Uveal Melanoma

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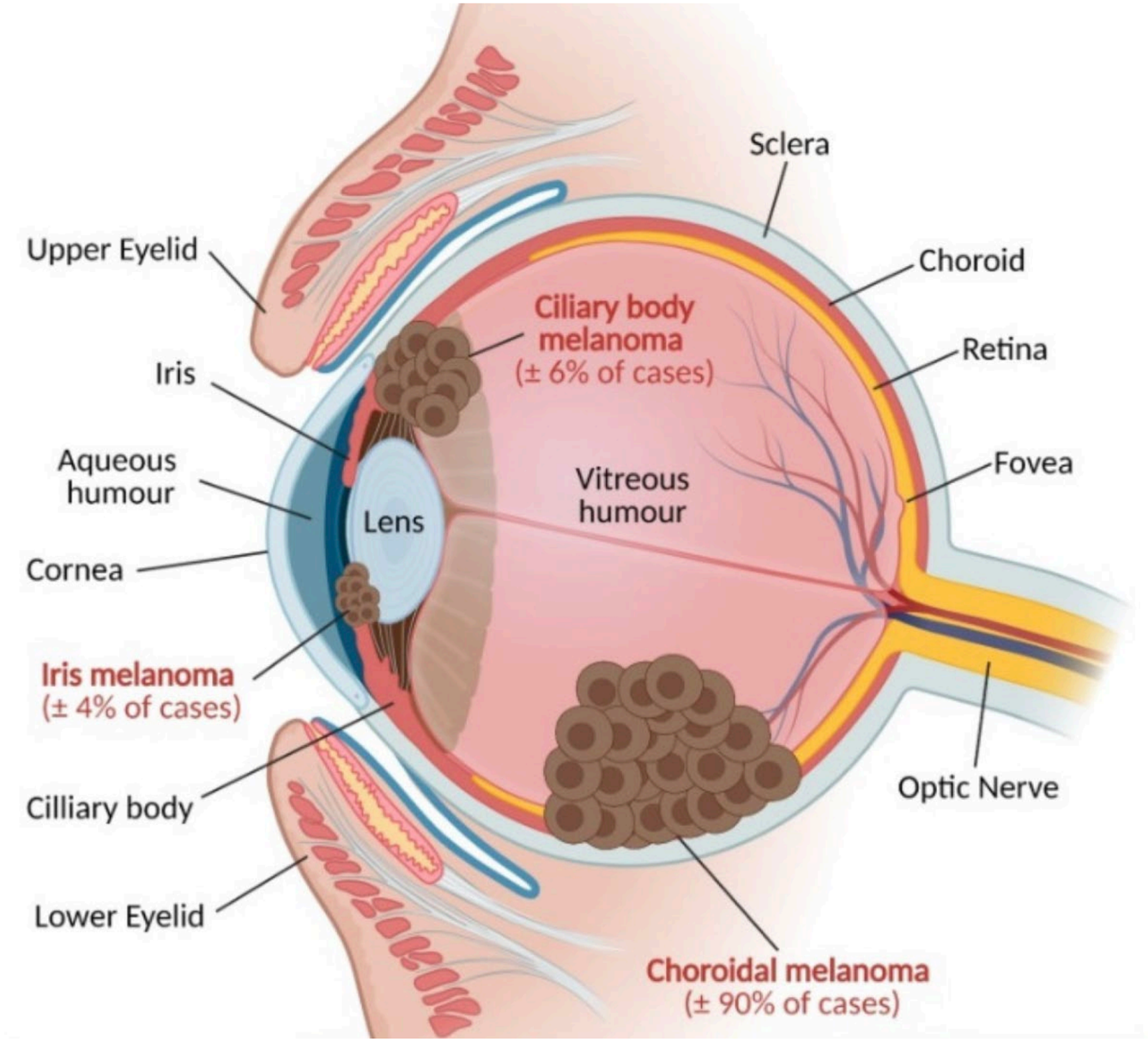
Uveal Melanoma is a rare disease



5% of melanoma

4 to 11 cases / million / year

Incidence stable these last 50 years

Median age 60 years (50-70 y)

More frequent in caucasians (150x)

More frequent in blue/grey eyes

Most of the time appearing *De Novo*

Prevalence of choroidal naevi = 4.5 to 8%

Risk of transformation (naevi to mel) = 1 in 9000

BAP-1 tumor predisposition syndrome

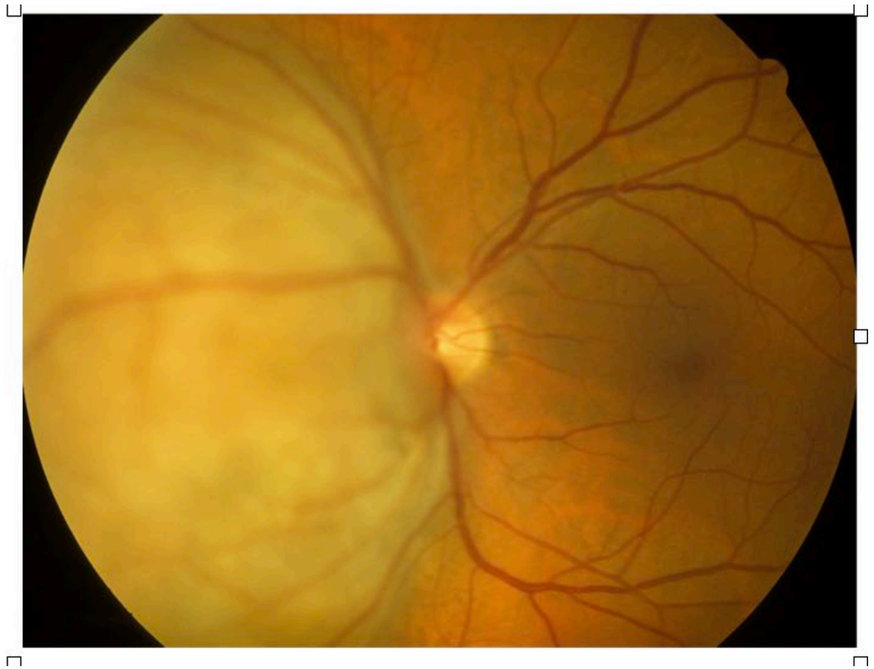
Characteristics of Uveal melanoma

SYMPTOMS	COMPLICATIONS
Blurred or distorted vision	Retinal detachment
Loss of visual fields	Glaucoma
Photopsia	Intraocular hemorrhage
Ocular pain	Cataract
1/3 are asymptomatic	Vision loss

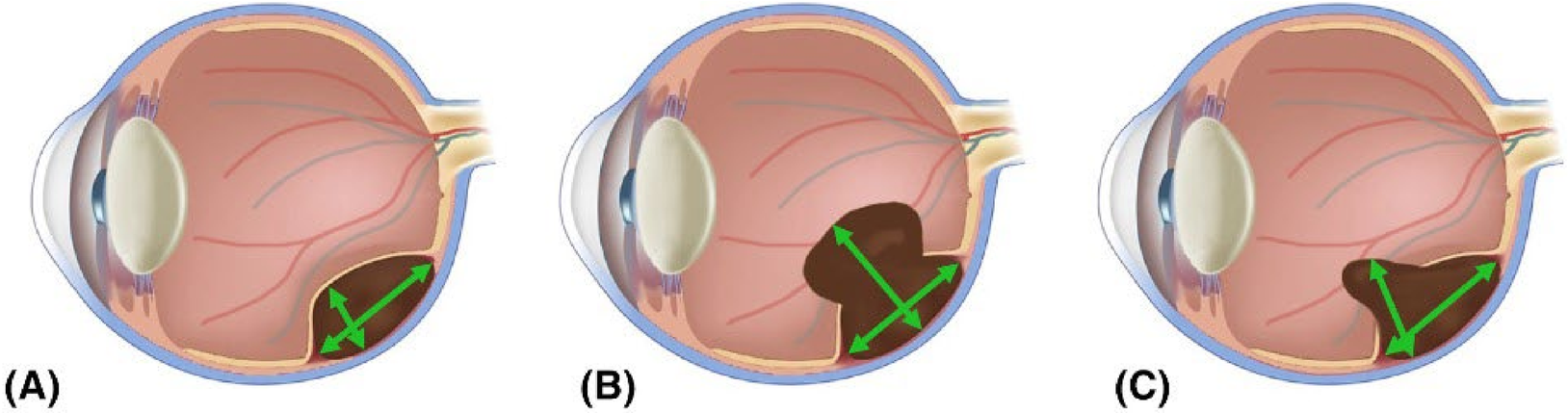
Clinical Features of Uveal Melanoma

Pigmented or Amelanotic

Circumscribed or Diffuse



Dome or Mushroom shaped



(A) dome-shape, (B) mushroom-shape and (C) marked asymmetry.

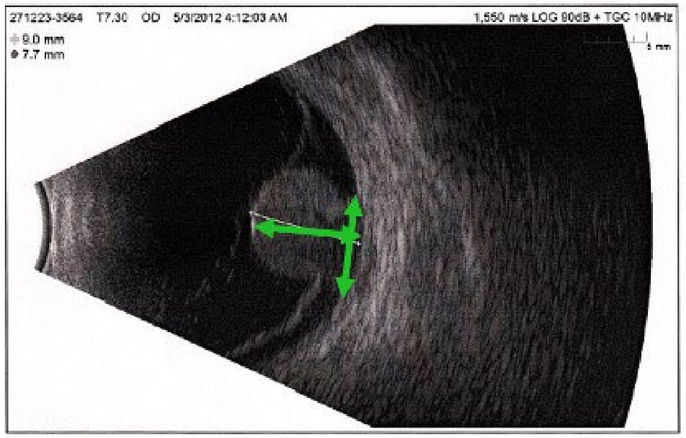
Acta Ophthalmologica, Volume: 96, Issue: 5, Pages: 510-518, First published: 16 January 2018, DOI: (10.1111/aos.13668)

Diagnostic Uveal melanoma

Eye Exam : measurement of tumor diameter

Echography of the retina : thickness

Rarely MRI



80% risk
of distant mets

Thickness (mm)							
>15.0					4	4	4
12.1-15.0				3	3	4	4
9.1-12.0		3	3	3	3	3	4
6.1-9.0	2	2	2	2	3	3	4
3.1-6.0	1	1	1	2	2	3	4
≤3.0	1	1	1	1	2	2	4
	≤3.0	3.1-6.0	6.1-9.0	9.1-12.0	12.1-15.0	15.1-18.0	>18.0
	Largest basal diameter (mm)						

10 % risk
of distant mets

AJCC = American Joint Committee on Cancer; TNM = tumor, node, metastasis.
This chart is a quick guide to determine T stage using tumor size as the criteria. The left vertical column (representing tumor thickness) can be matched to the horizontal column (representing largest tumor basal dimension) to yield the T staging (1-4). Reprinted with permission from: AJCC-UICC Ophthalmic Oncology Task Force: Malignant Melanoma of the Uvea Ophthalmic Sites: Part X. In: Edge SB, Byrd DR, Compton CC, eds. AJCC Cancer Staging Manual, 7th ed. New York, NY: Springer 2009 (16).

Clinical Risk Factors for Development of Metastases

Ciliary body involvement

Largest basal tumor diameter

Greater tumor thickness

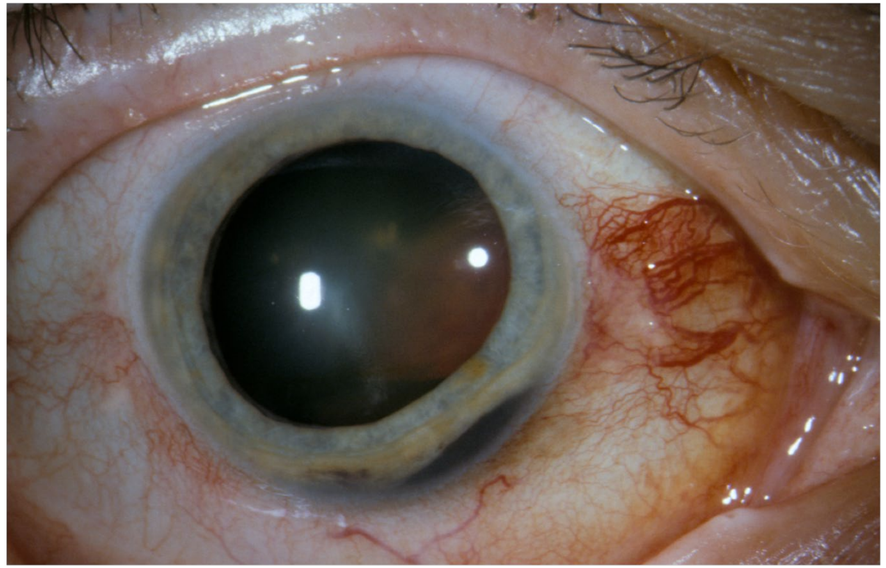
Extraocular extension

Diffuse pattern of growth

Older age

Male gender

Initial progression after brachytherapy



Histopathologic and Molecular Risk Factors for Development of Metastases

Monosomy 3

Epithelioid cells

High pigment content

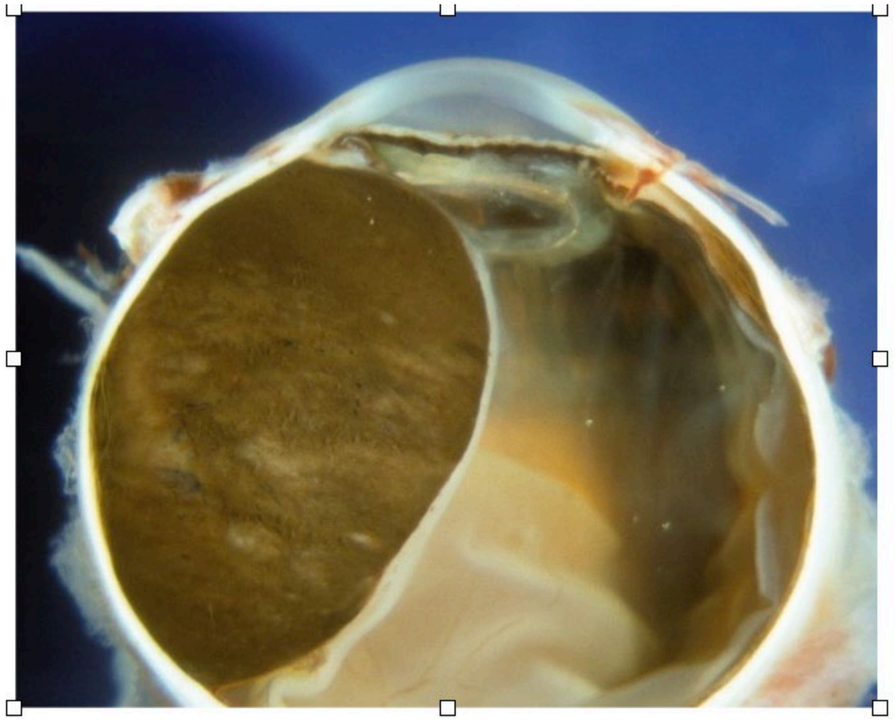
High mitotic figures

Microvascular density

Extravascular patterns (close loops, networks)

TIMs and TILs

MLN (mean of the 10 largest nucleoli)



Initial Work-up of Uveal Melanoma

Liver Echography

Lung Radiography

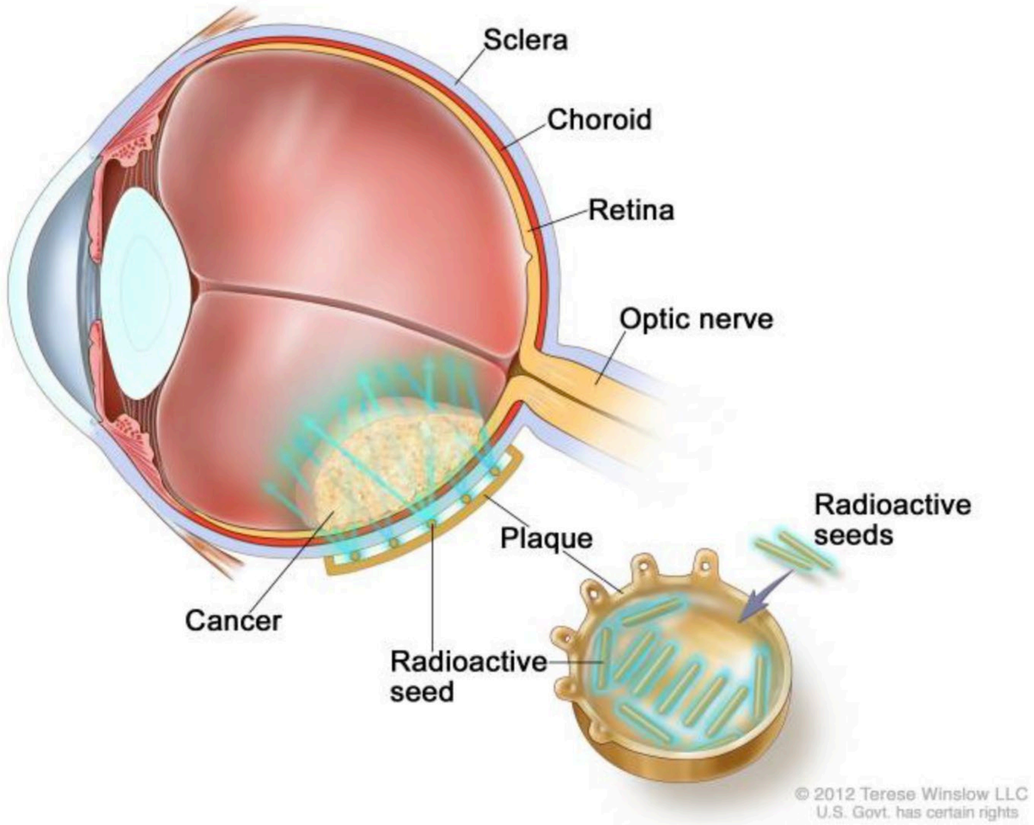
Blood Analysis

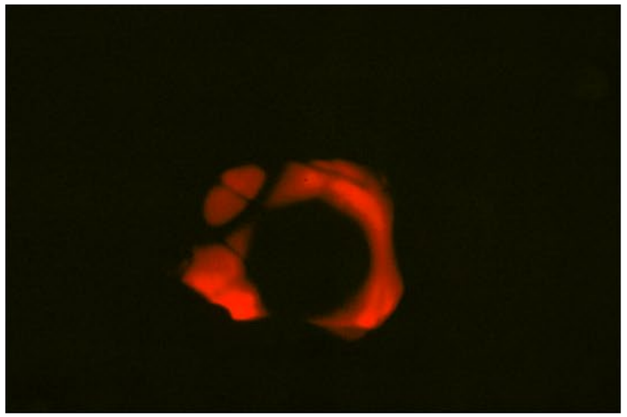
Enucleation as Primary Treatment of Uveal melanoma

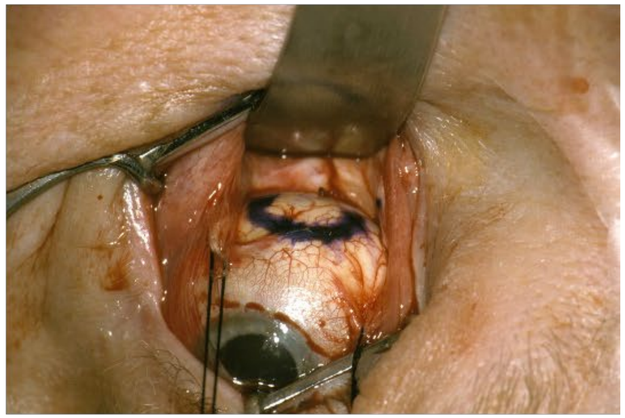
Standard Treatment for any size of uveal melanoma

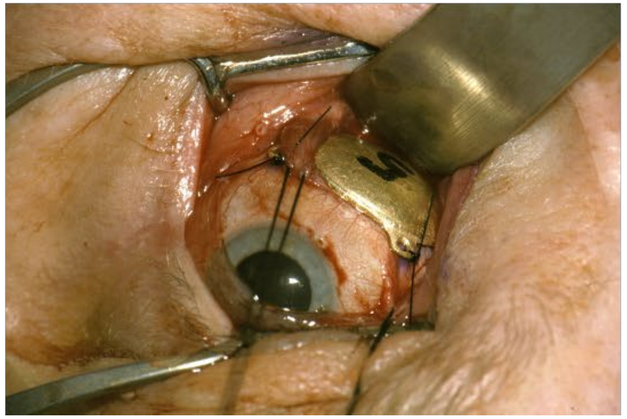
Brachytherapy as Primary Treatment of Uveal melanoma

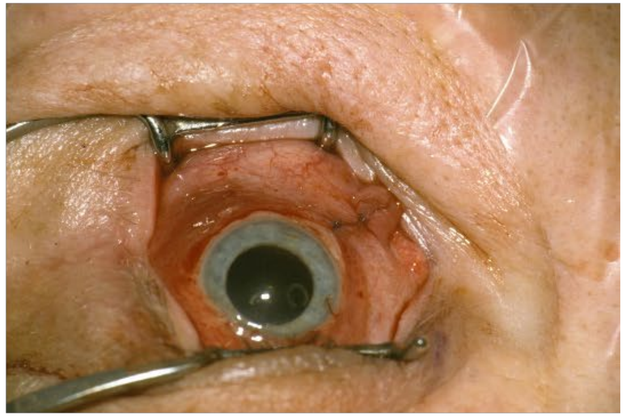
Enucleation = Iodine 125 plaque radiotherapy



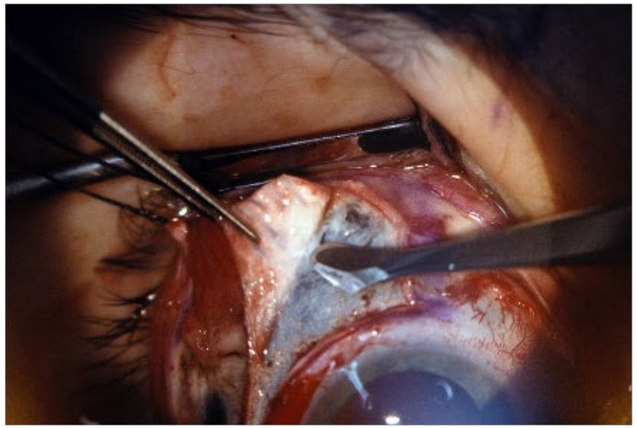


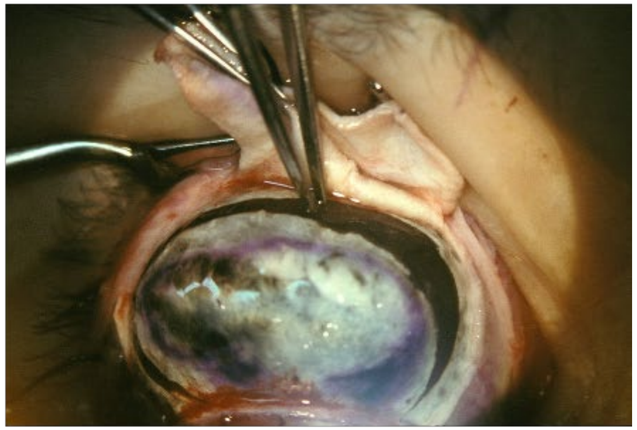


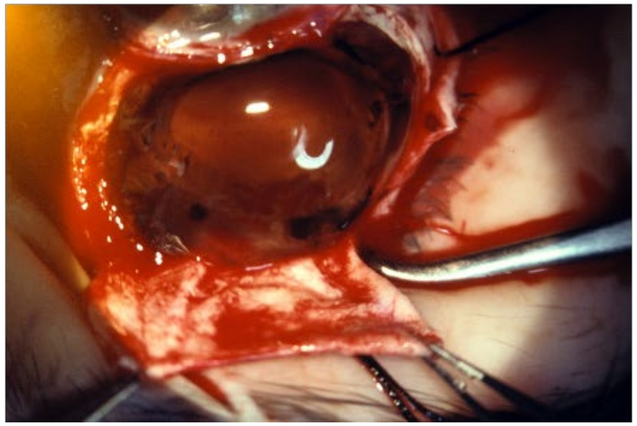


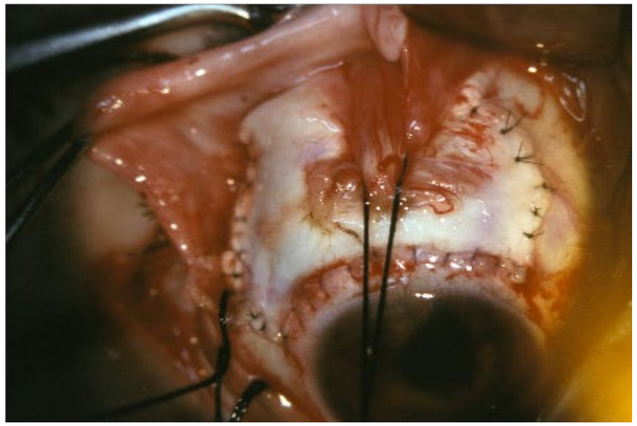


Tumor Resection as Primary Treatment of Uveal melanoma









Follow-up of Uveal Melanoma

Oncology FUP	Ophtalmology FUP
Echo liver, lung X-ray	Every 6 months for 2 years
Every 6 months for 5 years	Then every 9 months
If T3-T4 pursue semestral FUP	To be adapted based on complications
If T2 pursue annual FUP	

+/- 50% of the patients will develop metastases

Work-up for suspicion of relapsing Uveal Melanoma

Liver MRI

If suspicion

- **PET-scan**
- **Liver Biopsy**

Must have a Histology before treatment

HLA-A2 typing

Differences between Cutaneous and Uveal Melanoma

Genetic Alteration

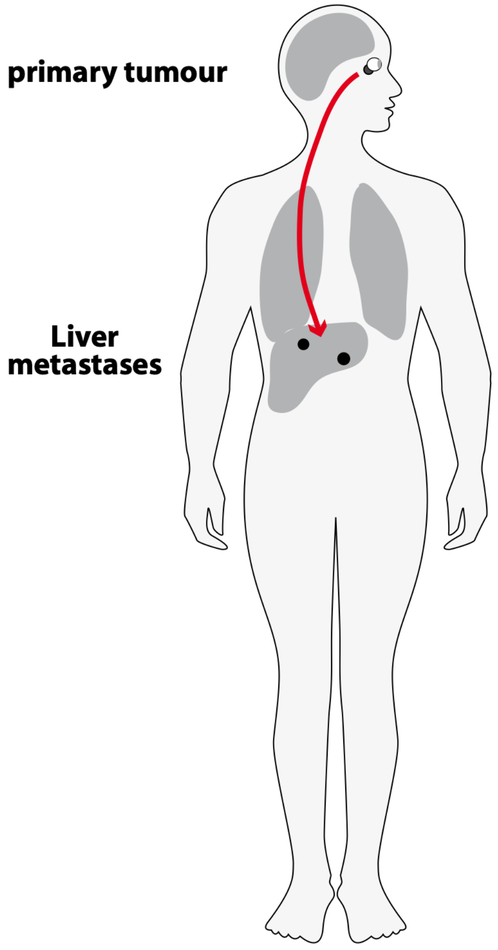
Uveal Melanoma	Cutaneous Melanoma
Low tumor mutational burden	High tumor mutational burden
GNAQ GNA11	BRAF NRAS

MUTATIONS IN

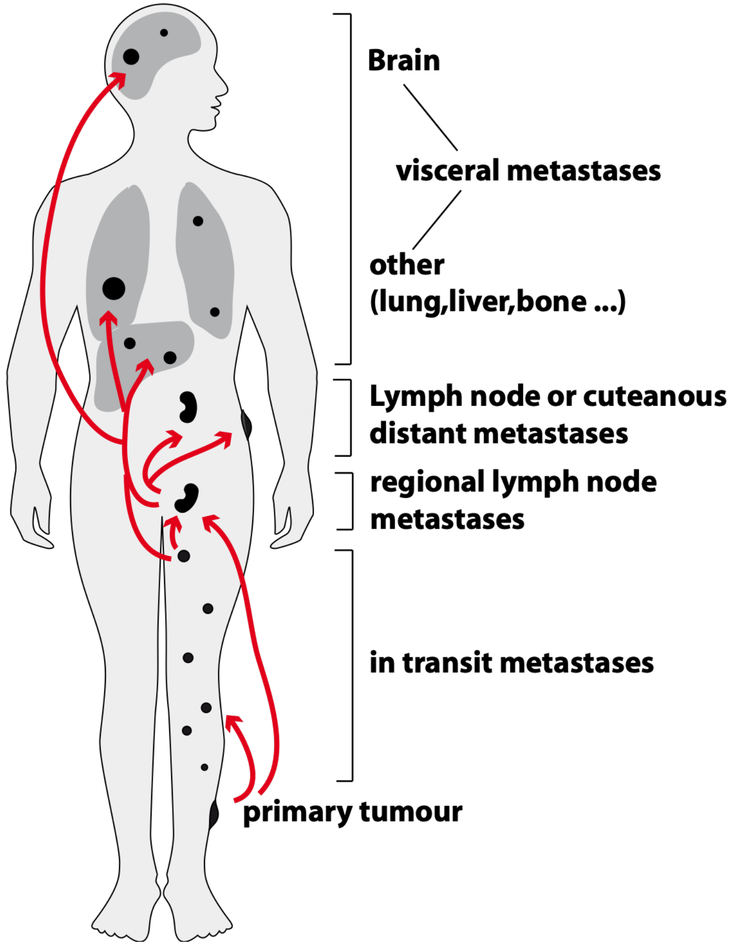
Both Leading to MAPK pathway activation

Pattern of Metastasis

Uveal Melanoma

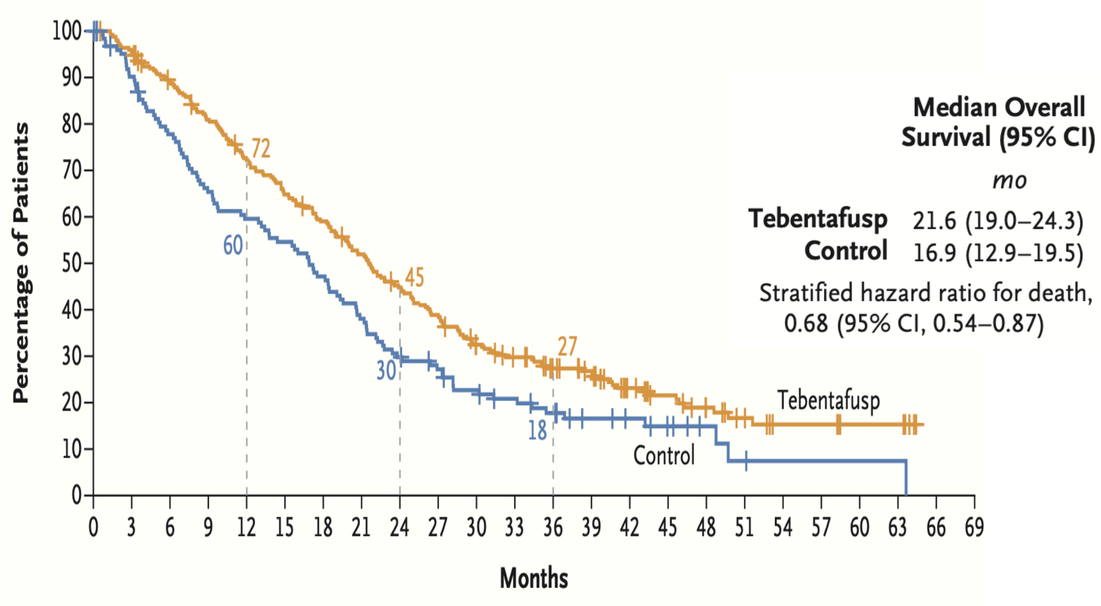


Cutaneous Melanoma

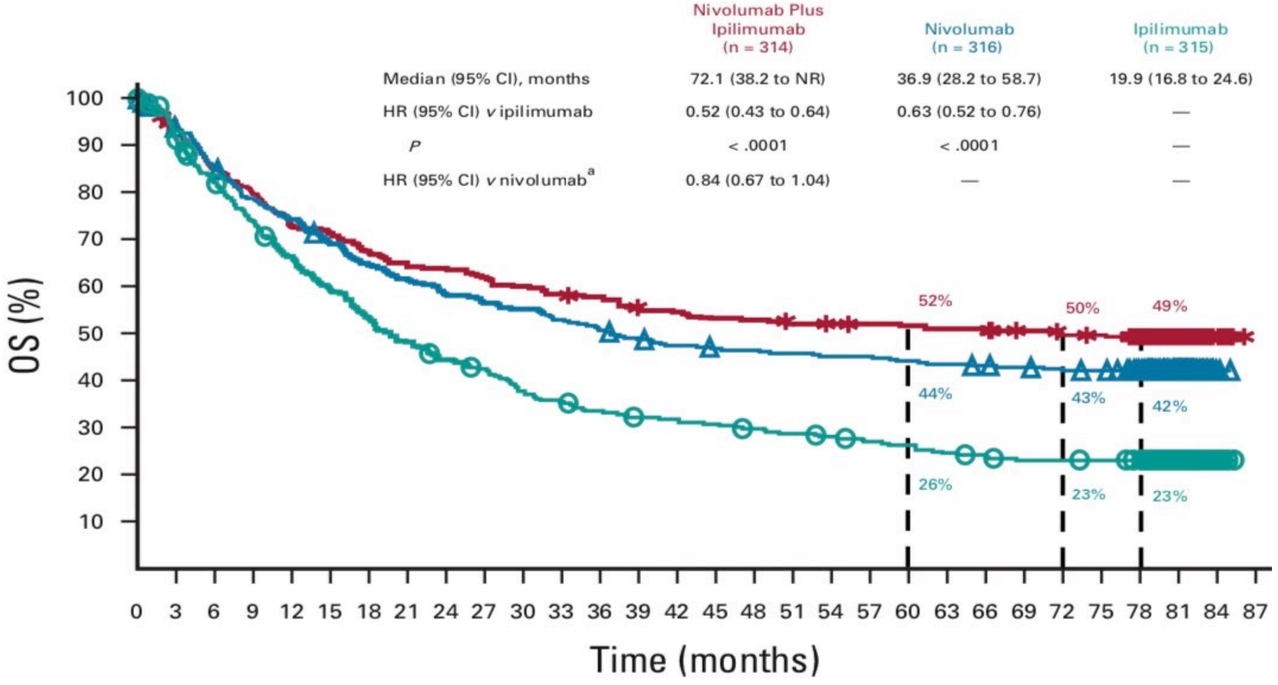


Differences between Cutaneous and Uveal Melanoma

Meta Uveal Melanoma
MUM



Meta Cutaneous Melanoma
MCM



Hassel JC. et al, NEJM 2023; Wolchok JD. et al., JCO 2021

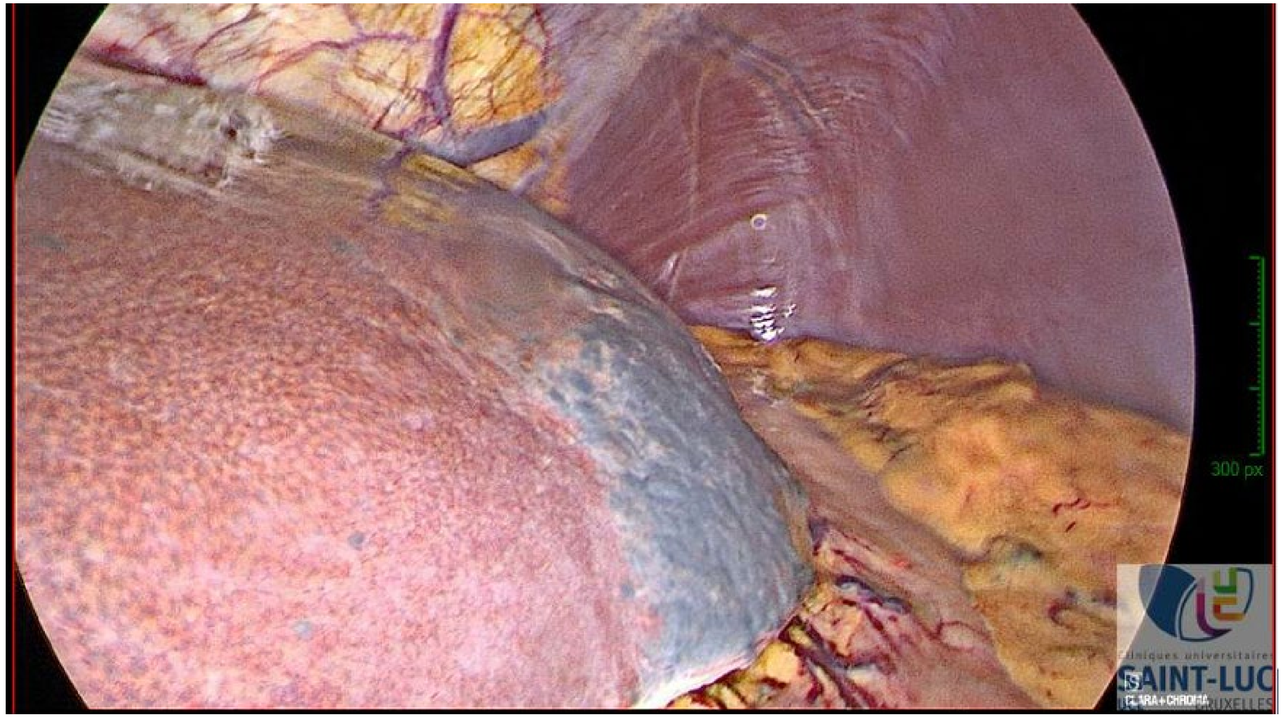
How to treat the metastases of Uveal melanoma ?

LOCAL TREATMENT

- Surgery
- Intra-arterial chemotherapy
- Transarterial (chemo)embolisation
- Hepatic Perfusion

SYSTEMIC TREATMENT

- Chemotherapy
- Targeted Therapy
- Immunotherapy



Is Surgery an option to treat Liver Metastases of Uveal Melanoma ?

Reference	Study Period	No. of Centers	Total Patients	Melanoma Type	Treatment(s)	Overall Survival[b] Median, mo	Overall Survival[b] 5-year, %
Noncomparative studies							
Adam et al[11]	1983-2004	41	1452	Ocular (n = 104)	Hepatic resection	19	21
				Cutaneous (n = 44)	Hepatic resection	27	22
de Ridder et al[12]	1994-2010	15	32	Ocular (n = 12), cutaneous (n = 16), unknown (n = 4)	Hepatic resection	29 (range, 4-64)	3
Groeschl et al[13]	1990-2009	4	420	Undefined (n = 31)	Hepatic resection	39 (95% CI, 14-74)	36
Pawlik et al[14]	1988-2004	4	40	Ocular (n = 16)	Hepatic resection	29.4	21
				Cutaneous (n = 24)	Hepatic resection	23.6	0
Pilati et al[15]	2000-2008	1	36	Ocular (n = 30), cutaneous (n = 6)	Hepatic resection	15	–
Ripley et al[16]	1980-2008	1	539	Cutaneous (n = 29), ocular (n = 1), unknown (n = 5)	Hepatic resection ± TIL	36 (range, 1-197)	–
Ryu et al[17]	1980-2012	1	33	Cutaneous (n = 24), ocular (n = 9)	Hepatic resection	29 (range, 2-139)	42
Studies comparing surgery and other treatments							
Frenkel et al[6]	1988-2008	1	74	Ocular (n = 74)	Hepatectomy (n = 35)	23.0 (95% CI, 13.3-41.3)	–
					No surgery (n = 39)	6.8 (95% CI, 3.6-12.5)	–
Mariani et al[7]	1991-2007	1	798	Ocular (n = 798)	Hepatic resection (n = 255)	14	7
					Chemotherapy/BSC (n = 543)	8	–
Marshall et al[5]	2000-2010	1	188	Ocular (n = 188)	Hepatic resection (n = 12)	R0: 24 (95% CI, 20.2-27.8)	–
					Chemotherapy/BSC (n = 37)	10 (95% CI, 8.1-11.9)	–
Piperno-Neumann et al[8]	2000-2008	1	470	Ocular (n = 470)	Hepatic resection (n = 42)	21	–
					Systemic therapy (n = 312)	12	–
					BSC	3	–
Rivoire et al[9]	1983-1996	1	63	Ocular (n = 63)	Hepatic resection (n = 28)	R0: 25 (range, 11-110) R2: 16 (range, 3-35)	–
					Chemotherapy/BSC (n = 35)	11 (range, 3-52)	–
Rose et al[10]	1971-1999	2	34	Cutaneous (n = 34)	Hepatic resection (n = 24)	28 (range, 2-147)	29
					Exploratory celiotomy (n = 10)	4	–
					No surgery (n = 899)[c]	6	4

60 days mortality is 2%
relapse rate 75%

Agarwala et al 2013, Cancer

Is Radiofrequency Ablation an Alternative Treatment for Surgery ?

Radiofrequency ablation (RFA) / microwave ablation (MWA) / cryo-ablation (CA) :

- Coagulation necrosis of the target tissue (60°-100° C)
- 1 cm thick tumor-free ablation margin
- Low procedural complications (1-2%)
- Median survival : 35 – 46 months (= surgical resection).

Is Chemotherapy an option to treat Liver Metastases of Uveal Melanoma ?

Reference	No. of Patients	Design	Patients With Liver Metastases, n	Treatment(s)	ORR[a]	Median Overall Survival, mo
Chemotherapeutic and immunomodulatory agents						
Bedikian et al[28]	14	Phase 2	14	Temozolomide	0%	6.7 (range, 1-12.7)
Homsi et al[29]	22	Phase 2	20	DHA-paclitaxel	5%	9.8
Kivelä et al[30]	24	Phase 2	24	BOLD + recombinant interferon alpha-2b	0%	10.6 (95% CI, 6.9-16.4)
O'Neill et al[31]	15	Phase 2	–	Dacarbazine + treosulfan	0%	6.9 (range, 0.5-14.7)
Pföhler et al[32]	14	Feasibility	–	Gemcitabine + treosulfan	29%	14.0 (95% CI, 12.4-30.6)
Pons et al[33]	58	Retrospective	56	Chemotherapy (n = 25)[b]	–	10.8 (95% CI, 5.4-16.3)
Pyrhönen et al[34]	22	Phase 2	17	BOLD + human leukocyte interferon	15%	12.3 (95% CI, 8-22)
Schmittel et al[35]	19	Phase 2	19	Cisplatin, gemcitabine + treosulfan	0%	7.7 (95% CI, 1.9-13.8)
Schmittel et al[36]	14	Phase 2	–	Gemcitabine + treosulfan $\leq$3000 mg/m^2	0%	6.0 (95% CI, 4-8)
	19		–	Gemcitabine + treosulfan $\geq$3500 mg/m^2	5%	9.0 (95% CI, 0-18)

Low response rate
Median OS ranging from 6 to 14 months

Agarwala et al 2013, Cancer

Is Intra-arterial Chemotherapy an option to treat Liver Metastases of UM ?

Reference	Design	Melanoma Type	No. of Patients	Technique	Agent(s)	ORR	Median Overall Survival, mo
Becker et al[46a]	Phase 2	Ocular (n = 48)	23	HIA	Fotemustine with sequential IFNα + IL-2	22%	12.1 (range, 5.3-33.5)
			25	Intravenous	Fotemustine with sequential IFNα + IL-2	8%	11.5 (range, 1.7-50.4)
Leyvraz et al[44] (EORTC 18021)	Phase 3	Ocular (n = 171)	86	HIA	Fotemustine	11%	14.6
			85	Intravenous	Fotemustine	2%	13.0
Agarwala et al[47]	Phase 1/2	Ocular	19	HIA ± embolization	Cisplatin	16%	8.5
Farolfi et al[48]	Retrospective	Ocular	18	HIA	Fotemustine or carboplatin	17%	21 (95% CI, 8-39)
Heusner et al[49]	Retrospective	Ocular	61	HIA	Melphalan ± other	–	10 (95% CI, 9.7-16.3)
Peters et al[50]	Retrospective	Ocular	101	HIA[c]	Fotemustine	36%	15 (95% CI, 12.1-17.6)[c]
Siegel et al[51]	Retrospective	Ocular (n = 18), cutaneous (n = 12)	36	HIA	Fotemustine	30%	14

Randomized Phase III trial fails to demonstrate superiority

Agarwala et al 2013, Cancer

Is chemo-embolisation an option to treat Liver Metastases of Uveal Melanoma ?

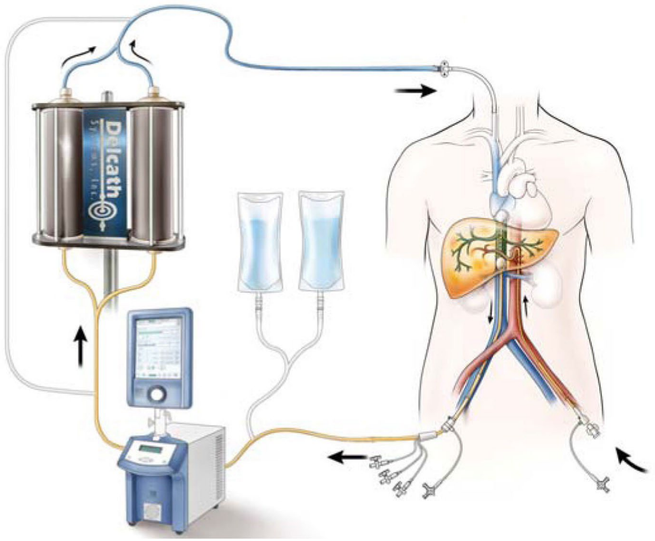
Reference	Design	Melanoma Type	No. of Patients	Technique	Agents	ORR[a]	Median Overall Survival, mo
TACE							
Ahrar et al[52]	Retrospective	Cutaneous	42	TACE ± HIA	Cisplatin ± paclitaxel or paclitaxel	39%	7.7 (95% CI, 6.5-9.7)
Edelhauser et al[53]	Retrospective	Ocular	21	TACE	Fotemustine	14%	–
Gupta et al[54]	Retrospective	Ocular	125	TACE ± HIA	Cisplatin[b]	28%	6.7 (95% CI, 4.9-8.5)
Patel et al[55]	Phase 2	Ocular	30	TACE	1,3-bis(2-chloro-ethyl) −1-nitrosourea	20%	5.2 (range, 0.1-27.6)
Schuster et al[56]	Retrospective	Ocular	25	TACE	Fotemustine or cisplatin	16%	5 (95% CI, 4-6)
Sharma et al[57]	Retrospective	Ocular (n = 17), cutaneous (n = 3)	20	TACE	Cisplatin + doxorubicin + mitomycin C	0%	8.9 (range, 1.2-38.9)
Immunoembolization							
Sato et al[58]	Phase 1	Ocular[c]	34	Immunoembolization	GM-CSF	32%	14.4 (95% CI, 11.2-22.3)
Eschelman et al[59]	Phase 2	Ocular[c]	27	Embolization	None	11%	17.2
			25	Immunoembolization	GM-CSF	20%	21.5
Radioembolization							
Gonsalves et al[60]	Retrospective	Ocular	32	Radioembolization	^{90}Y-resin microspheres	6%	10.0 (range, 1.0-29.0)

Higher response rate but no impact on Overall Survival

Agarwala et al 2013, Cancer

Is hepatic perfusion an option to treat Liver Metastases of Uveal Melanoma ?

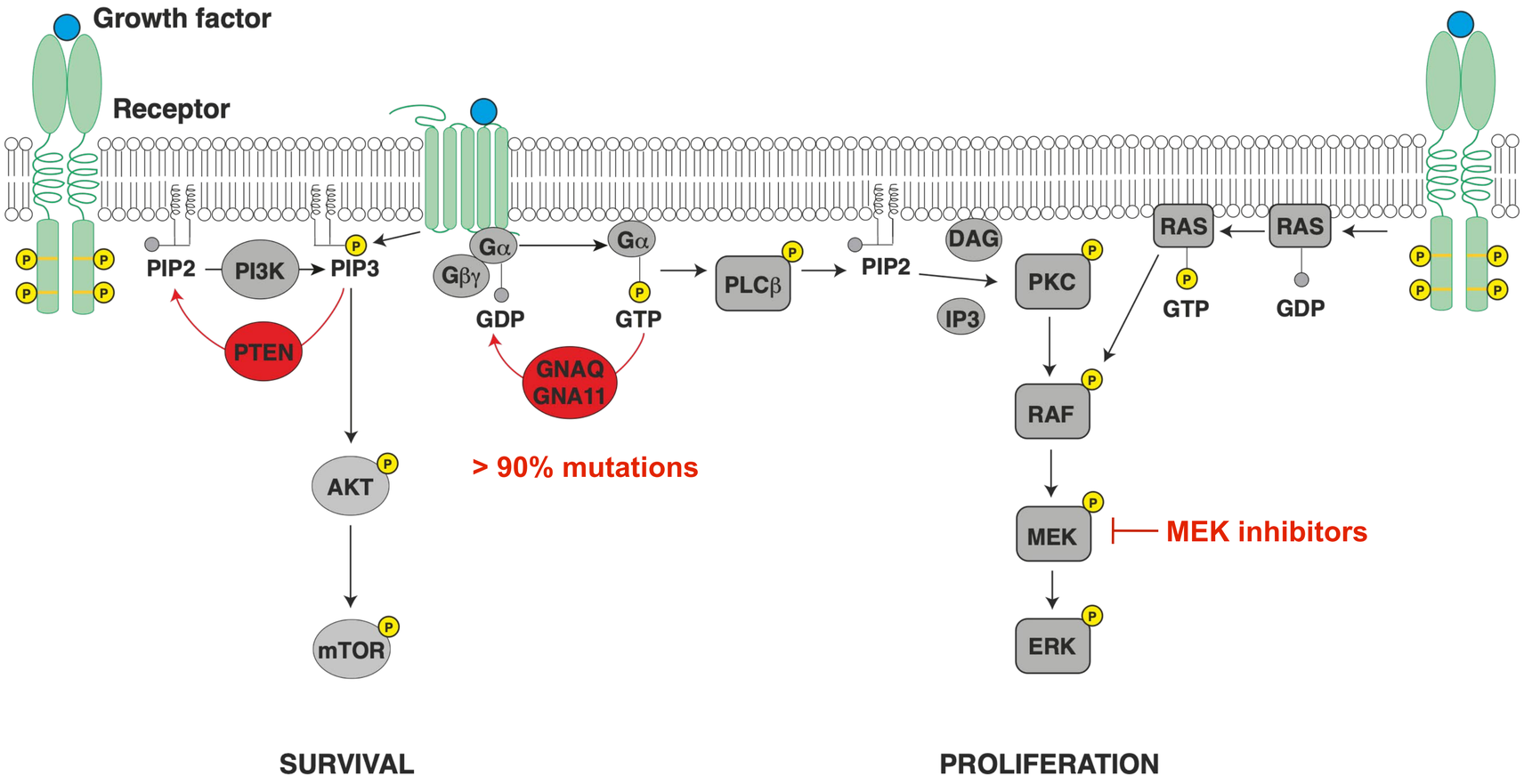
Reference	Design	Type of Melanoma, n	No. of Patients	Technique	Agent(s)	ORR	Median Overall Survival, mo
Pingpank et al[54,63]	Phase 3	Ocular, cutaneous	44	PHP	Melphalan	32%	11.4
			49	BAC[a]		2%	9.9
Alexander et al[64]	Phase 1/2	Ocular (n = 22)	22	IHP	Melphalan ± TNF	62%	11
Alexander et al[65]	Retrospective	Ocular (n = 29)	29	Hyperthermic IHP	Melphalan	62%	12.1 (range, 3-39+)
van Iersel et al[66]	Not stated	Ocular (n = 13)	19	IHP	Melphalan	33%	10 (range, 4.8-47.6)



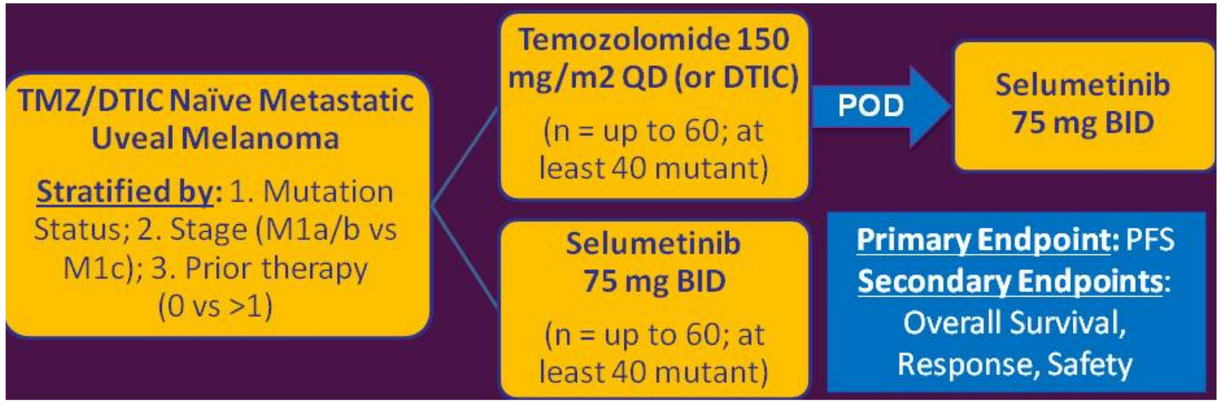
Higher response rate but no impact on Overall Survival

Agarwala et al 2013, Cancer

Could targeted therapies help MUM patients ?



Randomized Phase II trial with a MEK inhibitors in Metastatic Uveal Melanoma



Patient Characteristics
(as of 4/22/13)

	Selumetinib (n = 48)	TMZ/DTIC (n = 50)
Median Age, Years (Range)	62 (32-86)	61 (34-86)
Gender		
Male (%)	25 (52%)	31 (62%)
Female (%)	23 (48%)	19 (38%)
Median ECOG PS (Range)	0 (0-1)	0 (0-1)
AJCC Cutaneous Stage M1c (%)	46 (96%)	47 (94%)
Elevated LDH (%)	24 (50%)	29 (58%)
Median Prior Tx (Range)	0 (0-3)	0 (0-2)
Prior Ipilimumab (%)	8 (17%)	11 (22%)

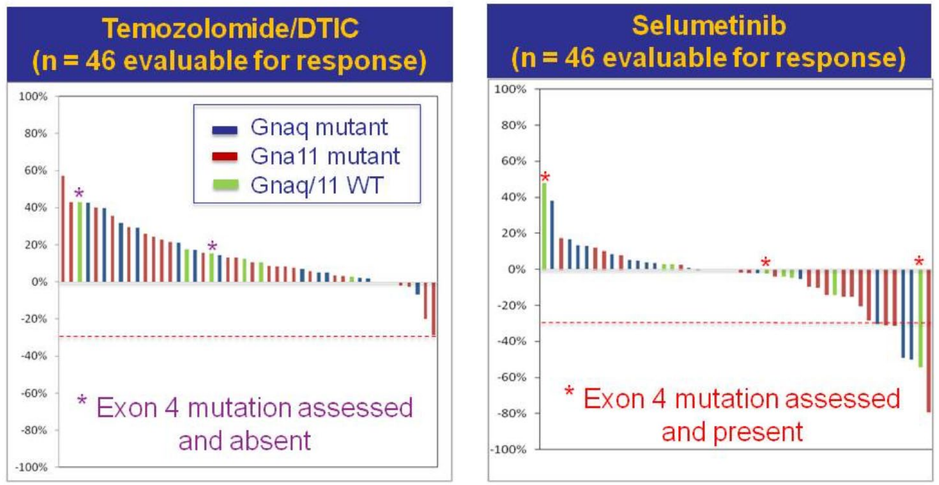
Presented by: RD Carvajal

PRESENTED AT: ASCO Annual '13 Meeting

Carjaval et al, ASCO 2013

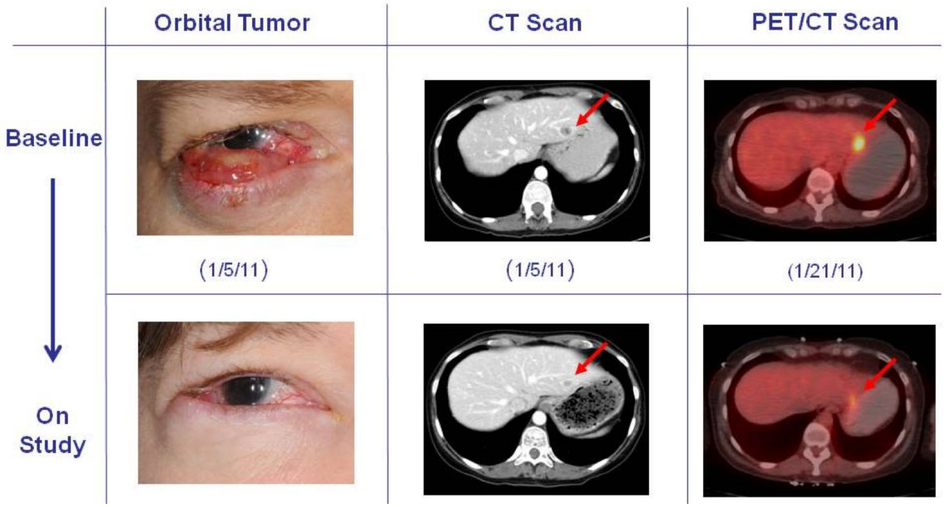
Randomized Phase II trial with a MEK inhibitors in Metastatic Uveal Melanoma

Response Pattern Differs Between Treatment Arms

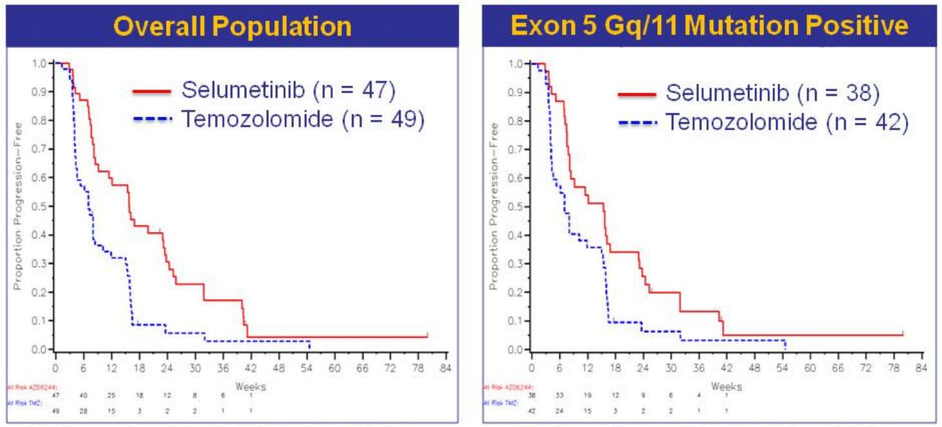


Responses in Liver and Orbital Tumors

(GNA11 Q209L Mutant)



Progression-Free Survival is Improved with Selumetinib in Both the Overall and Mutant Only Populations



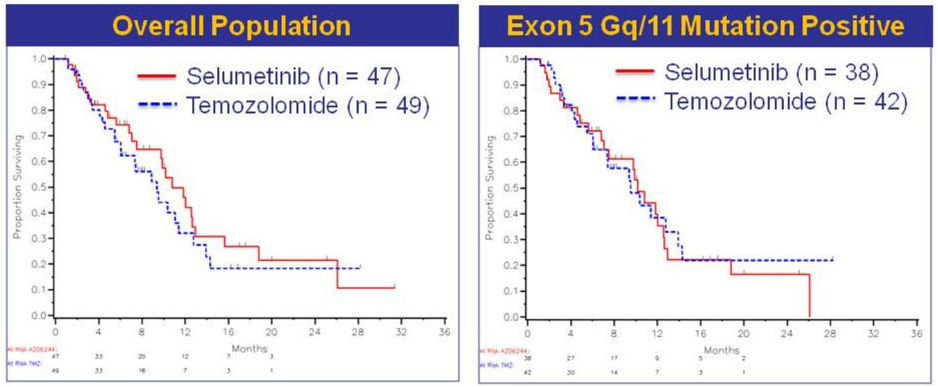
15.9 weeks (95% CI, 8.4 – 23.1) vs 7.0 weeks (95% CI, 4.3 – 8.4)

HR 0.46 (95% CI, .30 - .71) p = 0.0005

15.4 weeks (95% CI, 8.1 – 16.9) vs 7.0 weeks (95% CI, 4.3 – 11.9)

HR 0.55 (95% CI, .34 - .87) p = 0.011

No Significant Effect Upon Survival is Observed



10.8 months (95% CI, 7.5 – 12.9) vs 9.4 months (95% CI, 6.0 – 11.4)

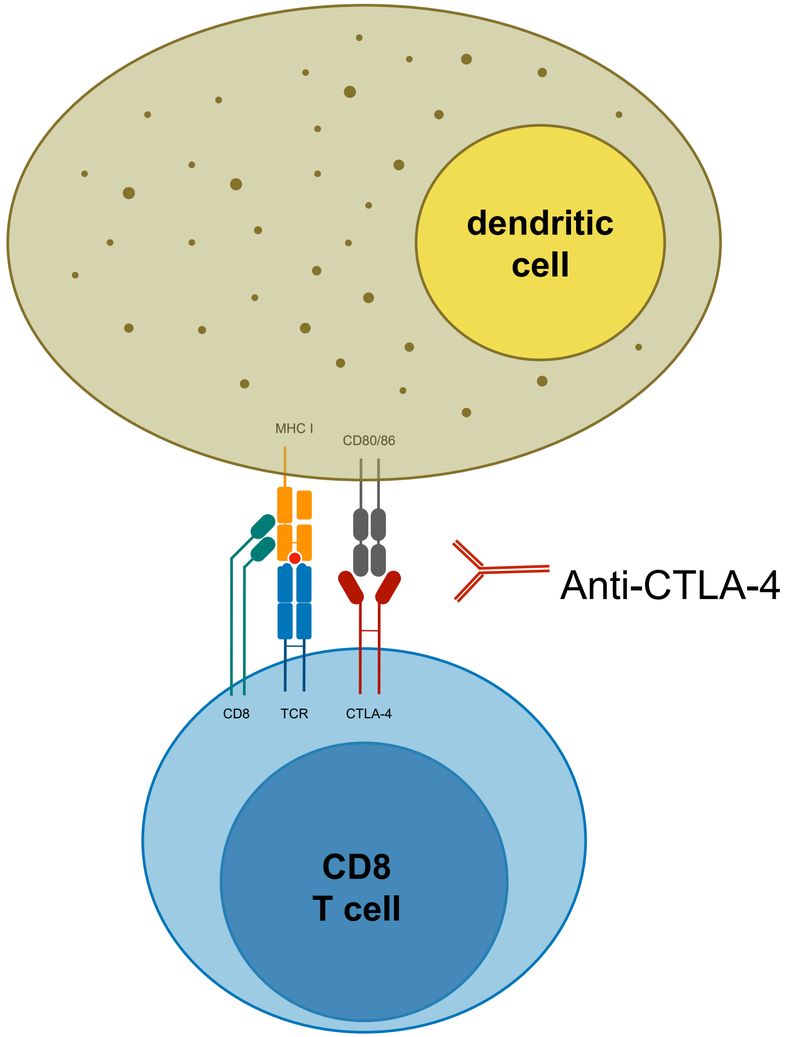
HR 0.79 (95% CI, 0.46 – 1.37) p = 0.4

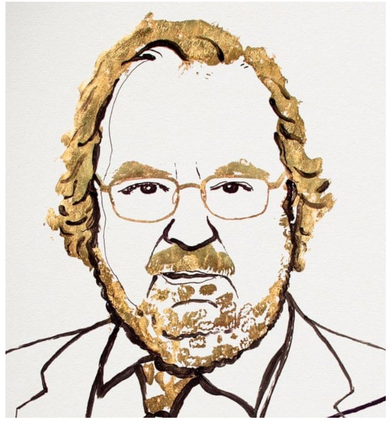
10.2 months (95% CI, 7.0 – 12.6) vs 9.5 months (95% CI, 6.1 – 13.9)

HR 1.05 (95% CI, 0.59 – 1.88) p = 0.88

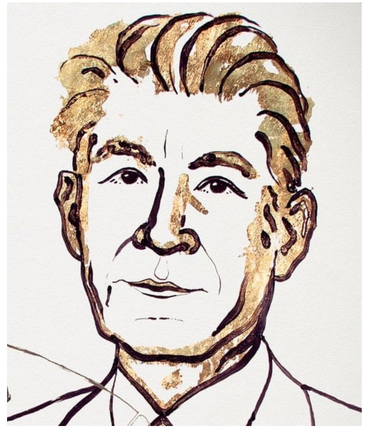
Carjaval et al, ASCO 2013

Immune Checkpoint Inhibitors (ICI)

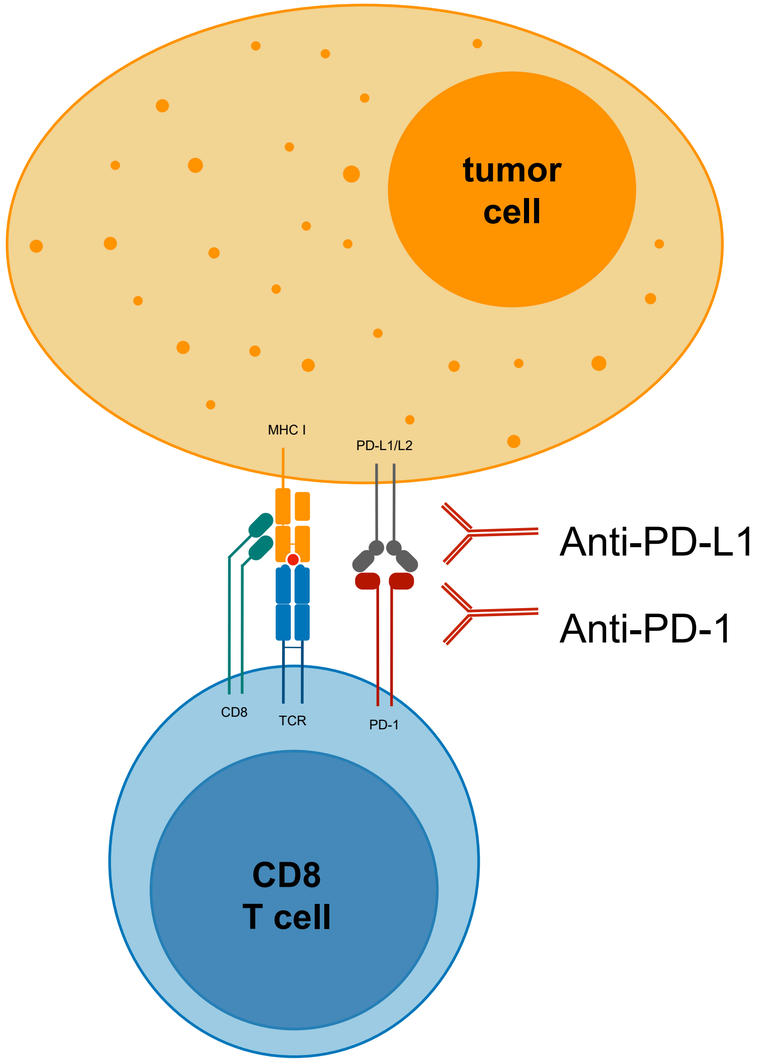




Jim Allison *et al.*
1994 - 1996
Nobel Prize 2018



Tasuku Honjo *et al.*
1992
Nobel Prize 2018

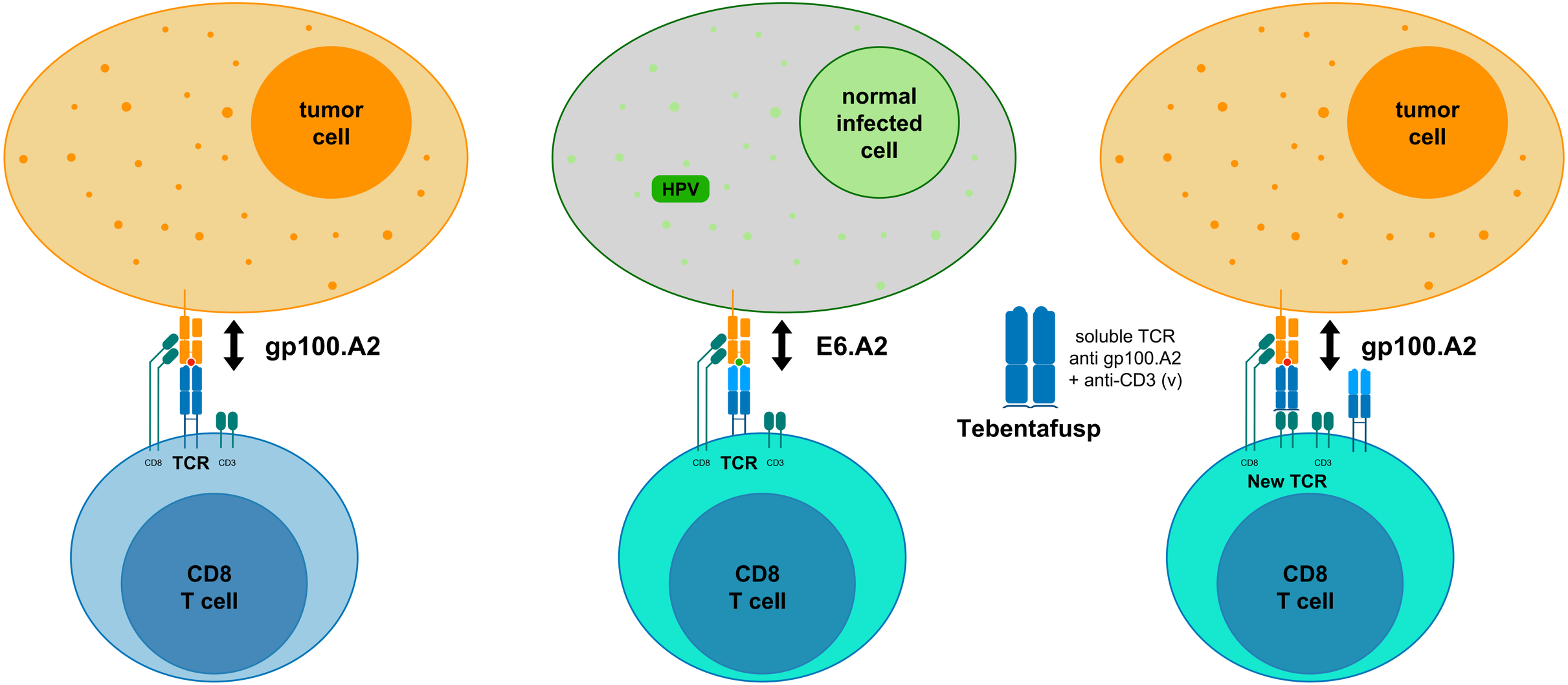


Immune Checkpoints Inhibitors as Treatment for MUM

Author	IO agent	N	Response Rate (%)	Median PFS (mo)	Median OS (mo)
Zimmer et al, Plos one 2015	Ipilimumab Phase II all lines	53	0	2,8	6,8
Maio et al Ann Oncol 2013	Ipilimumab EAP	82	5	3,6	6
Algazi et al, Cancer 2016	Pembrolizumab, nivolumab, atezolizumab retrospective	58	4	2,8	6,8
Najjar et al, J Immunother Cancer 2020	Ipilimumab-Nivolumab Retrospective cohort, 45 first line	89	12	2,7	15
Saint Ghislain et al, EJC 2022	Pembrolizumab, nivolumab, ipilimumab or combo Retrospective cohort, all lines	300	3,3 60% in 5/134 MBD4mutated pts	22,3 in CR/PR 4 in non-responding pts	36,6 in CR/PR 18,4 in non-responding pts
Piulats et al, JCO 2021	Nivolumab-Ipilimumab Phase II 1rst line	52	11,5	2,8	12,7
Pelster et al, JCO 2021	Nivolumab-Ipilimumab Phase II , 20 first line	35	18	3	19,1
Salaun et al, Oncoimmunology 2022	Nivolumab-Ipilimumab Retrospective cohort, 94% 1rst line	47	4,3	3	NA
Dummer et al, JCO 2023	CheckMate 401 subgroup Nivolumab-Ipilimumab	64	9	-	15,3

Zimmer L, et al. PLoS One. 2015;10:e0118564; Maio M, et al. Ann Oncol. 2013;24:2911-2915; Algazi AP, et al. Cancer. 2016;122:3344-3353; Najjar YG, et al. J Immunother Cancer 2020Jun;8(1):e000331. doi: 10.1136;68; Saint-Ghislain M, et al. Eur J Cancer. 2022;173:105-112; Piulats JM, et al. J Clin Oncol. 2021;39:586-598; Pelster MS, et al. J Clin Oncol. 2021;39:599-607; Salaün H, et al. OncoImmunology. 2022;11:1; Dummer R, et al, J Clin Oncol. 2023 Aug 10;41(23):3917-3929. doi: 10.1200.

Tebentafusp : a bispecific soluble TCR + anti-CD3, called ImmTAC



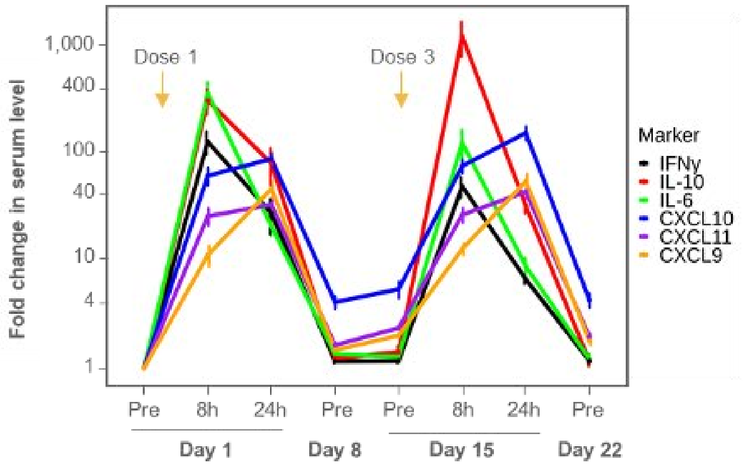
Tebentafusp : Mode of Administration

Weekly Administration : 20 micrograms then 30 and finally 68 micrograms

First three in Hospitalization then day care

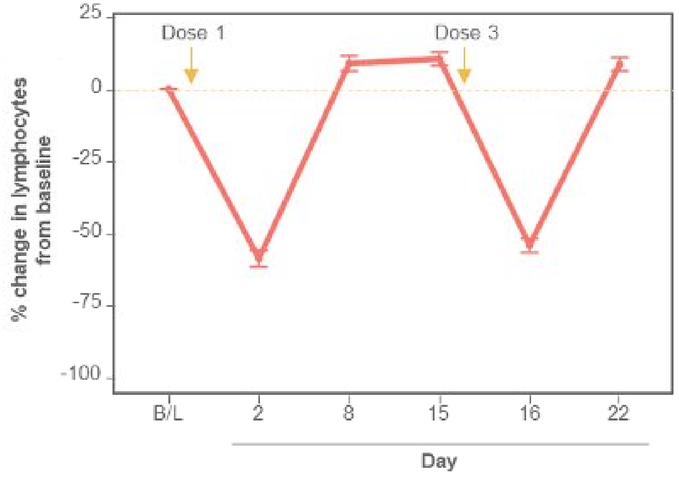
Cytokine induction

Peripheral blood

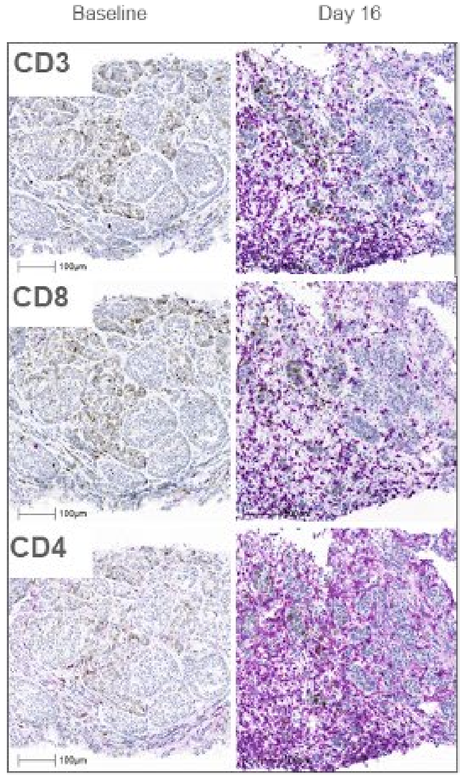


T cell trafficking

Peripheral blood



Tumour



Due to its bispecific design and MoA, tebentafusp induces:

- Immediate cytokine release consistent with T cell activation
- Lymphopenia and an increase in tumour infiltration of T cells (CD3+, CD8+, CD4+), which supports trafficking of T cells from blood into tumour
  - Based on this T cell trafficking, tebentafusp may convert cold tumours into hot tumours, leading to tumour inflammation (consistent with progression by RECIST)

Butler MO, et al. Presented at AACR 2021

IMC202 : Phase III with Tebentafusp in metastatic uveal melanoma

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*

Table 1. Demographic and Disease Characteristics at Baseline (Intention-to-Treat Population).*

Characteristic	Tebentafusp Group (N=252)	Control Group (N=126)
Median age (range) — yr	64 (23–92)	66 (25–88)
Male sex — no. (%)	128 (51)	62 (49)
Median time since primary diagnosis (range) — yr	3.0 (0.1–25)	2.4 (0.1–36)
ECOG performance-status score — no. (%)†		
0	192 (76)	85 (67)
1	49 (19)	31 (25)
2	0	1 (1)
Data missing	11 (4)	9 (7)
Lactate dehydrogenase >ULN — no. (%)	90 (36)	46 (37)
Largest metastatic lesion — no. (%)‡		
≤3.0 cm, stage M1a	139 (55)	70 (56)
3.1 to 8.0 cm, stage M1b	92 (37)	46 (37)
≥8.1 cm, stage M1c	21 (8)	10 (8)
Location of metastasis — no. (%)		
Hepatic only	131 (52)	59 (47)
Extrahepatic only	9 (4)	10 (8)
Hepatic and extrahepatic	111 (44)	55 (44)
Data missing	1 (<1)	2 (2)
Previous surgical therapy for metastatic disease — no. (%)	24 (10)	9 (7)

Inclusion criteria
- mUM
- HLA-A*0201-positive
- No prior systemic therapy in the advanced setting
- No prior LDT, except surgery
- Any LDH

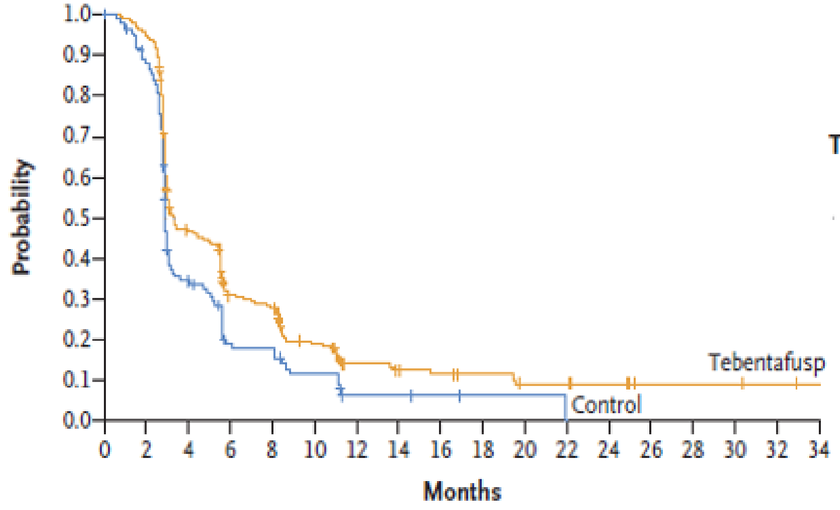
→ **Randomised 2:1**

Stratification by LDH level (>ULN vs ≤ULN)

Tebentafusp:
- 20 µg C1D1
- 30 µg C1D8
- 68 µg C1D15+

Investigator's choice:
- Dacarbazine 1,000 mg/m² Q3W
- Ipilimumab 3 mg/kg Q3W
- Pembrolizumab 2 mg/kg Q3W

B Progression-free Survival



Median Progression-free Survival

	mo (95% CI)
Tebentafusp	3.3 (3.0–5.0)
Control	2.9 (2.8–3.0)

Stratified hazard ratio for disease progression or death, 0.73 (95% CI, 0.58–0.94)

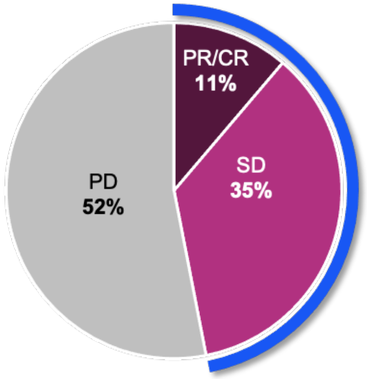
No. at Risk

Tebentafusp	252	233	107	64	58	32	18	14	12	10	7	7	5	2	2	2	1	0
Control	126	97	35	17	16	9	3	3	2	1	1	0						

Nathan P. et al , NEJM 2022

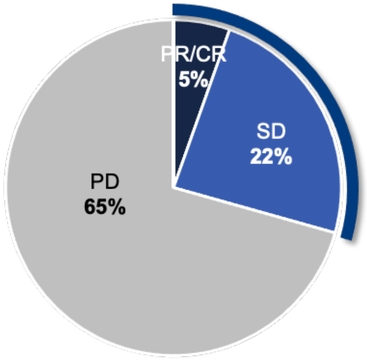
IMC202 : Phase III with Tebentafusp in metastatic uveal melanoma

Tebentafusp

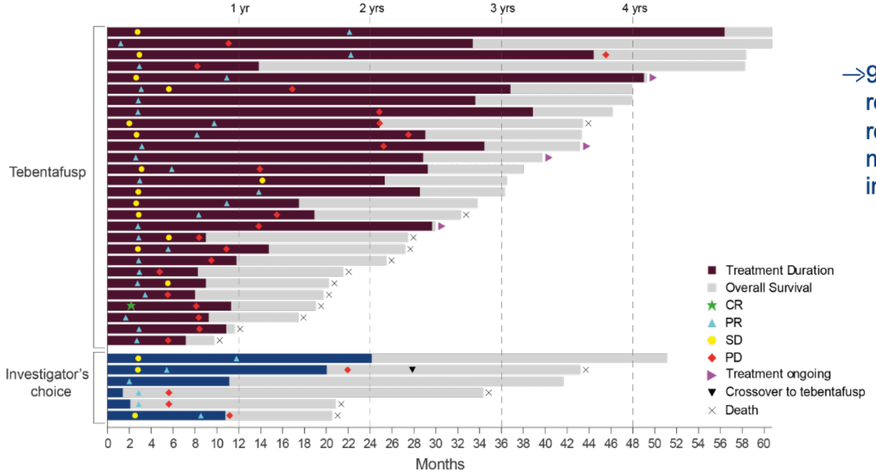


46%
disease control

Investigator's Choice



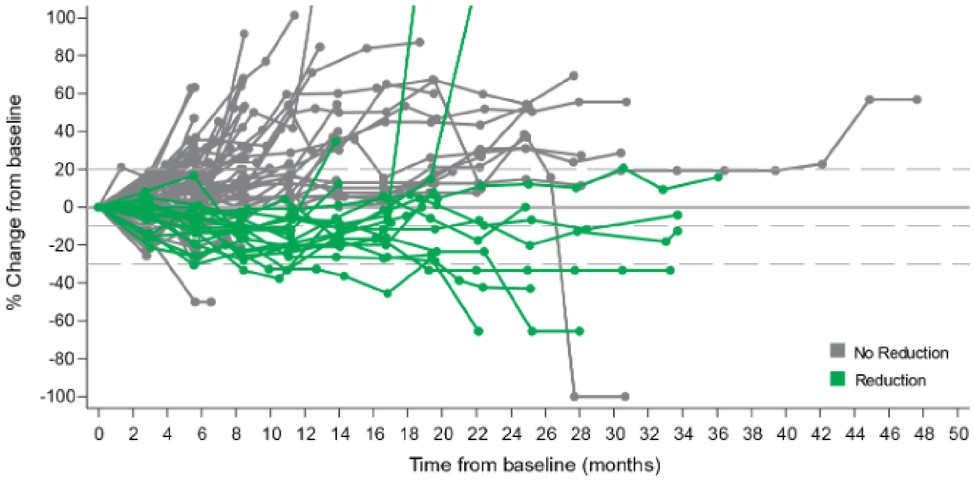
27%
disease control



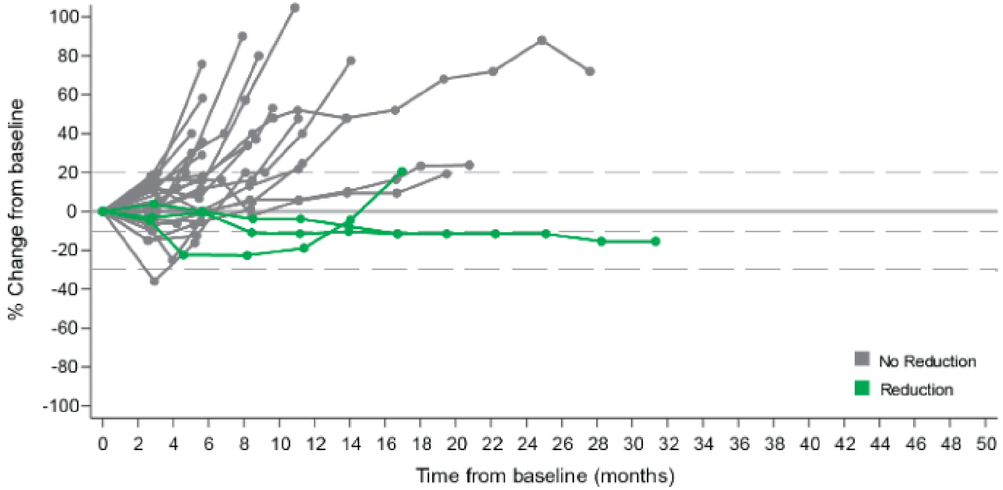
→9/28 (32%) tebentafusp responders maintained response for at least 18 months versus none in the investigator's choice group

BOR = SD

Tebentafusp



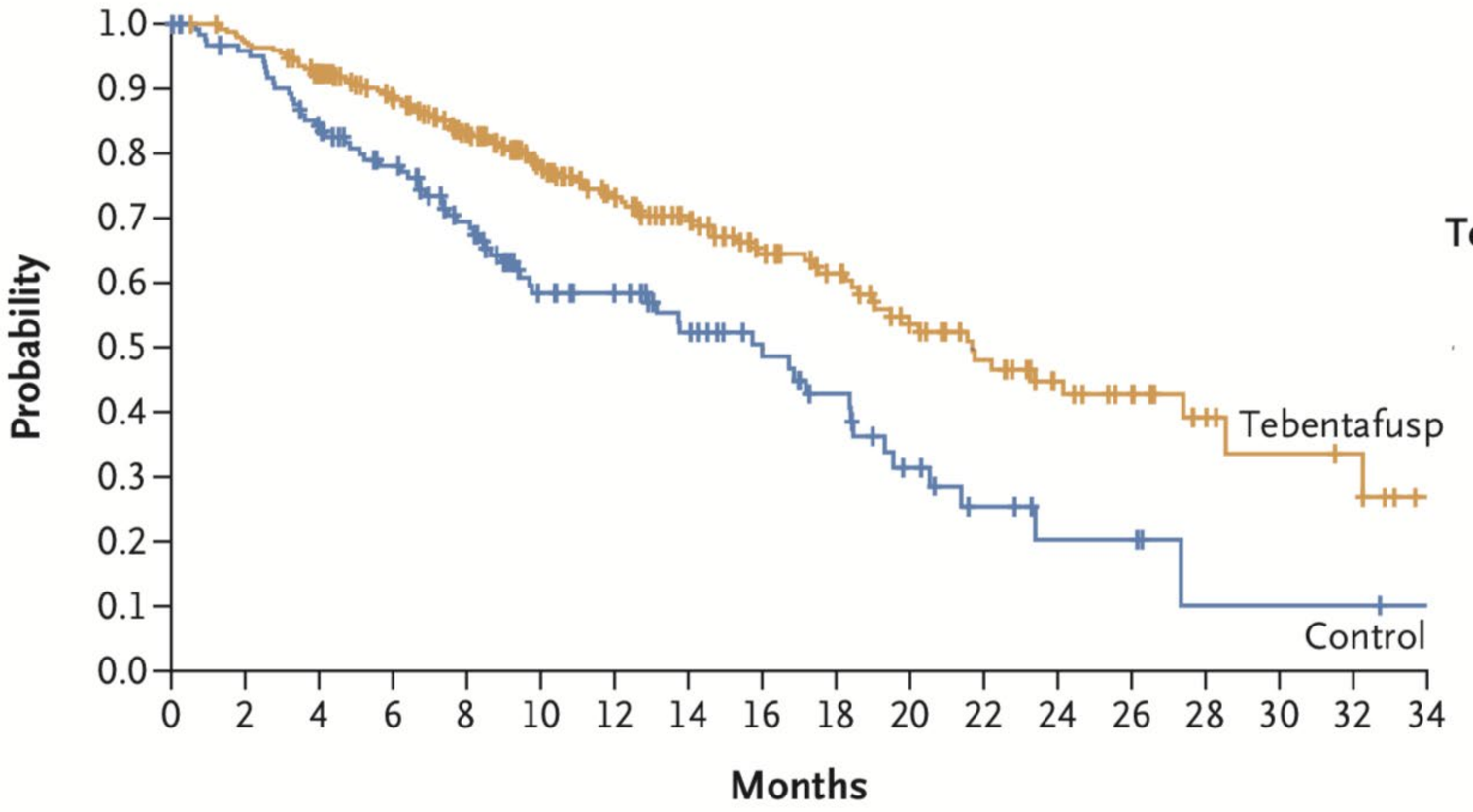
Investigator's choice



→12/87 (14%) SD pts on tebentafusp had tumor burden reduction at Month 18 versus 2/28 (7%) in investigator's choice arm

Nathan P. et al , NEJM 2022

IMC202 : Phase III with Tebentafusp in metastatic uveal melanoma



	Median Overall Survival (95% CI)
	mo
Tebentafusp	21.7 (18.6–28.6)
Control	16.0 (9.7–18.4)

Stratified hazard ratio for death, 0.51 (95% CI, 0.37–0.71)

Median FUP = 14.1 mos

No. at Risk

Tebentafusp	252	242	221	197	167	132	109	90	71	59	44	33	22	17	9	6	5	0
Control	126	116	100	86	69	48	43	34	27	20	12	7	4	4	1	1	1	0

Nathan P. et al , NEJM 2022

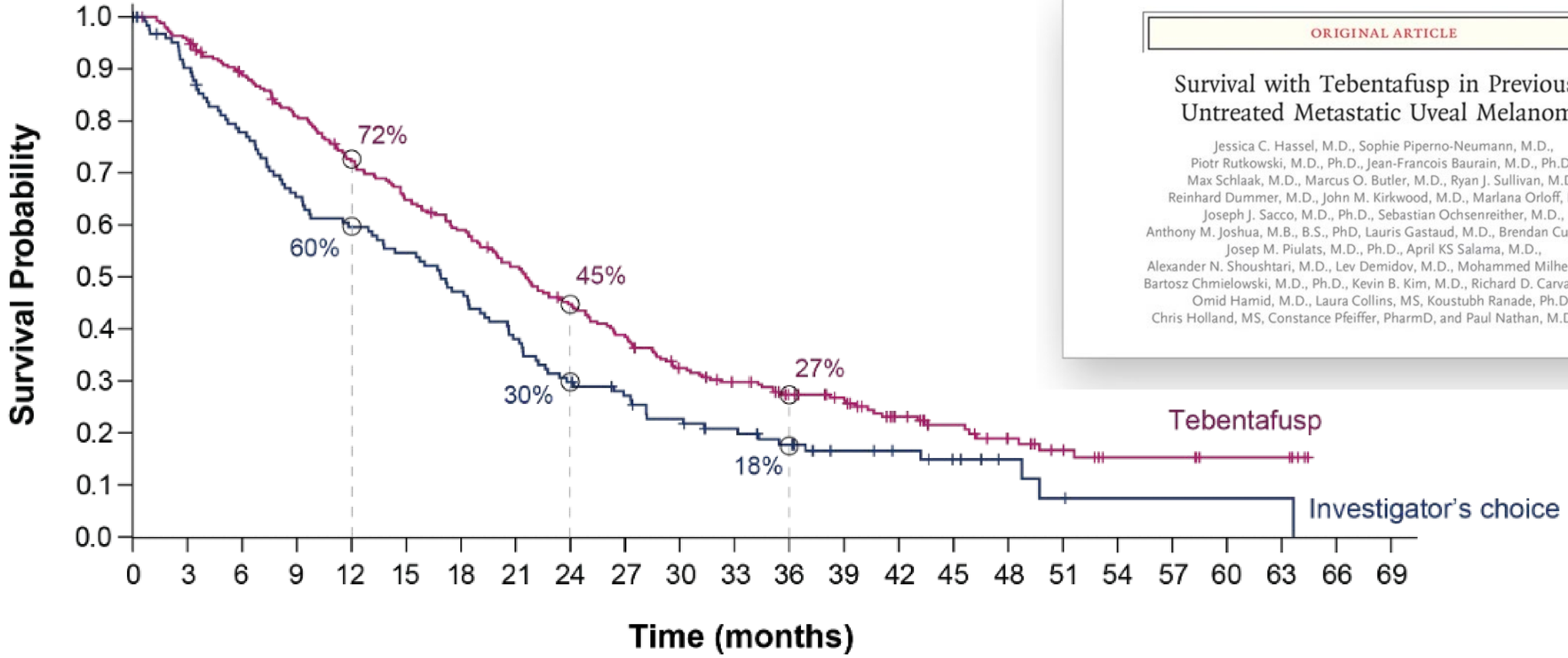
IMC202 : Phase III with Tebentafusp in metastatic uveal melanoma 3y update

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Survival with Tebentafusp in Previously Untreated Metastatic Uveal Melanoma

Jessica C. Hassel, M.D., Sophie Piperno-Neumann, M.D., Piotr Rutkowski, M.D., Ph.D., Jean-Francois Baurain, M.D., Ph.D., Max Schlaak, M.D., Marcus O. Butler, M.D., Ryan J. Sullivan, M.D., Reinhard Dummer, M.D., John M. Kirkwood, M.D., Marlana Orloff, M.D., Joseph J. Sacco, M.D., Ph.D., Sebastian Ochsenreither, M.D., Anthony M. Joshua, M.B., B.S., PhD, Lauris Gastaud, M.D., Brendan Curti, M.D., Josep M. Piulats, M.D., Ph.D., April KS Salama, M.D., Alexander N. Shoushtari, M.D., Lev Demidov, M.D., Mohammed Milhem, M.D., Bartosz Chmielowski, M.D., Ph.D., Kevin B. Kim, M.D., Richard D. Carvajal, M.D., Omid Hamid, M.D., Laura Collins, MS, Koustubh Ranade, Ph.D., Chris Holland, MS, Constance Pfeiffer, PharmD, and Paul Nathan, M.D., Ph.D.

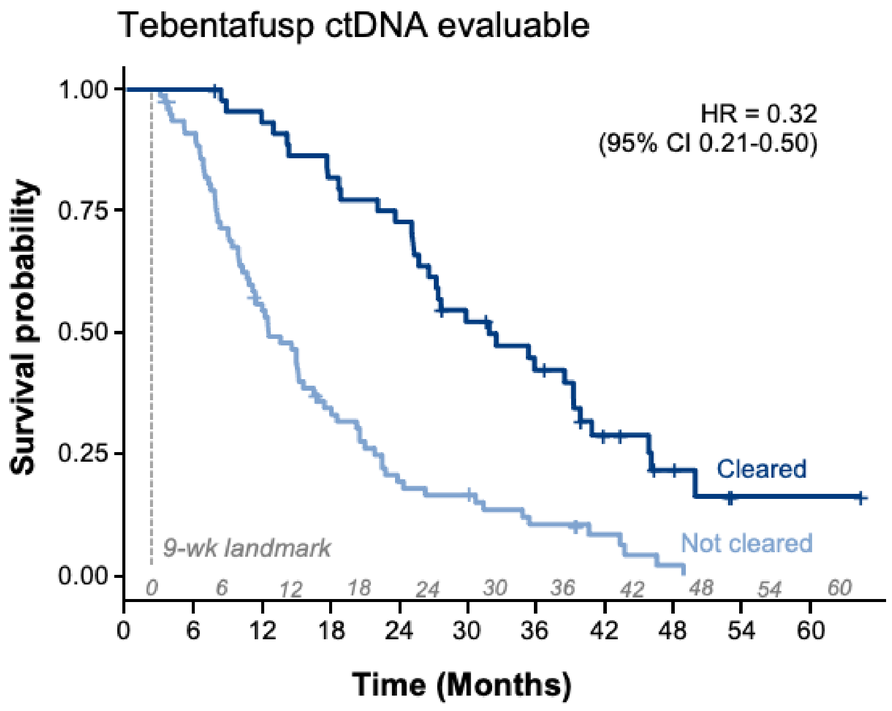


No. at risk

Tebentafusp	252	239	218	197	175	157	142	124	106	92	73	64	53	47	32	25	18	13	8	8	5	5	0
IC	126	110	94	79	72	66	57	46	36	31	25	21	17	12	10	7	4	2	1	1	1	1	0

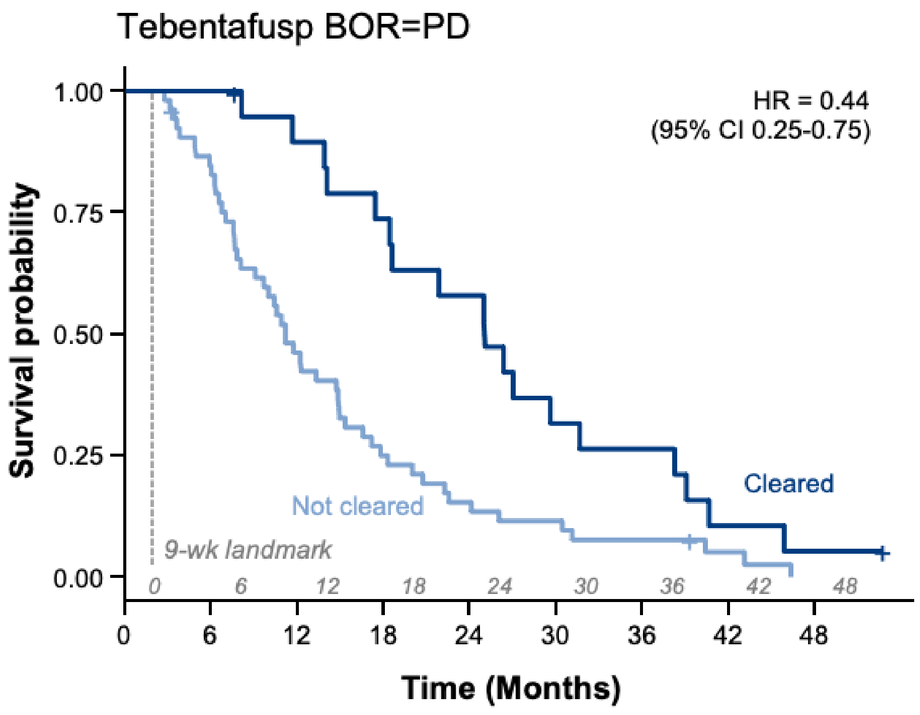
Hassel J.. et al , NEJM 2023

How to explain increase OS without major responses



No. at risk

Not cleared	78	55	36	22	12	9	7	2	0	0	0
Cleared	45	44	38	34	28	20	16	8	3	1	1



No. at risk

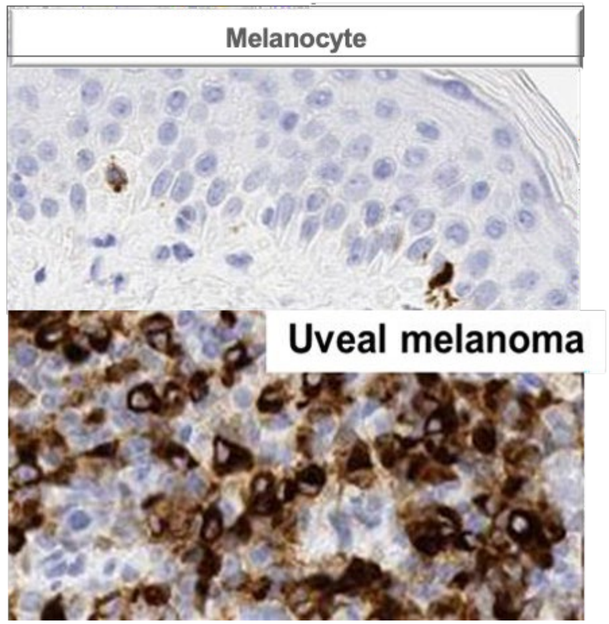
Not cleared	53	33	21	11	6	4	4	1	0
Cleared	20	19	15	12	9	5	5	2	1

1. Sullivan et al. Presented at AACR 2023
All groups analysed based on week 9 landmark

Side Effects of Tebentafusp

>80% UM versus 63% cutaneous melanoma (CM) express gp100 by IHC

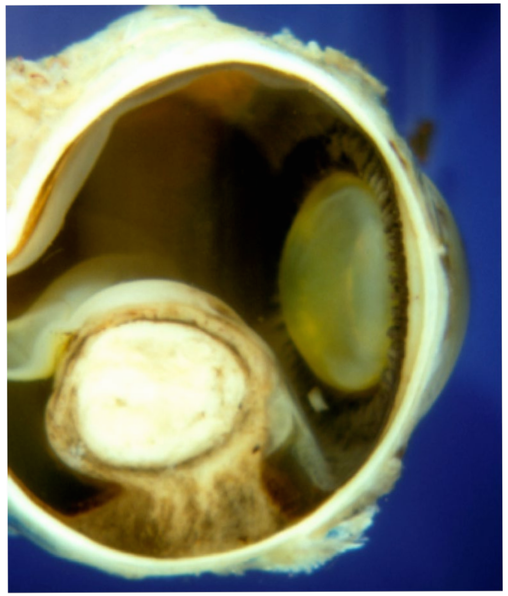
Martinez-Perez et al, Cancers 2021



AE linked with tebentafusp's MoA
Majority AEs occurred in first weeks
AEs are manageable
Discontinuation rate : 2%
No related deaths
CRS AEs : 89% of patients, 1% grade 3
Rash AEs : 83% of patients, 18% grade 3

Table 2. Treatment-Related Adverse Events (Safety Population).*

Event	Tebentafusp Group (N=245)		Control Group (N=111)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any treatment-related adverse event	243 (99)	109 (44)	91 (82)	19 (17)
Cytokine release syndrome†	217 (89)	2 (1)	3 (3)	0
Rash‡	203 (83)	45 (18)	27 (24)	0
Pyrexia	185 (76)	9 (4)	3 (3)	0
Pruritus	169 (69)	11 (4)	23 (21)	0
Chills	114 (47)	1 (<1)	3 (3)	0
Nausea	105 (43)	2 (1)	21 (19)	0
Fatigue	101 (41)	7 (3)	29 (26)	1 (1)
Hypotension	93 (38)	8 (3)	0	0
Dry skin	72 (29)	0	4 (4)	0
Vomiting	64 (26)	1 (<1)	7 (6)	0
Erythema	56 (23)	0	1 (1)	0
Headache	53 (22)	1 (<1)	3 (3)	1 (1)
Aspartate aminotransferase increased	47 (19)	11 (4)	9 (8)	0
Alanine aminotransferase increased	43 (18)	7 (3)	8 (7)	2 (2)
Lipase increased	32 (13)	9 (4)	7 (6)	6 (5)
Diarrhea	31 (13)	2 (1)	16 (14)	3 (3)
Lymphopenia	22 (9)	6 (2)	2 (2)	0
Hyperbilirubinemia	21 (9)	5 (2)	2 (2)	0
Hypophosphatemia	19 (8)	7 (3)	1 (1)	0
Hypertension	15 (6)	9 (4)	2 (2)	1 (1)



Pending Issues in MUM

In MUM patients should we use first local or systemic treatment ?

When do we have to stop Tebentafusp ?

Are Brain Mets an issue for MUM patients ?

Oligometastatic Disease in MUM ?

Mrs T30493W - a woman of 50 years old

Nov 2007
cT4b - left eye
Enucleation

+/- 6 years

Sep 2013
Lung Met
10x11 mm
ILL

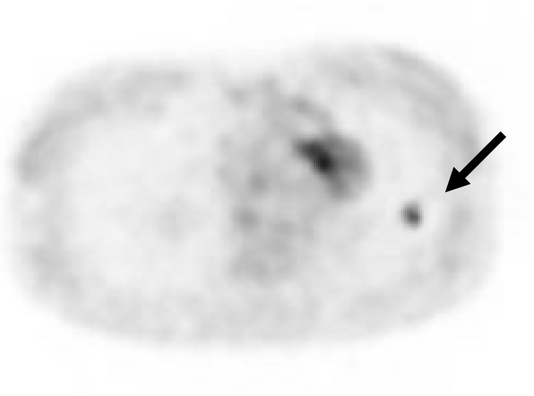
SURGERY
20 Sept 2013

+/- 10years

Oct 2023
CR

CT-SCAN

PET



Sep 2013

YES, we can

Oligometastatic Disease in MUM ?

Mr HD5504L - a man of 55 years old

Dec 2019

cT2a - right eye
Brachytherapy

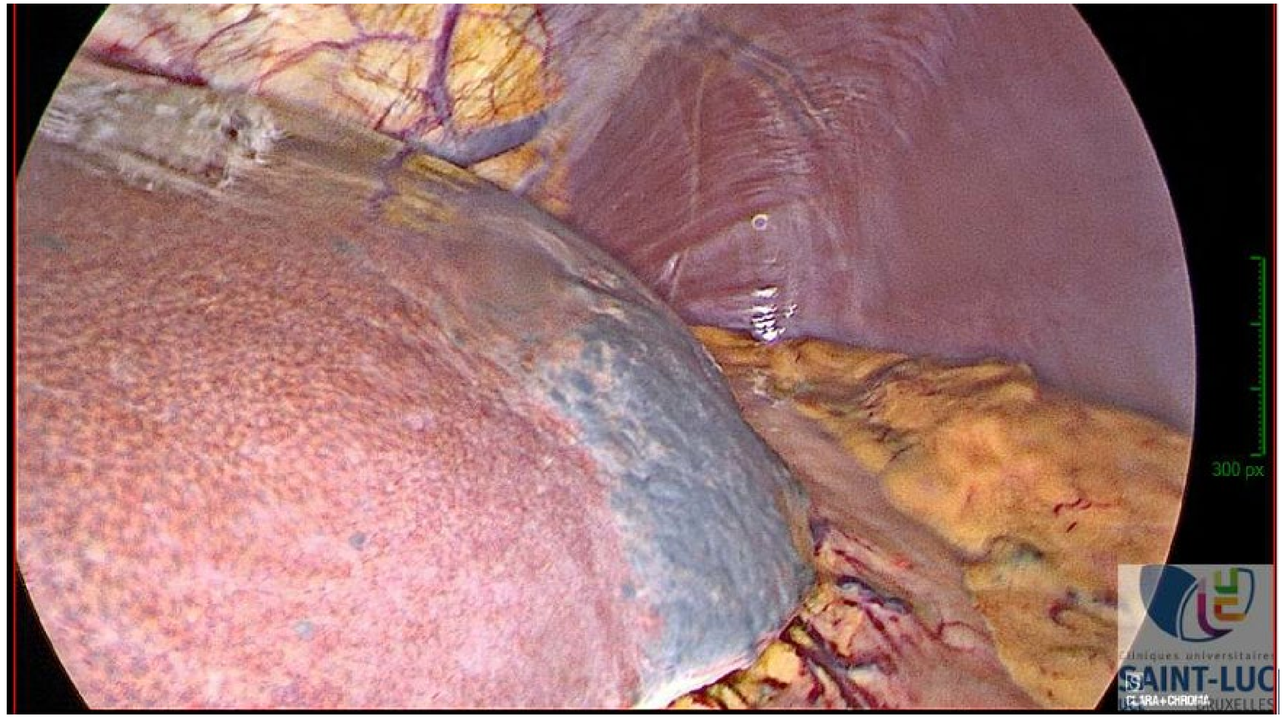
+/- 2 years

Dec 2021

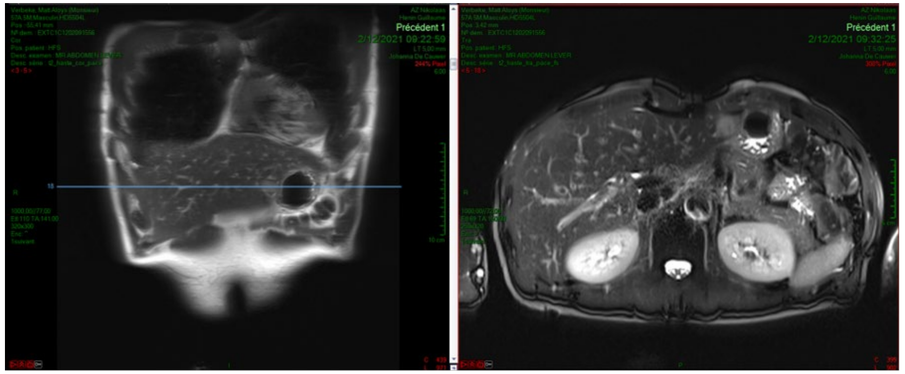
Liver Met

SURGERY

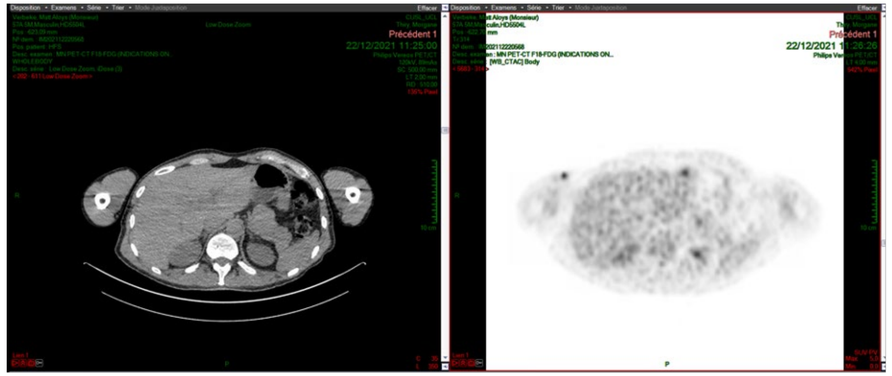
25 Jan 2022



MRI

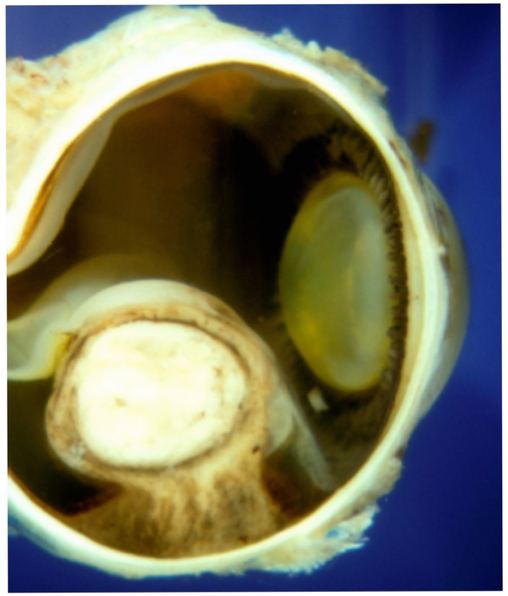


PET-scan



Dec 2021

NO, we can't



Pending Issues in MUM

When do we have to stop Tebentafusp ?

When to Stop Tebentafusp ?

Mr HD5504L - a man of 55 years old

Dec 2019
cT2a - right eye
Brachytherapy

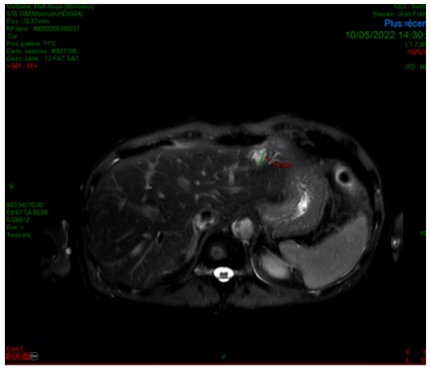
+/- 2 years

Dec 2021
Liver Met

SURGERY
25 Jan 2022

TEBENTAFUSP
+/- 6 mois

MRI



May 2022

Relapse tumor bed
One new lesion

When to Stop Tebentafusp ?

Mr HD5504L - a man of 55 years old

Dec 2019
cT2a - right eye Brachytherapy

+/- 2 years

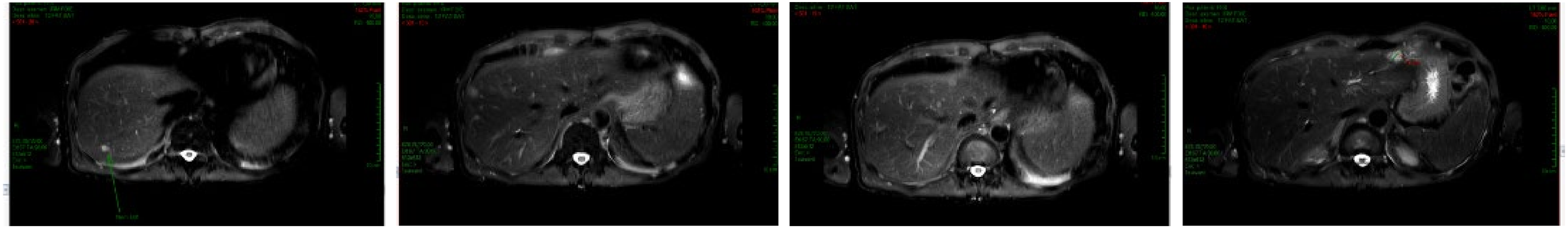
Dec 2021
Liver Met

SURGERY
25 Jan 2022

TEBENTAFUSP
+/- 6 mois

Aug 2022
Liver Mets

MRI



Aug 2022

When to Stop Tebentafusp ?

Mr HD5504L - a man of 55 years old

Dec 2019
cT2a - right eye
Brachytherapy

+/- 2 years

Dec 2021
Liver Met

SURGERY
25 Jan 2022

TEBENTAFUSP

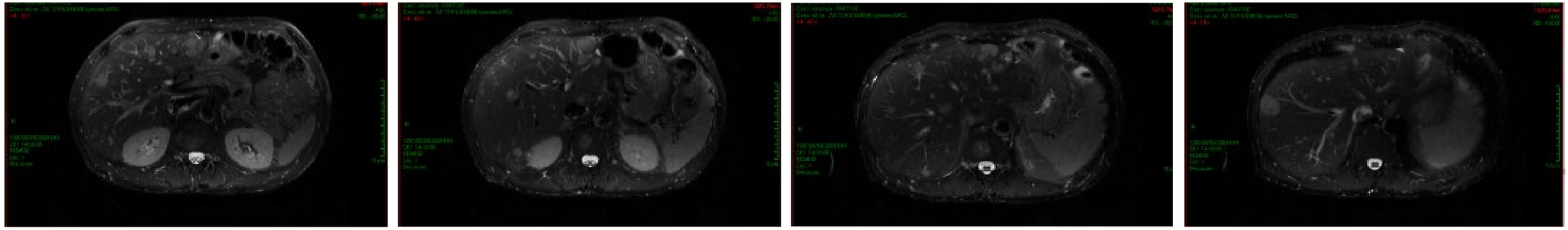
+/- 6 mois

Aug 2022
Liver Mets

NIVO + IPI

Nov 2022

MRI



Nov 2022

When to Stop Tebentafusp ?

Mr HD5504L - a man of 55 years old

Dec 2019
cT2a - right eye
Brachytherapy

+/- 2 years

Dec 2021
Liver Met

SURGERY
25 Jan 2022

TEBENTAFUSP

+/- 6 mois

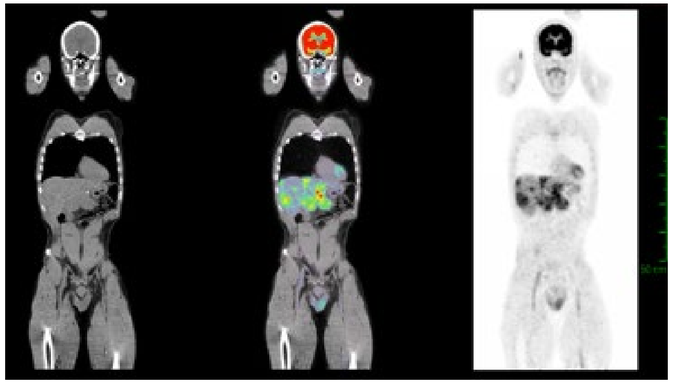
Aug 2022
Liver Mets

NIVO + IPI

Nov 2022

TMZ

PET-scan



Feb 2023

Passed away in May 2023

When to Stop Tebentafusp ?

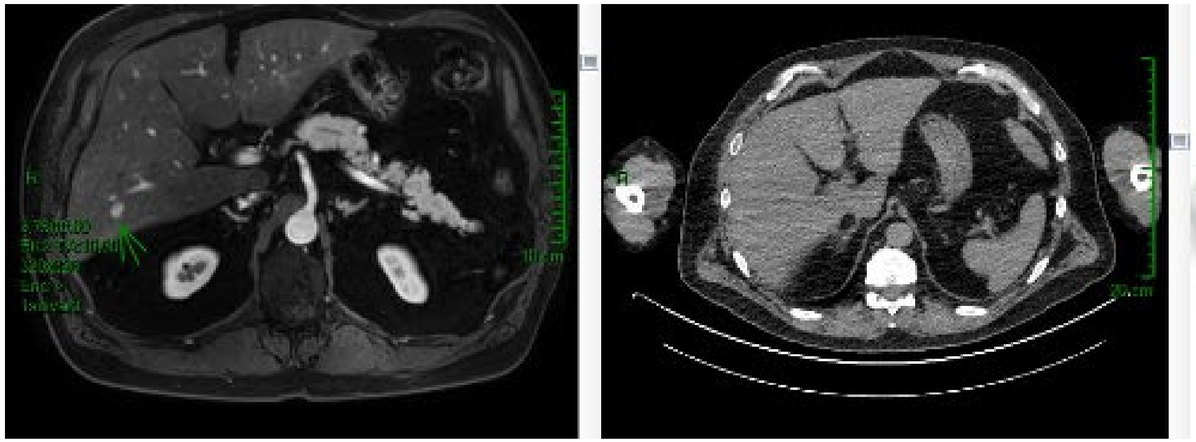
Mr H83122F - a man of 59 years old

Fev 2014 — +/- 2 years — **Sep 2022**

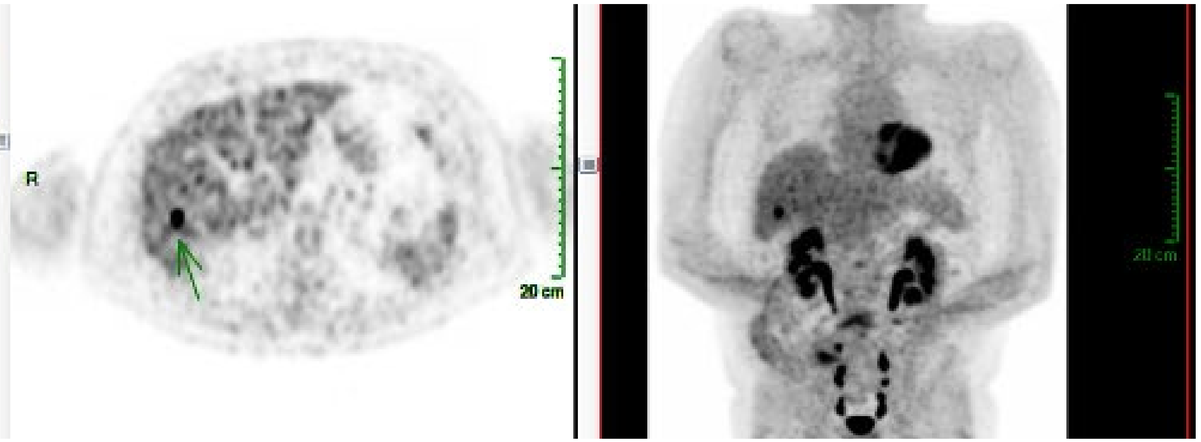
cT4b - right eye
Brachytherapy

Liver Mets

IRM



PET-scan



Sep 2022

When to Stop Tebentafusp ?

Mr H83122F - a man of 59 years old

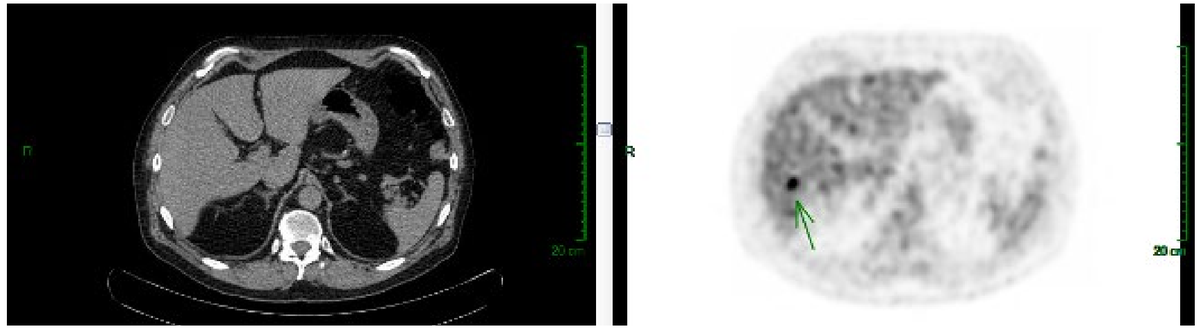
Fev 2014
cT4b - right eye
Brachytherapy

+/- 2 years

Sep 2022
Liver Mets

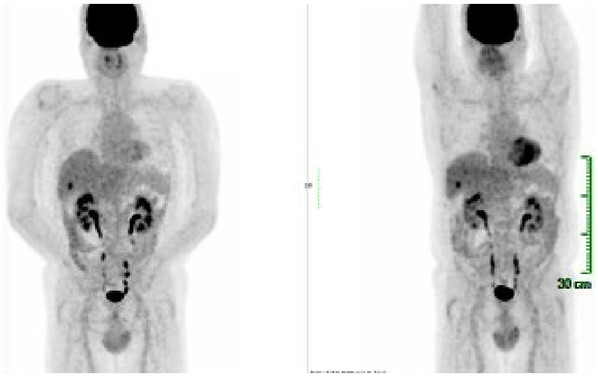
TEBENTAFUSP

PET-scan



Feb 2023

PET-scan



May 2023 **Feb 2023**

When to Stop Tebentafusp ?

Mr H83122F - a man of 59 years old

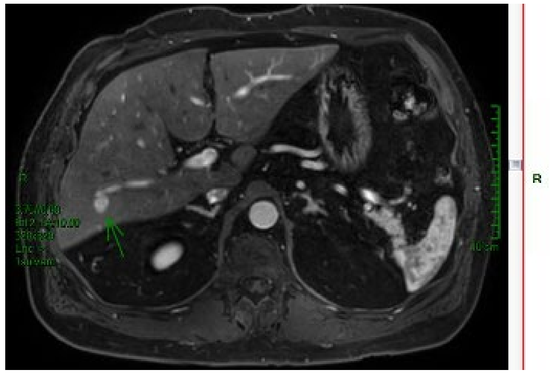
Fev 2014
cT4b - right eye
Brachytherapy

+/- 2 years

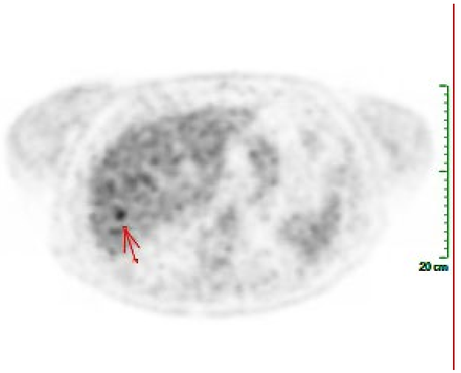
Sep 2022
Liver Mets

TEBENTAFUSP

IRM

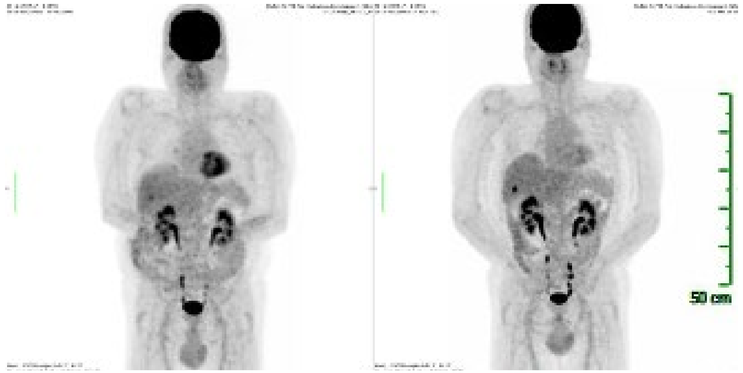


PET-scan



Aug 2023

PET-scan



Aug 2023 **May 2023**

Still in Response

Long Evolution with Immunotherapy is possible for MUM patients

Mr S17655J - a man of 71 years old

Oct 2008
cT3 - left eye
Radiotherapy

+/- 6 years

Jun 2014
Hepatic Met

SURGERY

+/- 1 year

Jan 2015
Hepatic mets multiples

CHEMOTH

PD

Apr 2015
Hepatic mets multiples

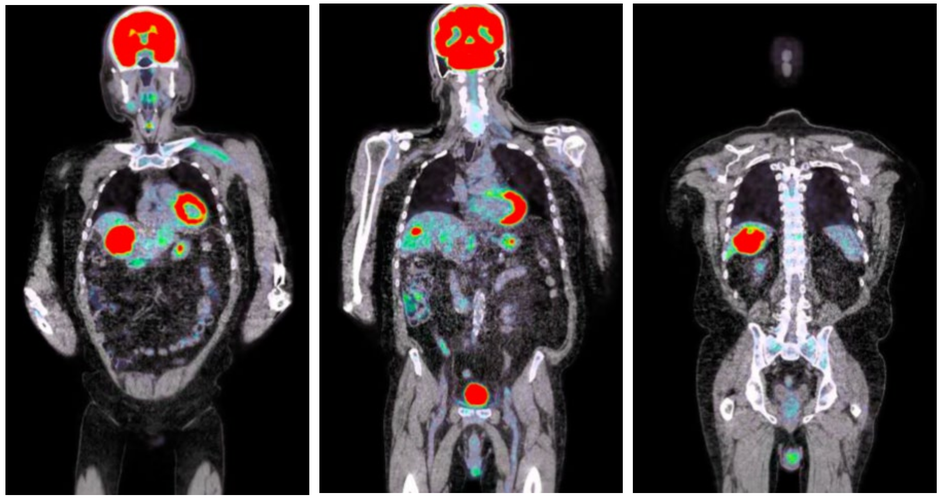
IPILI

CR
colitis
hypophysitis

Mar 2016
Hepatic mets multiples

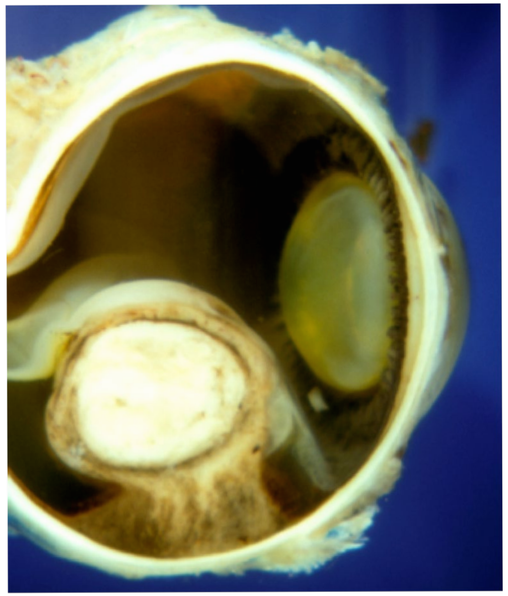
PEMBRO

SD
51 infusions



Fev 2019

Passed away in July 2020



Pending Issues in MUM

Are Brain Mets an issue for MUM patients ?

When to Stop Tebentafusp

Mrs EP4305R - a woman of 59 years old

May 2018
cT3c - right eye
Brachytherapy

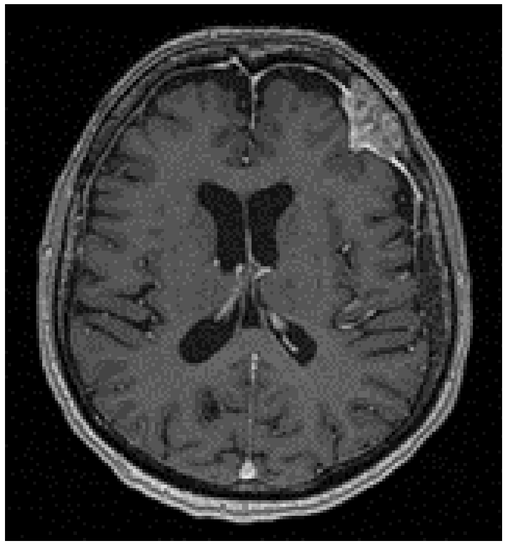
Dec 2020
cT3b - right eye
Brachytherapy

Jul 2021
Liver Mets
Min 4 Lesions

TEBENTAFUSP

Jul 2022
CR for liver
Brain met

IRM



Jul 2022

When to Stop Tebentafusp

Mrs EP4305R - a woman of 59 years old

May 2018
cT3c - right eye
Brachytherapy

Dec 2020
cT3b - right eye
Brachytherapy

Jul 2021
Liver Mets
Min 4 Lesions

TEBENTAFUSP

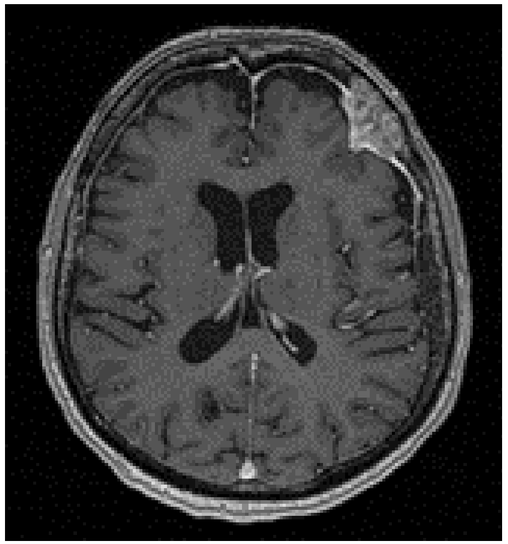
Jul 2022
CR for liver
Brain met

TEBE

Dec 2022
CR for liver
Brain met

NIVO + IPI

IRM



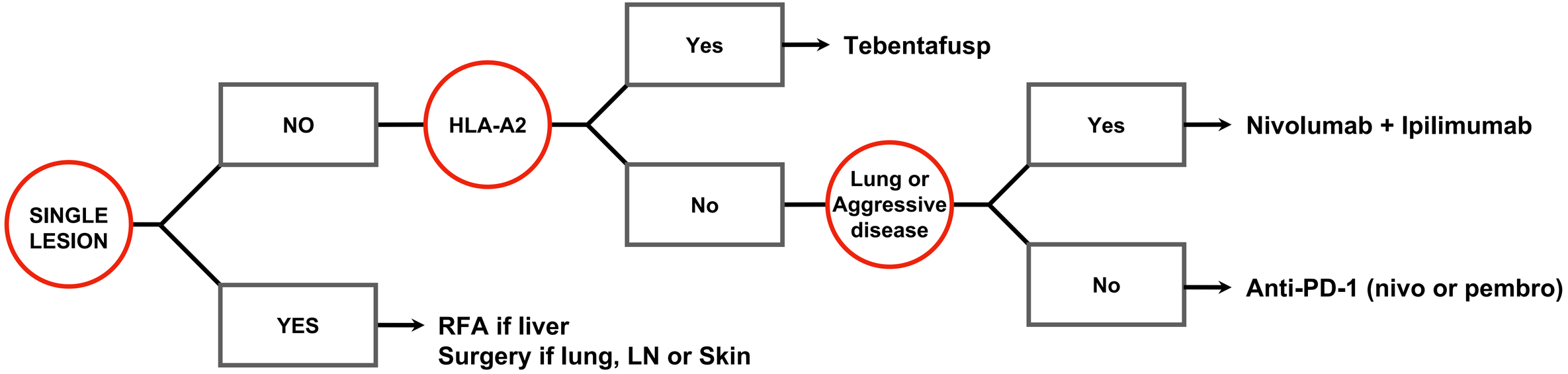
Jul 2022

IRM

Dec 2022

Passed away in Mar 2023

Metastatic Uveal Melanoma - Treatment Algorithm



Metastatic Uveal Melanoma - Keep up the Fight, Keep Believing !