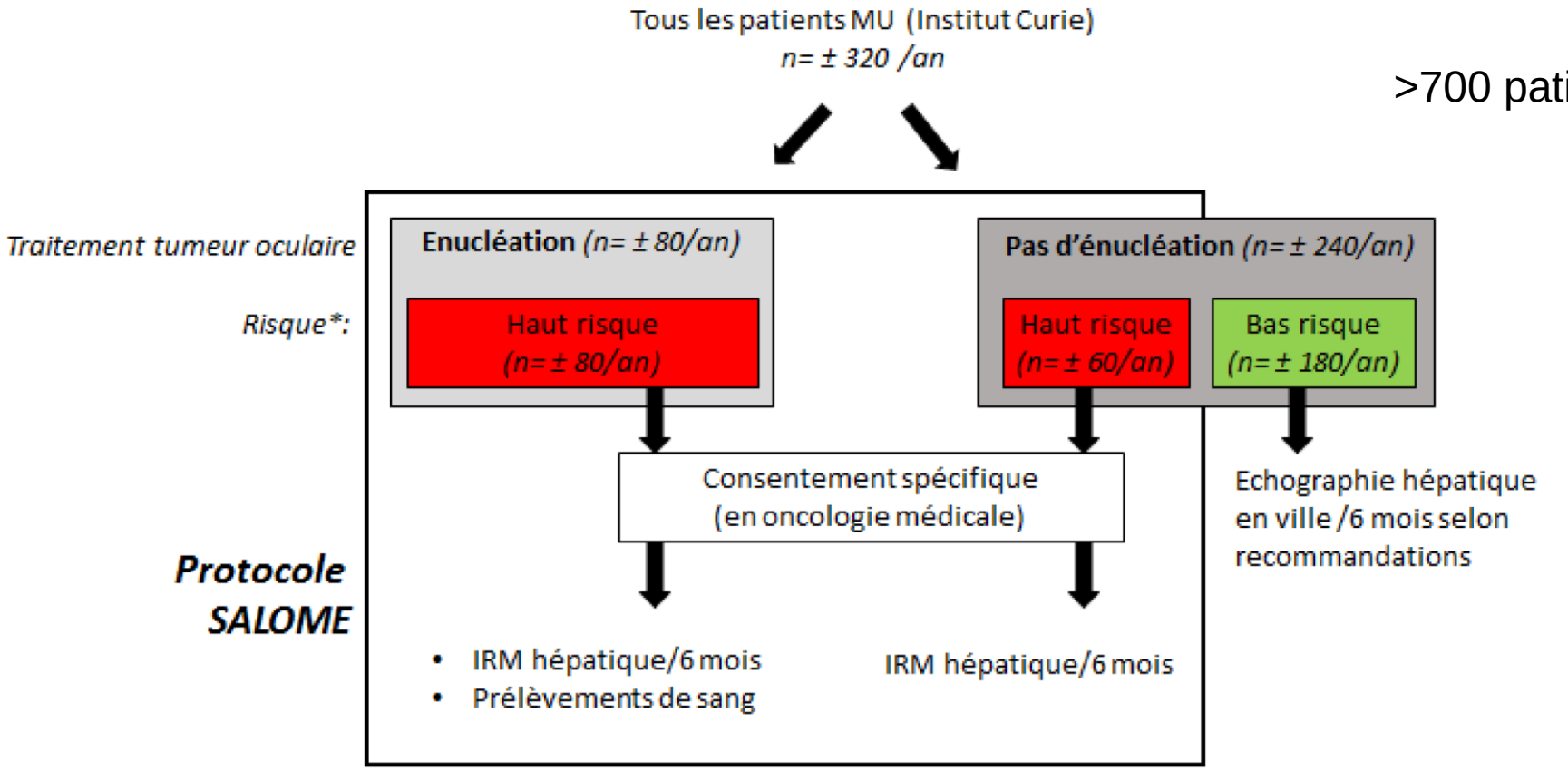


→ Now in routine to assess tebentafusp efficacy
→ Next: agnostic ctDNA

Mailly-Giacchetti et al. ESMO 2023

institutCurie

Ongoing studies – « SALOME » cohort (adjuvant setting)



>700 patients to be included

** Définition du risque:*

- ***Haut risque** : T2b/c/d ou ≥ T3 (AJCC Ophthalmic Oncology Task Force. International validation of the American Joint Committee on Cancer's 7th edition classification of uveal melanoma. JAMA Ophthalmol. 2015; 133: 376–383) **OU** anomalie du chromosome 3 et/ou du chromosome 8.*
- ***Bas risque** : tous les autres cas.*
- *Les patients dont le risque génomique est inconnu seront suivis selon leur risque clinique.*
- *Les patients énucléés sont à haut risque >95% et seront par définition suivis comme des patients à haut risque.*

institutCurie

Acknowledgments

Development

- **Circulating biomarkers lab**
  - Shufang Renault
  - Dr Marc-Henri Stern
  - Prof François-Clément Bidard
  - Caroline Hego
  - Aurore Rampanou

Clinics

- **Somatic Genetic Unit**
  - Prof Ivan Bièche
  - Emmanuelle Jeannot
- **UM clinical team**
  - Dr Pascale Mariani (surgery)
  - Dr Manuel Rodrigues (medical oncology)
  - Dr Sophie Piperno-Neumann (medical oncology)
  - Dr Vincent Servois (radiology)
  - Dr Toulsie Ramtohul (radiology)
- **Genomic of UM research team**
  - Dr Marc-Henri Stern
  - Dr Manuel Rodrigues

institutCurie