foro debate oncología

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Experiencia en el uso de Tebentafusp en Melanoma Uveal, manejo práctico

Josep M Piulats

IDIBELL Institut d'Investigació Biomèdica de Bellvitge
ICO Institut Català d'Oncologia
Universitat de Barcelona
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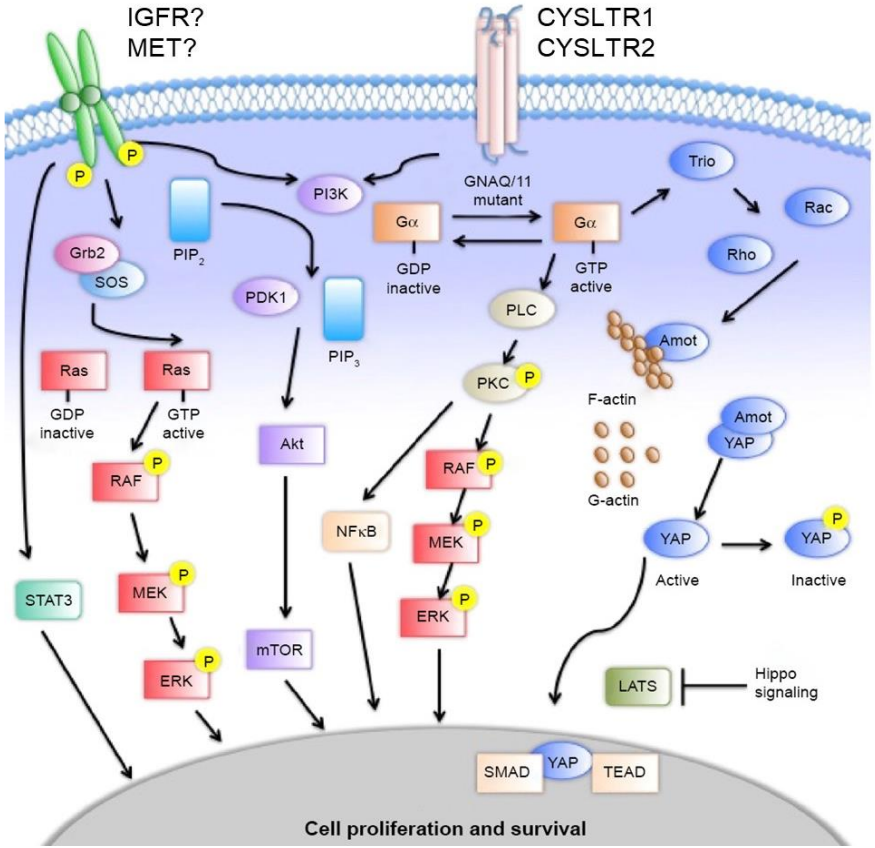
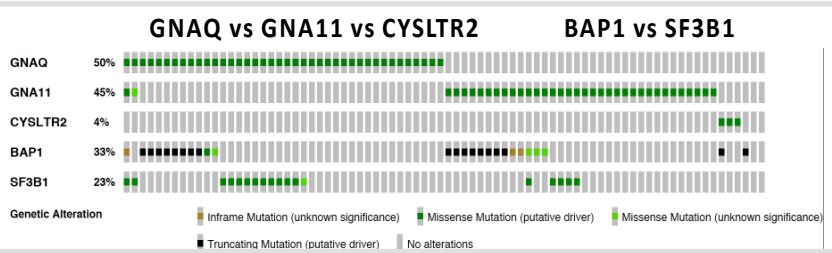
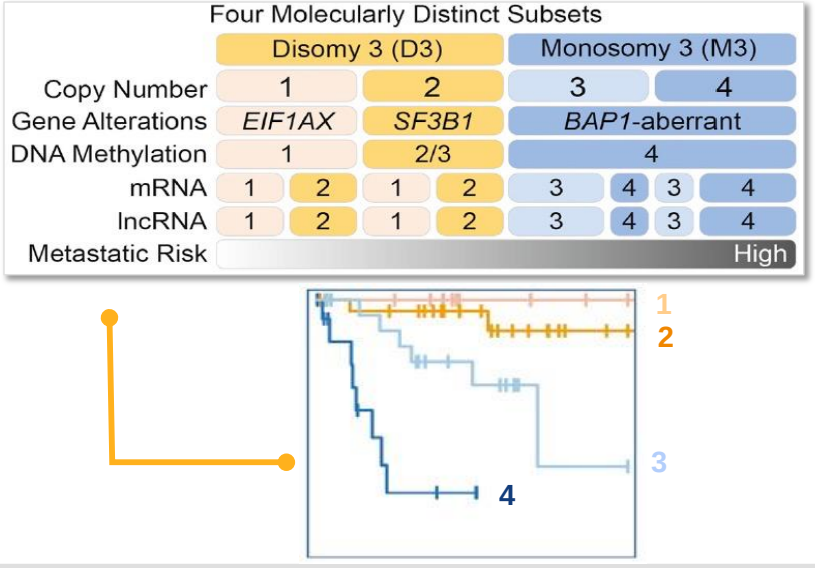
UM vs CM

Parameter	Uveal melanoma (UV)	Cutaneous melanoma (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 tumour[1,2] Predominantly liver[1,4] Haematogenous dissemination[1,4]	15.5% develop metastases[3] Most common sites (in order): lungs, liver, bones, brain[1,3,4] Lymphatic and haematogenous spread[1,4]
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[16–19] 1-year survival rate of 36–81%[16,20,12] 5-year survival rate of 10–70%[17–19,21]
Responsiveness to immunotherapy	**Low response rates to immunotherapy, ICI combination therapy has yielded results inferior to those seem in CM**[1,4,13,22–24]	Higher response to ICIs (anti-CTLA4, anti-PD-1, anti-PD-L1) than UM, especially to ICI combination (up to 58% ORR)[1,26]
Targeted therapies	**None**[1,25]	Anti-BRAF, anti-MEK[1]
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]	

Molecular Biology



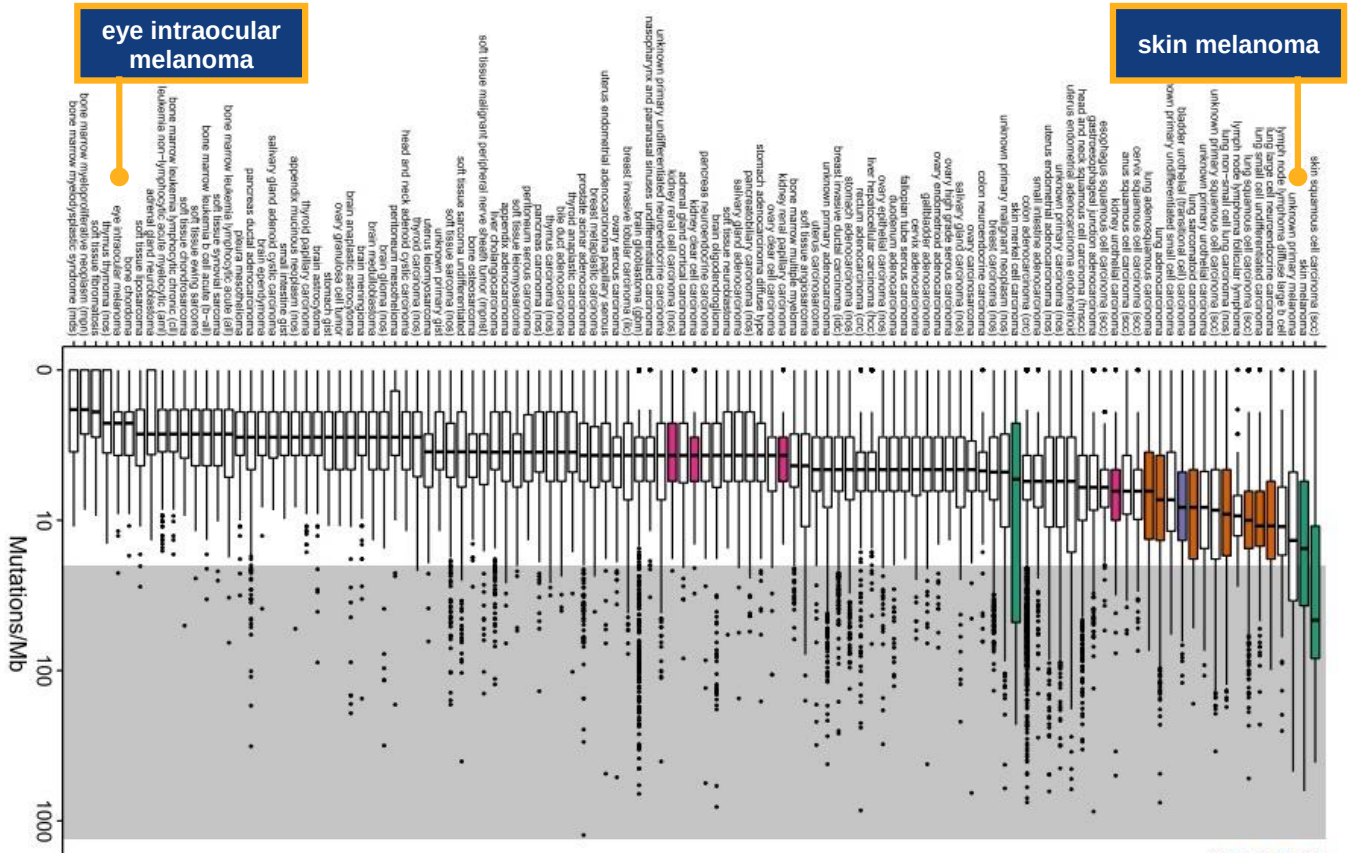




Krantz BA, et al. Clin Ophthalmol. 2017 Jan 31;11:279-289
Carvajal RD, et al. J Clin Oncol. 2018 Apr 20;36(12):1232-1239

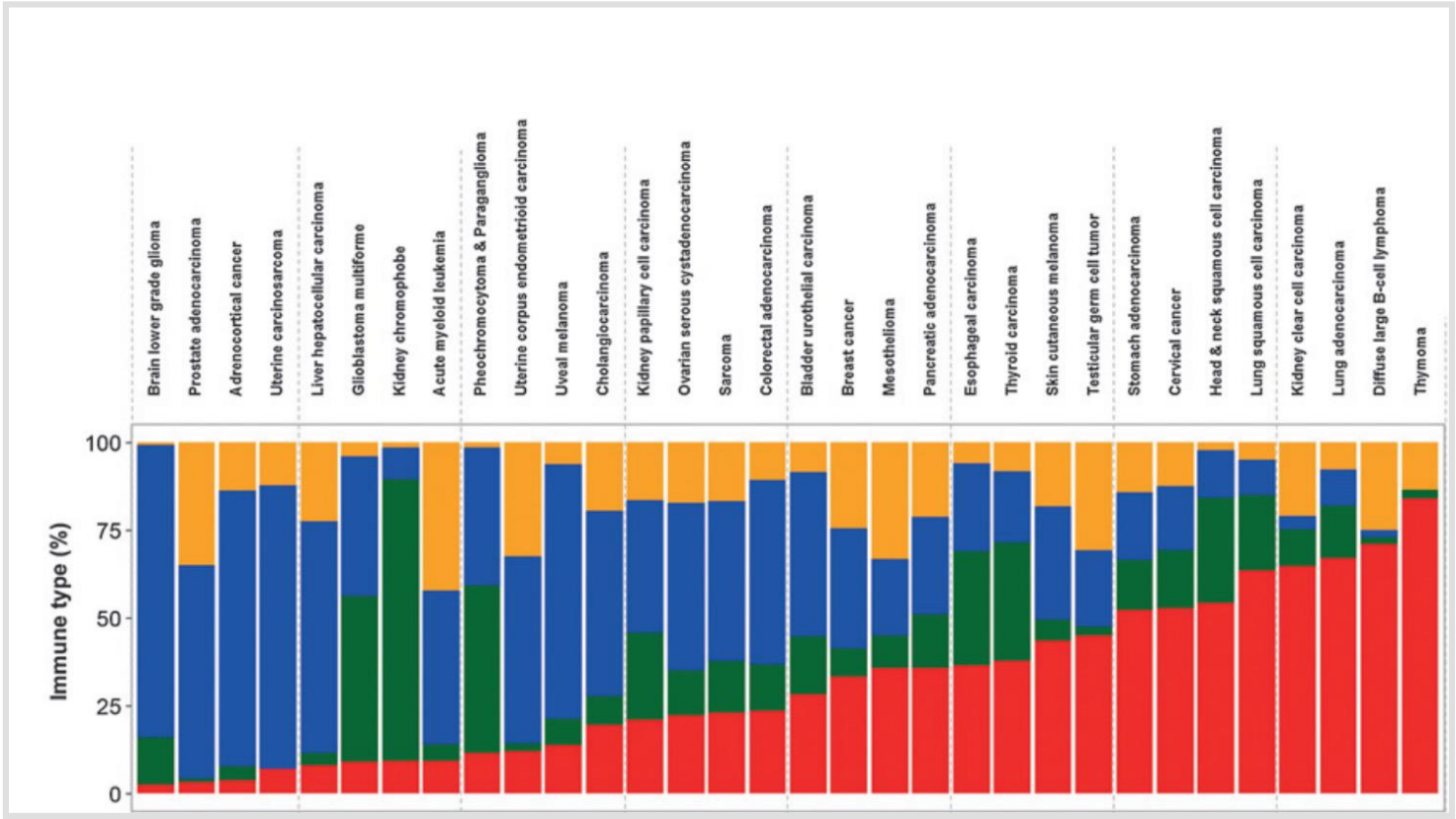
Antigenicity

The landscape of **tumor mutation burden**.
For all disease types with greater than 100 samples, the median **mutation burden** is plotted for each disease type.



Chalmers ZR, et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. Genome Med. 2017 Apr 19;9(1):34.

Immunogenicity



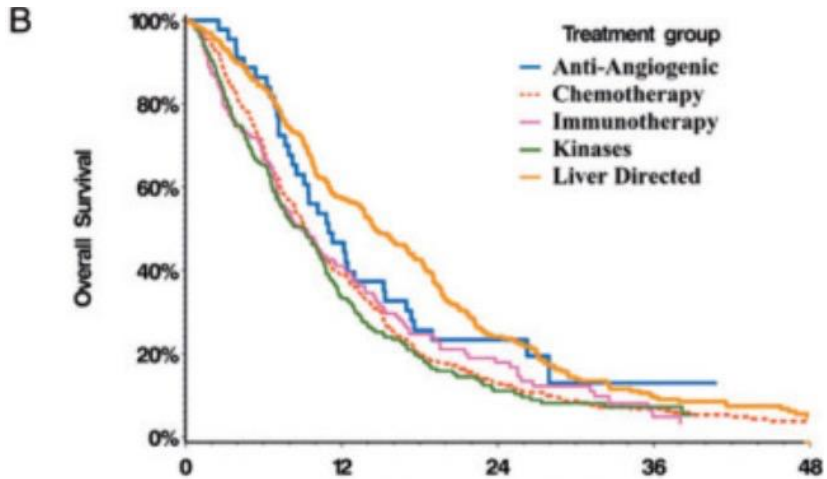
CY Ock et al. Clin Cancer Res **22**, 2261-2270 (2016)

Systemic Treatment

Management of metastatic disease[1]

- **Clinical trials** (preferred)
- **LDTs:** chemoembolisation, radioembolisation, regional isolation perfusion (PHP, IHP), immunoembolisation
- **Local therapies:** thermal ablation, cryotherapy, surgery, radiotherapy (photon beam or SRS)
- **Systemic therapies:** immunotherapy, cytotoxic regimens, targeted therapy
- **Palliative care**

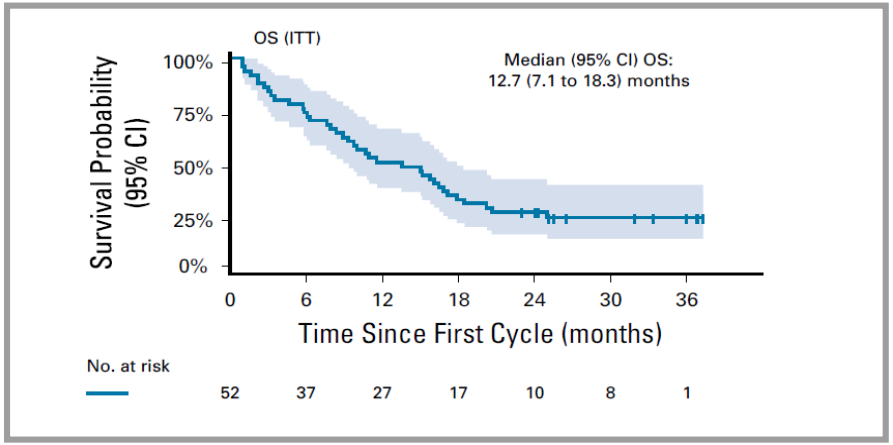
IHP, isolated hepatic perfusion; LDT, liver-directed therapy;
PHP, percutaneous hepatic perfusion; SRS, stereotactic radiosurgery;

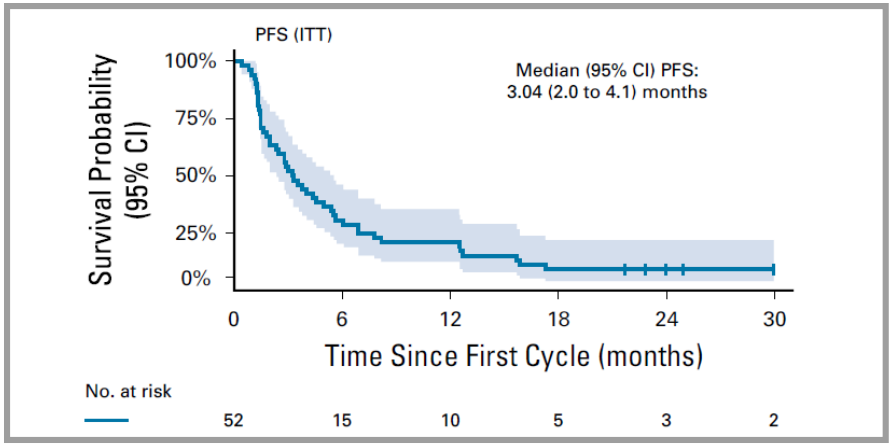


Patients at Risk					
Anti-Angiogenic	44	20	7	1	0
Chemotherapy	306	111	31	15	6
Immunotherapy	133	53	17	3	2
Kinases	198	63	16	7	2
Liver Directed	231	129	53	19	8

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Uveal Melanoma V.1.2023. Accessed [July, 2023].; Khoja L, et al. Ann Oncol. 2019 Aug 1;30(8):1370-1380.

Ipilimumab + Nivolumab



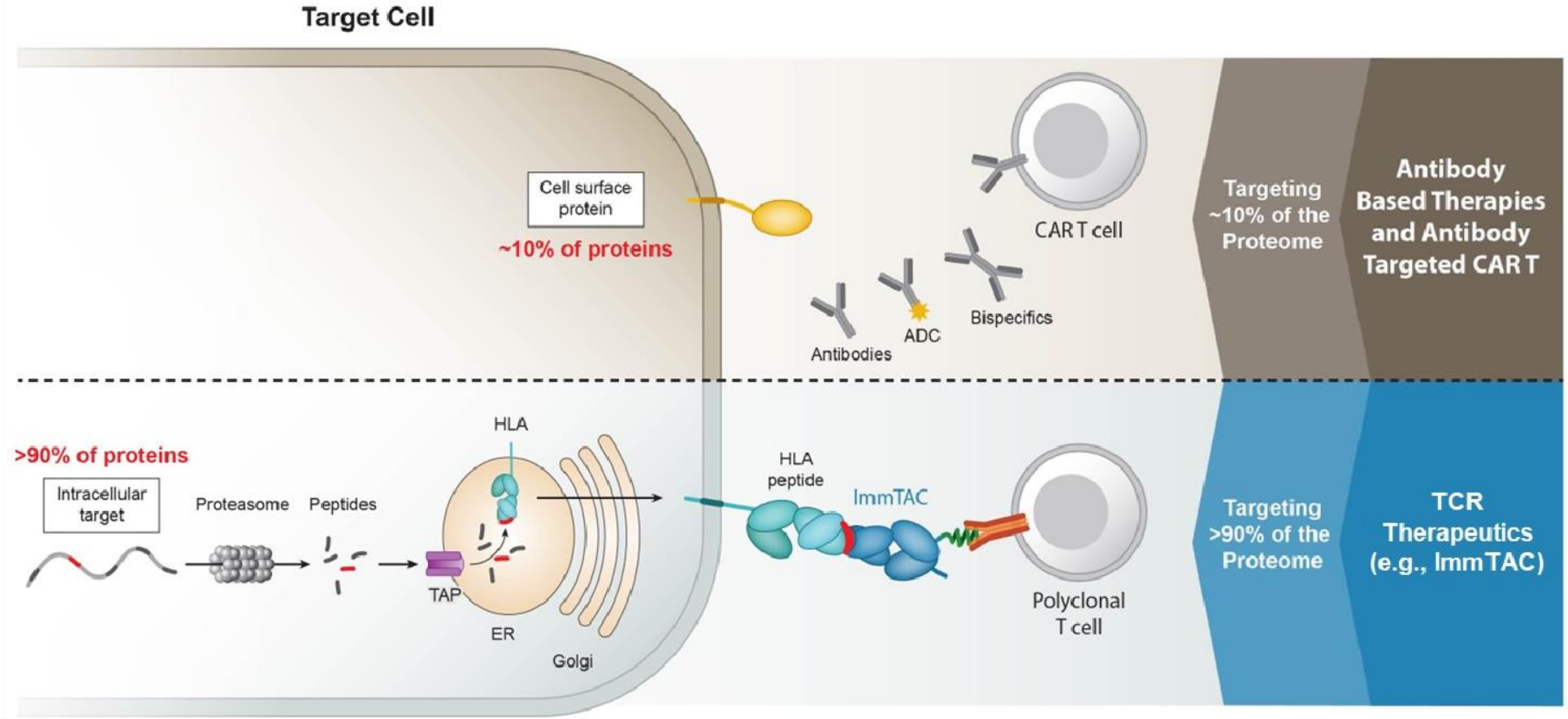


All TR-AEs

Event	n	%
Total	49	94,2
Skin-related events[b]	32	61,5
Fatigue	30	57,7
Liver toxicity/liver-related events[b]	19	36,5
Diarrhea	15	28,8
Fever	8	15,4
Nausea	7	13,5
Hypothyroidism	7	13,5
Edema	4	7,7
Hypophysitis	4	7,7
Hepatitis	4	7,7
Vomiting	3	5,8
Thyroiditis	3	5,8
Constipation	3	5,8
Arthralgia	3	5,8

Piulats JM,et al. J Clin Oncol. 2021 Feb 20;39(6):586-598.

ImmTAC

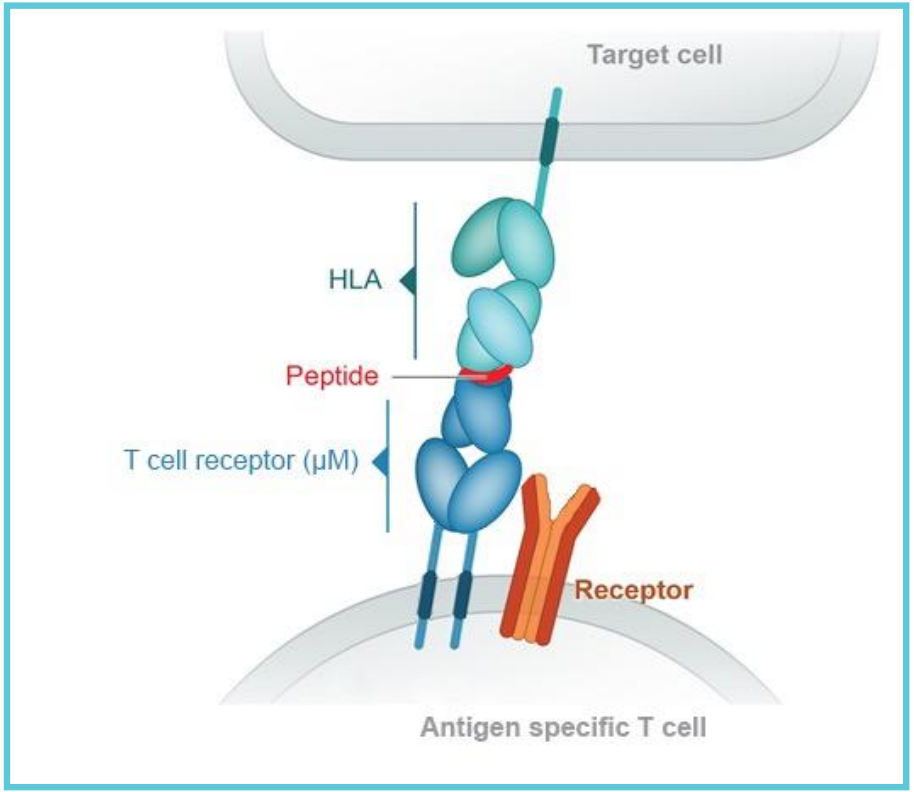


ImmTAC, Immune mobilizing T cell receptor Against Cancer; TCR, T cell receptor.

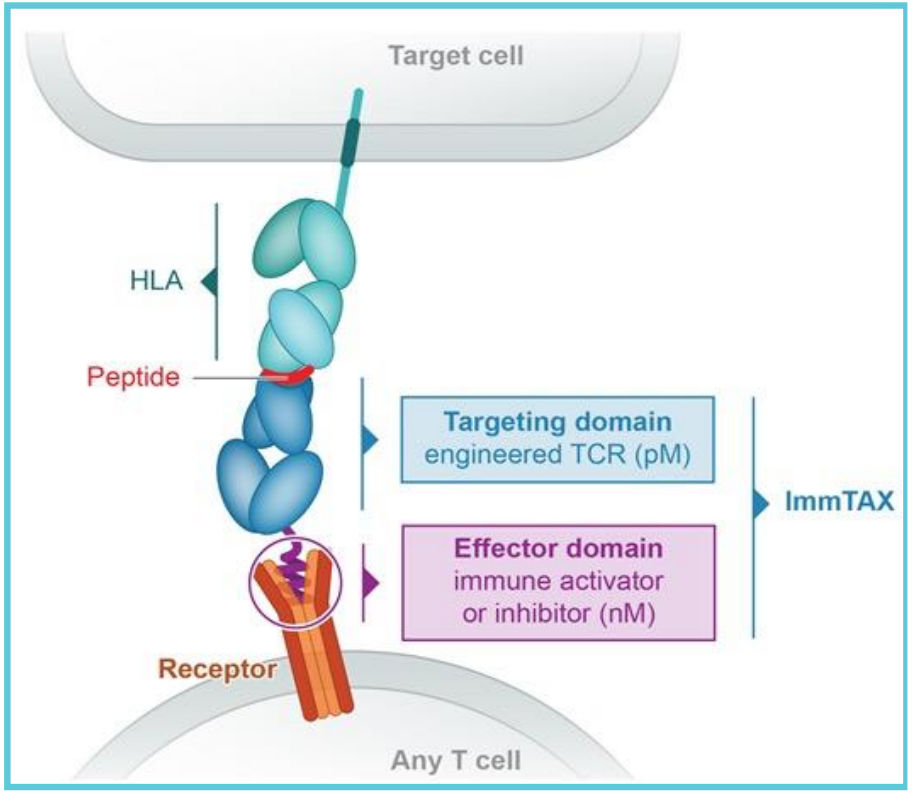
Piperno-Neumann S, et al. Presented at AACR 2021.

Tebentafusp

Natural TCR

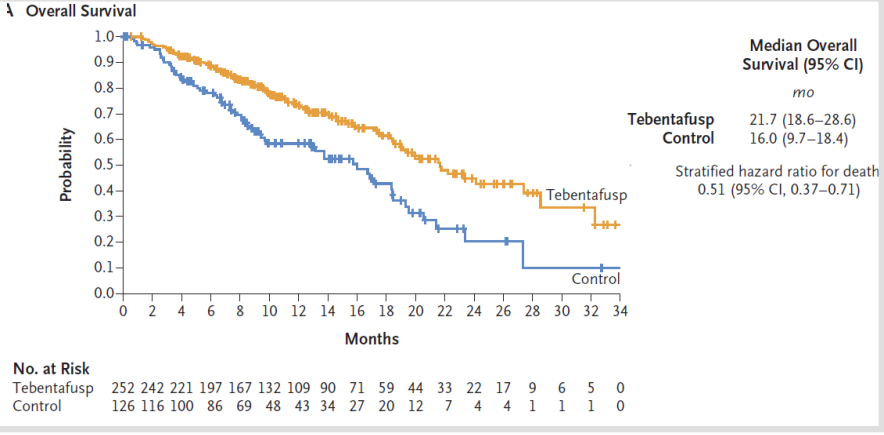


ImmTAC



1. Damato BE, *et al. Cancers (Basel)* 2019;11:971;

Tebentafusp Phase III



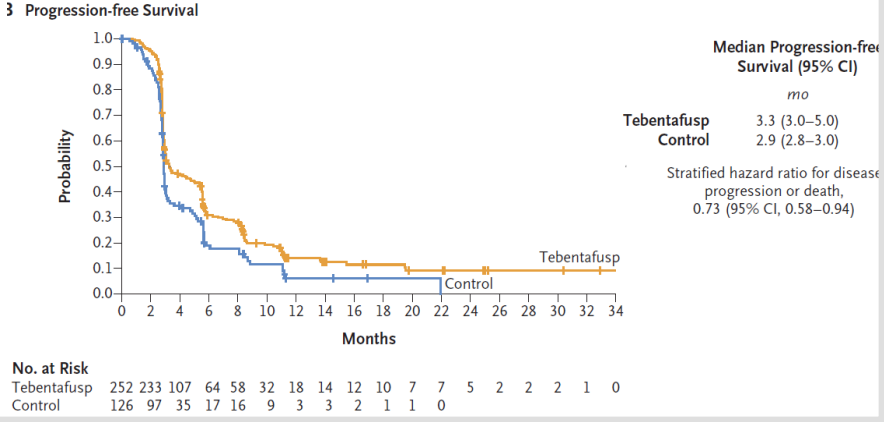


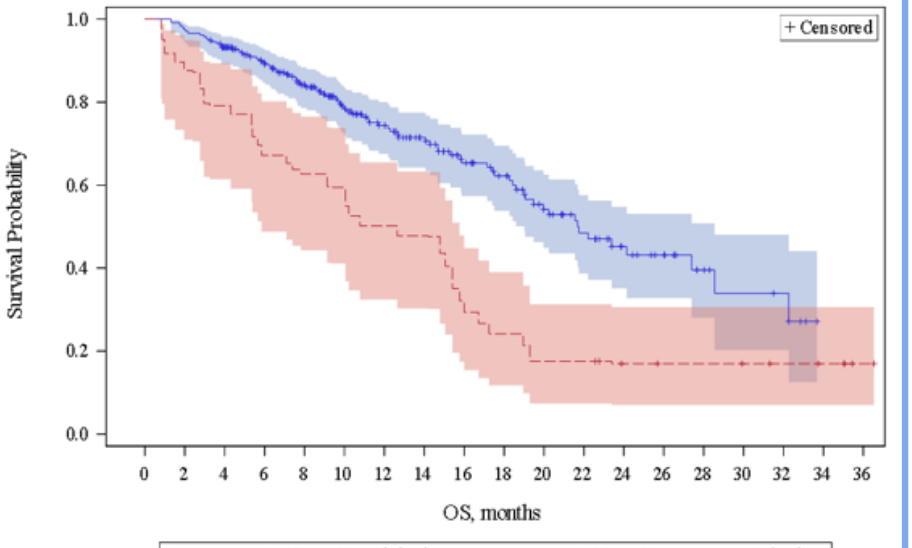
Table 2. Treatment-Related Adverse Events (Safety Population).*

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)

Nathan P, et al. N Engl J Med. 2021 Sep 23;385(13):1196-1206.

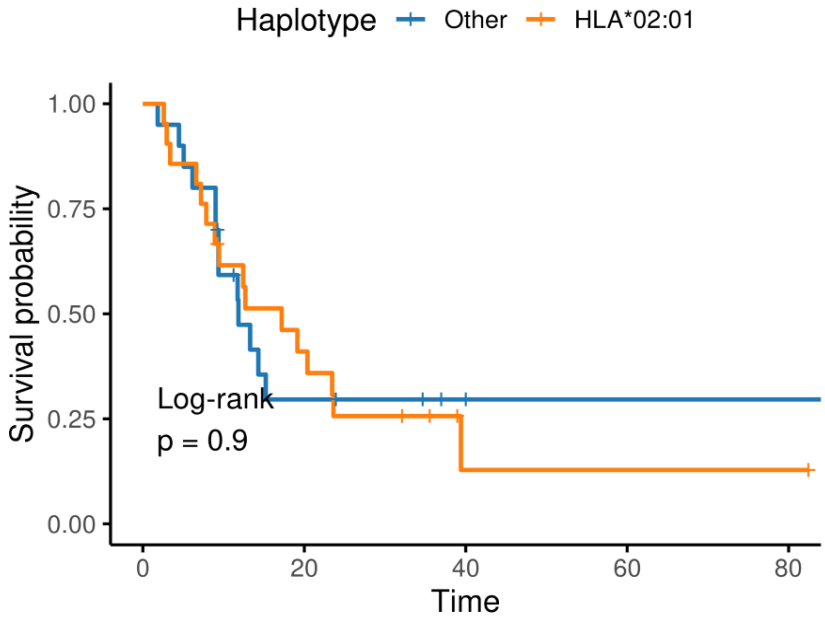
Tebentafusp vs I+N

Adjusted Product-Limit Survival Estimates
With Number of Subjects at Risk and 95% Confidence Limits



IMCgp100	237	231	214	190	161	127	106	87	69	58	43	33	22	17	9	6	5	0
Ipi+Nivo	239	209	189	160	150	142	120	114	77	58	42	42	32	31	31	24	18	13	1

HLA-A*02:01 is **not a prognosis** factor for UM



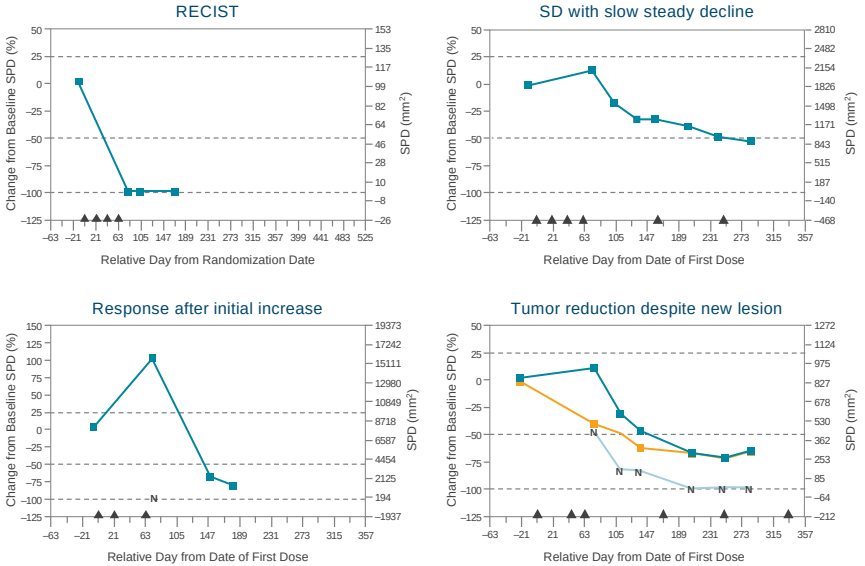
OS favored tebetafusp vs ipilimumab + nivolumab in propensity score analysis

Piulats JM, et al. Presented at ESMO 2022.

Response Assesment

Landmark paper identified four responses to ipilimumab

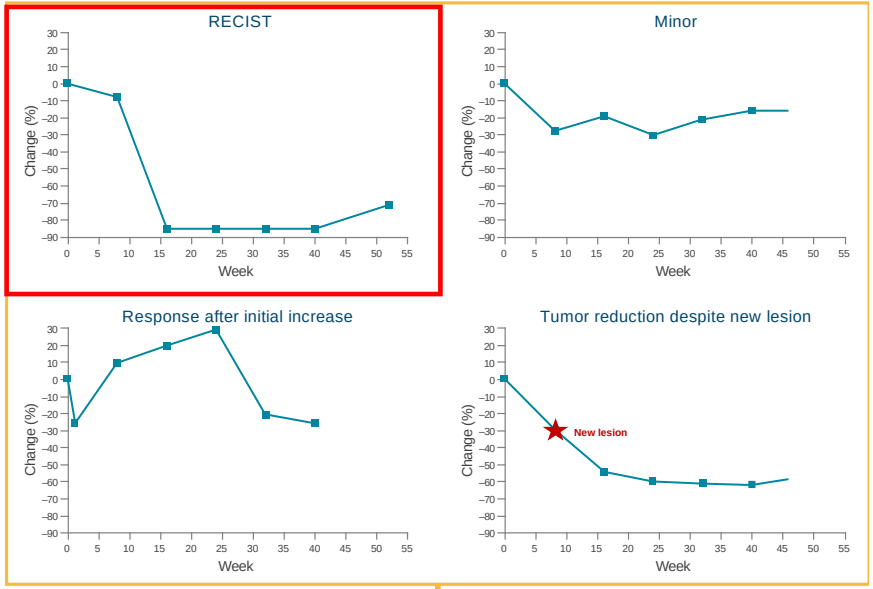
1



PD: progressive disease; irPD: immune-related progressive disease; OS: overall survival; RECIST: Response Evaluation Criteria in Solid Tumors; SD: stable disease; SPD: sum of the product of perpendicular diameters.

Only endpoint in study – 102

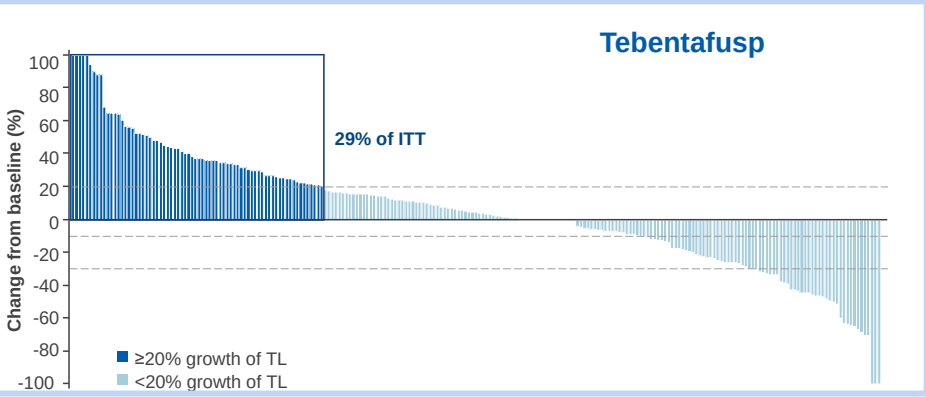
2

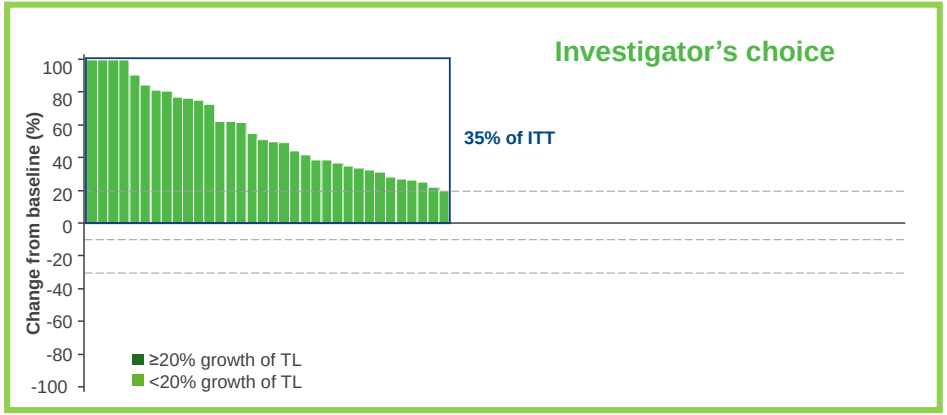


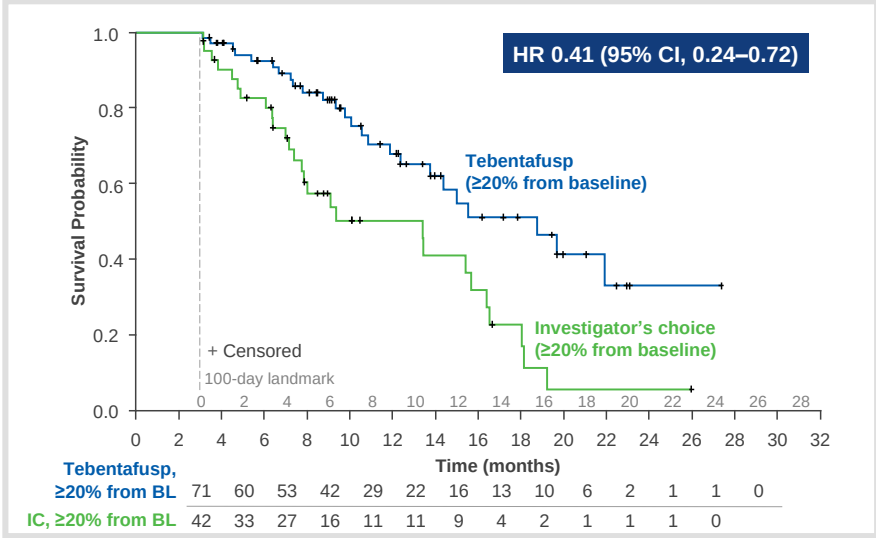
All captured in OS for study – 202

1. Wolchok JD, et al. *Clin Cancer Res* 2009;15:7412–20; 2. Immunocore data on file.

Response Assessment







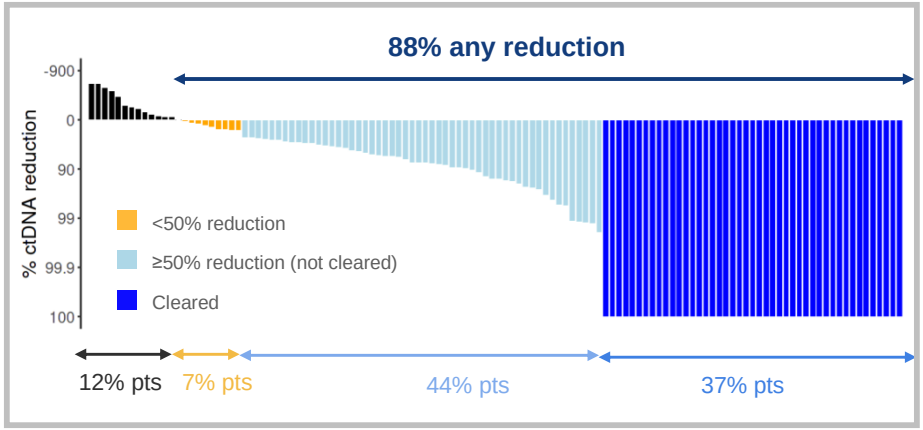
Landmark OS analysis investigated patients who had tumor growth > 20% from baseline as their best change in tumor size in study

- These patients are traditionally considered to have **worst prognosis**
- In this subset, the patients treated with tebentafusp **had similar OS benefit** of 60% relative to the IC arm
- **OS benefit remained** when adjusted for baseline age, sex, LDH or ALP>ULN, ECOG =1 and time since primary diagnosis (p<0.0001; ChiSq

Joshua AM, et al. Presented at ASCO 2021. Abstract 9509.

ctDNA

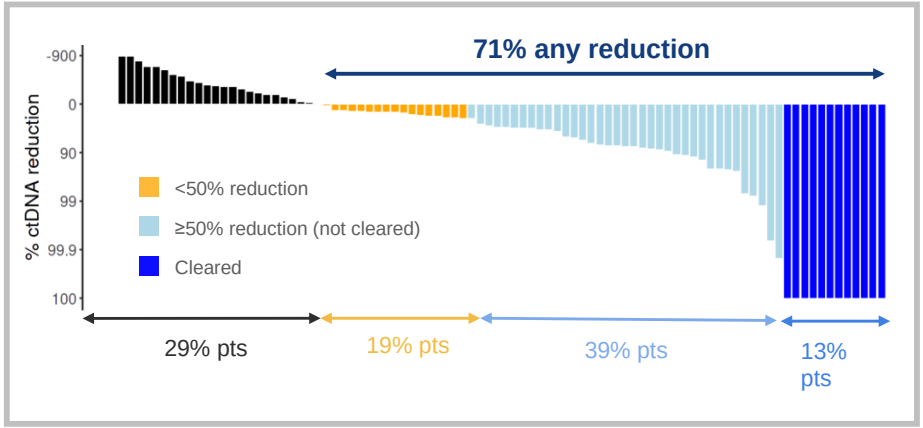
1L untreated patients



BOR	n	No change/ increase	<50% reduction	≥50% reduction (not cleared)	Cleared
PD	73	12 (16%)	6 (8%)	35 (48%)	20 (27%)
SD	36	2 (6%)	3 (8%)	15 (42%)	16 (44%)
PR	14	1 (7%)	0 (0%)	4 (29%)	9 (64%)

ctDNA reductions observed in vast majority of **1L untreated patients** with best RECIST response of PD (61/73), SD (34/36) and PR (13/14), although **RECIST response rates were 5%** (2L+ Phase 2 patients) and 10% (1L Phase 3 patients)

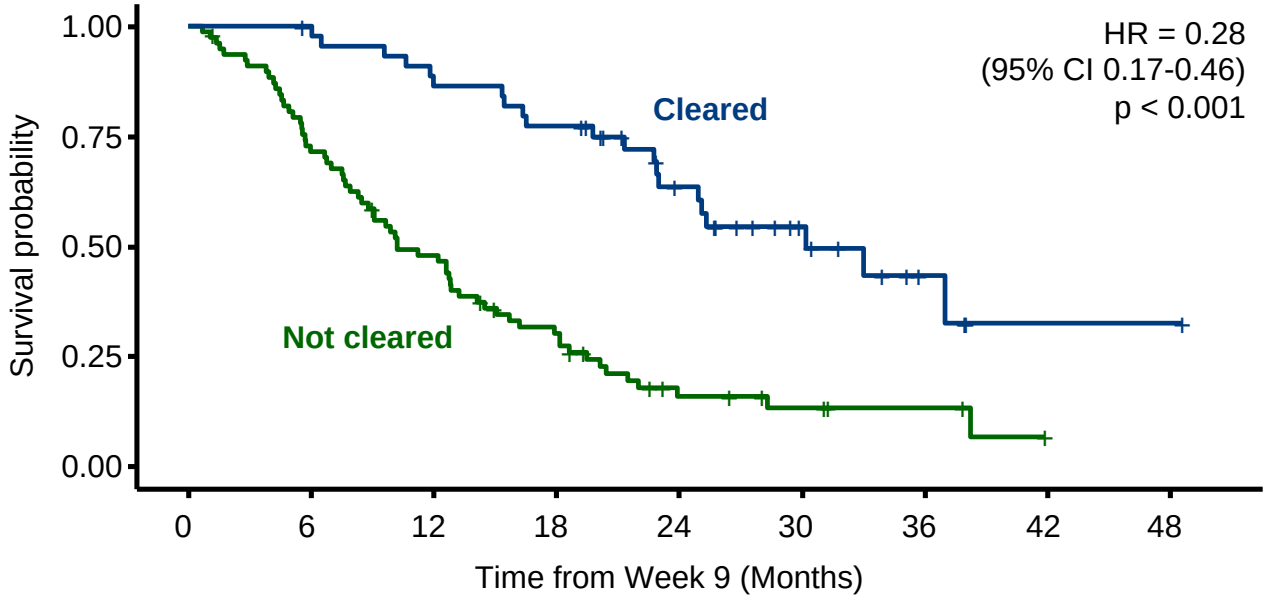
2L+ treated patients



BOR	n	No change/ increase	<50% reduction	≥50% reduction (not cleared)	Cleared
PD	47	17 (36%)	11 (23%)	16 (34%)	3 (6%)
SD	41	8 (20%)	6 (15%)	20 (49%)	7 (17%)
PR	4	2 (50%)	0 (0%)	1 (25%)	1 (25%)
NE	2	0 (0%)	1 (50%)	0 (0%)	1 (50%)

Sullivan R, et al. Presented at AACR 2023.

ctDNA



Not cleared	78	55	36	21	8	5	3	0	0
Cleared	45	44	38	34	21	11	4	1	1

- **37% phase 3 patients cleared ctDNA**, including many with best RECIST response of SD or PD
- Best objective response for patients who cleared ctDNA **by week 9 consisted of 9 (20%) PR, 16 (36%) SD and 20 (44%) PD**

Sullivan R, et al. Presented at AACR 2023.

CRS

CRS* incidence in the IMCgp100-202 study population (N=252):

Overall	Grade 1	Grade 2	Grade 3	Grade 4
89%	12%	76%	0.8%	0%

Observed CRS symptoms:

Most common: chills, nausea, vomiting, fatigue, hypotension and headache

Grade 3: tachycardia, hypoxia, angina pectoris, atrial flutter and left ventricular dysfunction

Further information:

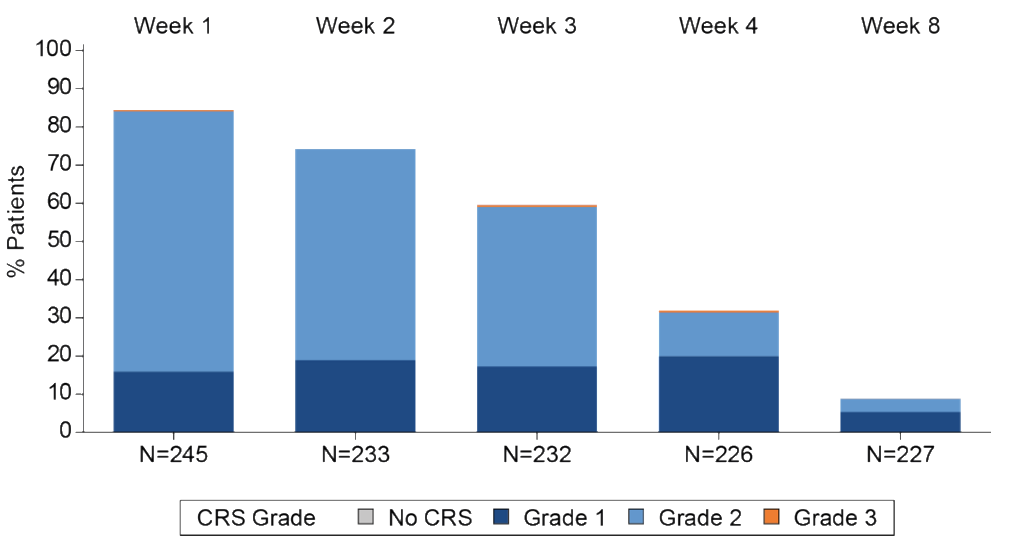
- CRS onset on day of infusion: **84%**
- Median time to symptom resolution: **2 days**
- Discontinuation due to CRS: **1.2%**
- Patients who received tocilizumab: **0.8%†**

In patients in IMCgp100-202 who experienced CRS, all symptoms were reversible and treatment continued in the majority

*Based on American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading of CRS criteria (Lee, et al. 2019); †n=2.
CRS, cytokine release syndrome.

CRS

Frequency and severity of new CRS episodes by dose



Note: patients could experience a distinct CRS episode after more than one dose.

CRS, cytokine release syndrome.

CRS episodes **most commonly occurred after the first dose** of tebentafusp, with decreased frequency and severity after subsequent doses

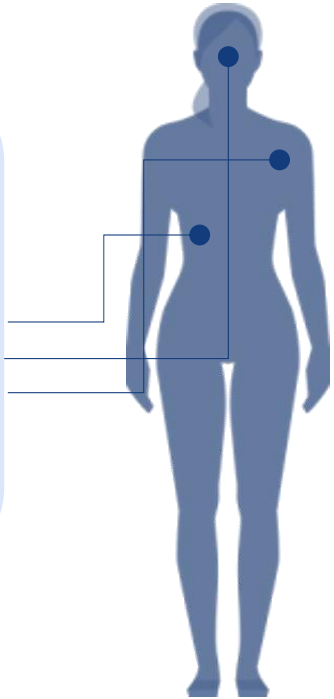
Three Grade 3 CRS episodes were observed in **two patients** (1 at week 1; 1 at week 3; 1 at week 4)

Salama AKS, *et al.* Presented at ESMO 2021 (Presentation 4020).

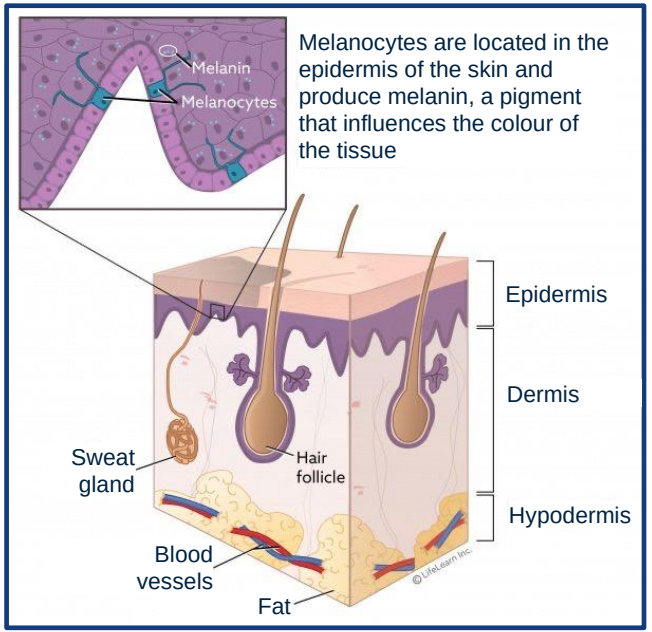
Cutaneous Toxicity

Patients administered tebentafusp **frequently experience rash** as a consequence of on-target, off-tumor activity against gp100 in melanocytes[1]

gp100 is expressed in **UM cells and melanocytes** in the skin and hair[2*]



Melanocytes within the skin[2]



*Other tissues that are known to contain melanocytes, but to our knowledge have not been directly tested for gp100 expression, include gp-100.
MoA, mechanism of action; UM, uveal melanoma.

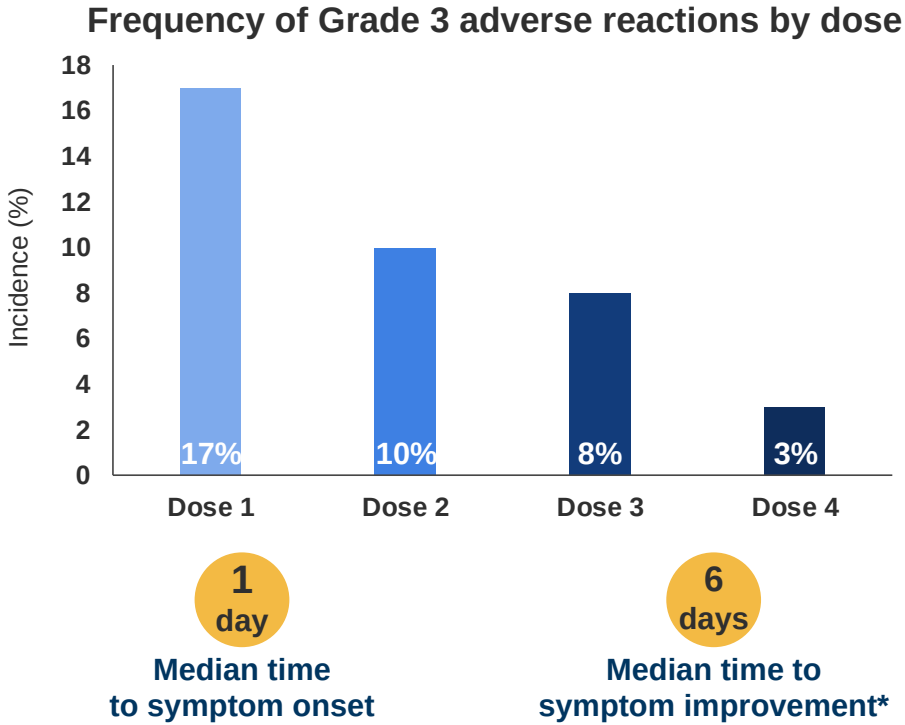
1 Nathan P, *et al. N Eng J Med* 2021;385:1196–206, 2021;
2. Melanomas of the Skin and Toes | VCA Animal Hospital (vcahospitals.com) accessed May 2022.

Cutaneous Toxicity

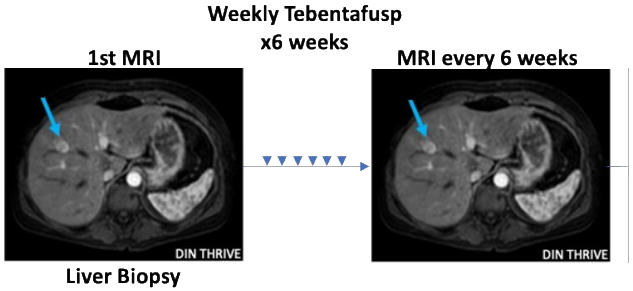
Acute skin reaction incidence in the IMCgp100-202 study population (N=252):

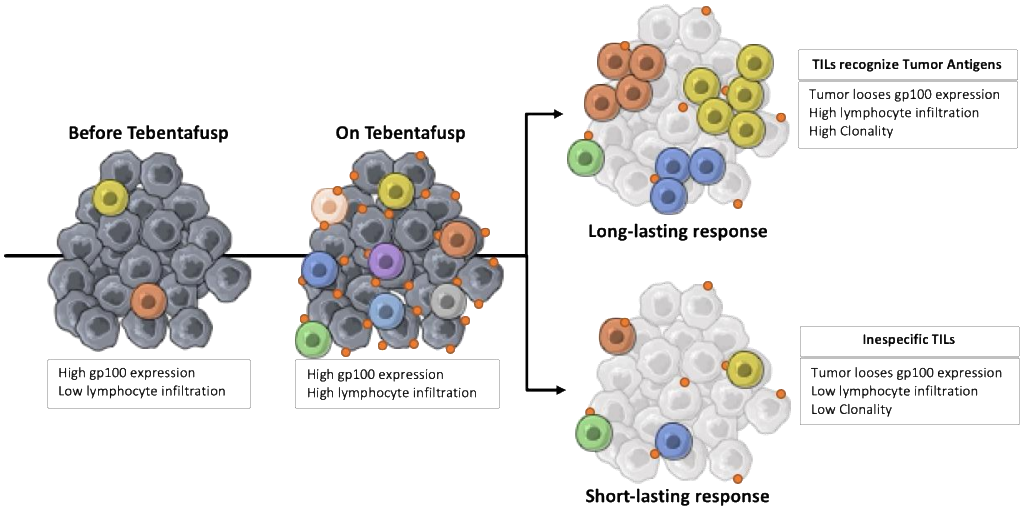
Adverse reaction	Incidence, %
Overall	**91**
Grade 1	**28**
Grade 2	**44**
Grade 3	**21**
Rash *(any grade)*	**83**
Rash	55
Maculopapular	31
Skin exfoliation	21
Grade 3 rash	5
Pruritus *(any grade)*	**69**
Erythema *(any grade)*	**25**
Cutaneous oedema *(any grade)*	**27**

*Defined as symptom Grade ≤1

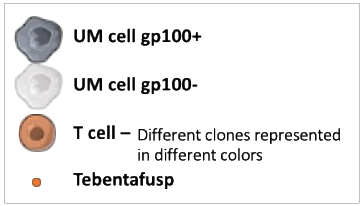


FUTURE





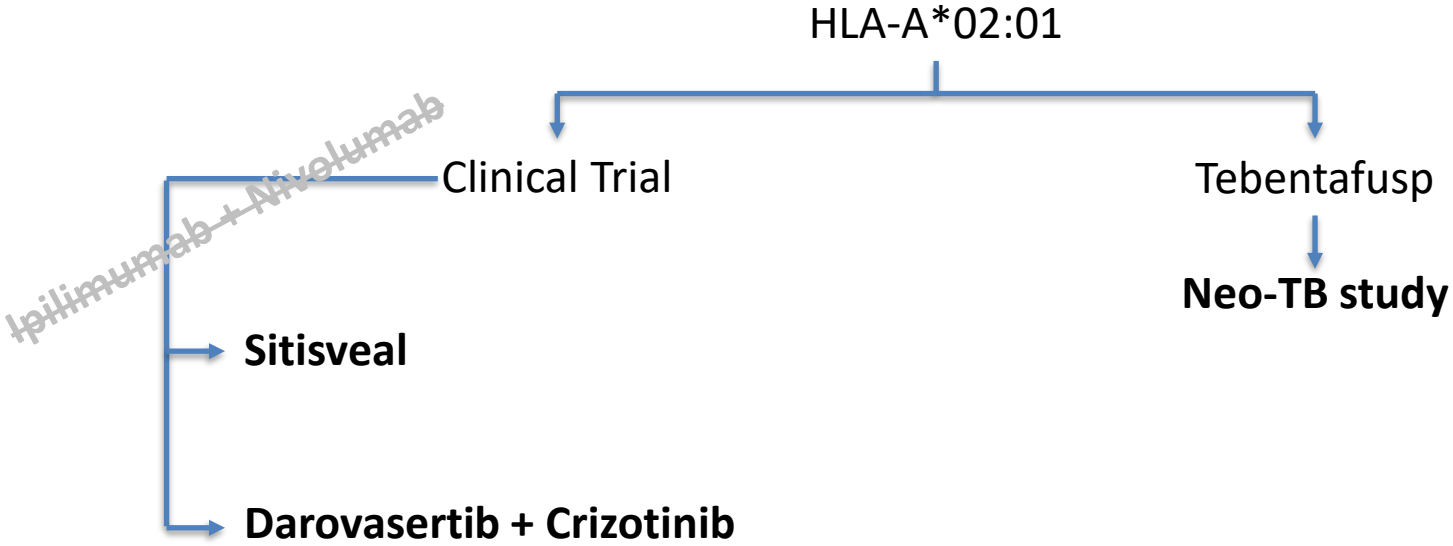
The biological goal is to study capacity of TILs activated with Tebentafusp against tumor antigens; **Antigen spreading**.



Conclusions

- UM is a rare tumor that should be managed in specific referral centers to:
  - *Centralize experience and improve management with a trained multidisciplinary team.*
  - *Optimize recruitment to clinical trials.*
  - *Generate sample biobanks.*
- Tebentafusp should be the first line systemic treatment option for patients with HLA-A02:01 (40-45%).
- Patients with other HLAs should be offered to participate in clinical trials.
- Ipilimumab+Nivolumab is a treatment option for patients that are able to tolerate the treatment, specially if only extra-hepatic disease is present (15-20%).
- To define role of adjuvant therapy and re-define role of liver directed therapies as more active therapies appear.

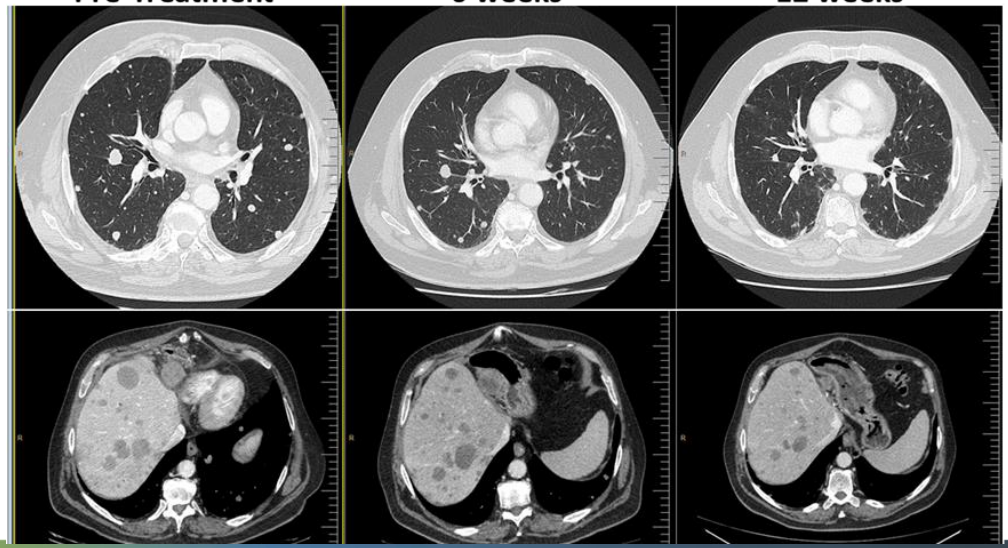
Current Scenario in Spain



Current Scenario in Spain

HLA-A*02:01

- Clinical Trial
  - ~~Ipilimumab + Nivolumab~~
  - **Sitisveal**
  - **Darovasertib + Crizotinib**
- Tebentafusp
  - **Neo-TB study**



Current Scenario in Spain

HLA-A*02:01

- Clinical Trial
  - ~~Ipilimumab + Nivelumab~~
  - **Sitisveal**
  - **Darovasertib + Crizotinib**
- Tebentafusp

Chanel to Evaluate Patients through the GEM

Neo-TB study