GETTHI

Grupo Español de Oncología Transversal y Tumores Huérfanos e Infrecuentes

VII SIMPOSIO GETTHI

Sesión 3: Vías de desarrollo de la oncología transversal (I)

2 de diciembre de 2021 - *Formato virtual*

Terapia Celular en tumores sólidos.

Elena Garralda, MD MSc

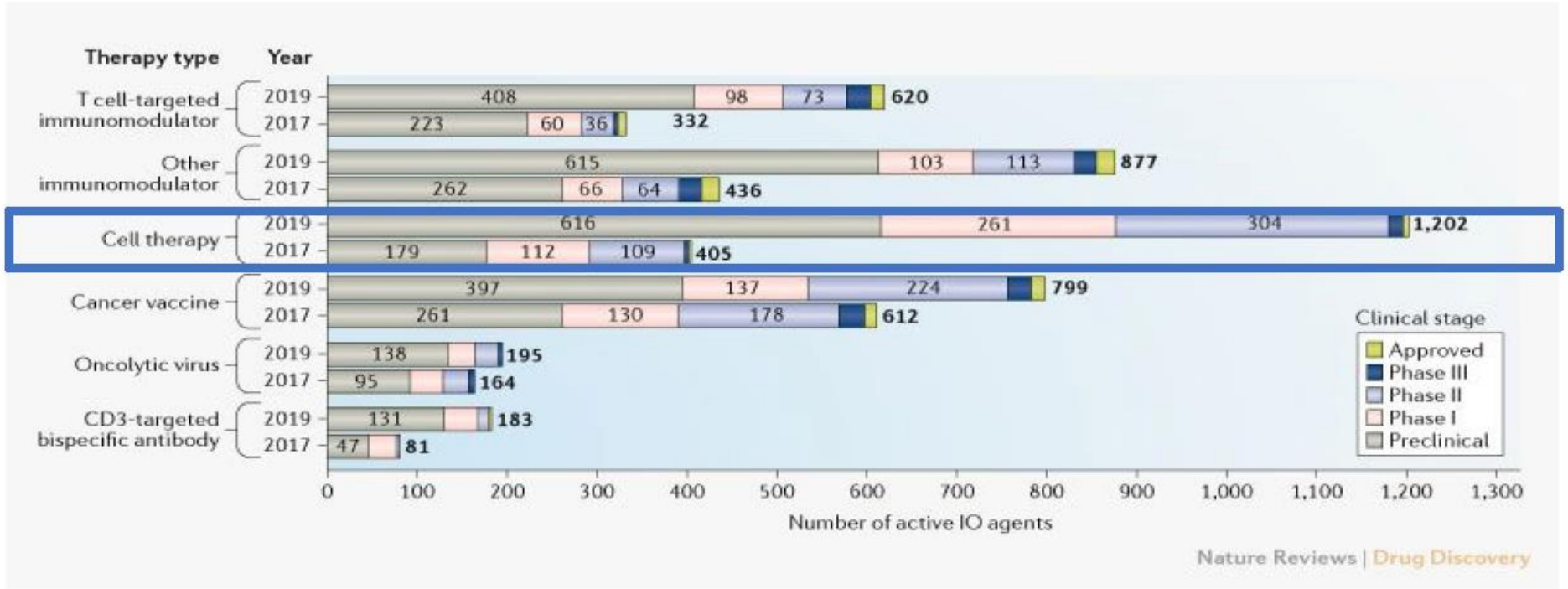
Disclosures

- Research: Novartis / Roche / Thermo Fisher / AstraZeneca / Taiho / BeiGene
- Consultant/Advisor: Roche/Genentech - F.Hoffmann/La Roche - Ellipses Pharma - Neomed Therapeutics1 Inc - Boehringer Ingelheim - Janssen Global Services – SeaGen – TFS – Alkermes – Thermo Fisher - Bristol-Mayers Squibb – MabDiscovery – Anaveon – F-Star Therapeutics
- Speakers Bureau: Merck Sharp & Dohme / Roche / Thermo Fisher / Lilly
- Clinical Trials PI or Co-PI (Institution): Affimed Gmbh - Amgen SA – Anaveon AG – AstraZeneca AB – Biontech Gmbh – Catalym Gmbh - Cytomx - F.Hoffmann La Roche Ltd – F-Star Beta Limited - Genentech Inc - Genmab B.V. – Hutchison Medipharma Limited – Icon - Imcheck Therapeutics – Immunocore Ltd - Janssen-Cilag SA – Medimmune Llc – Merck Kgga - Novartis Farmacéutica, S.A – Peptomyc – Ribon Therapeutics – Roche Farma SA – Seattle Genetics Inc – Symphogen A/S – Taiho Pharma Usa Inc

Disclosures

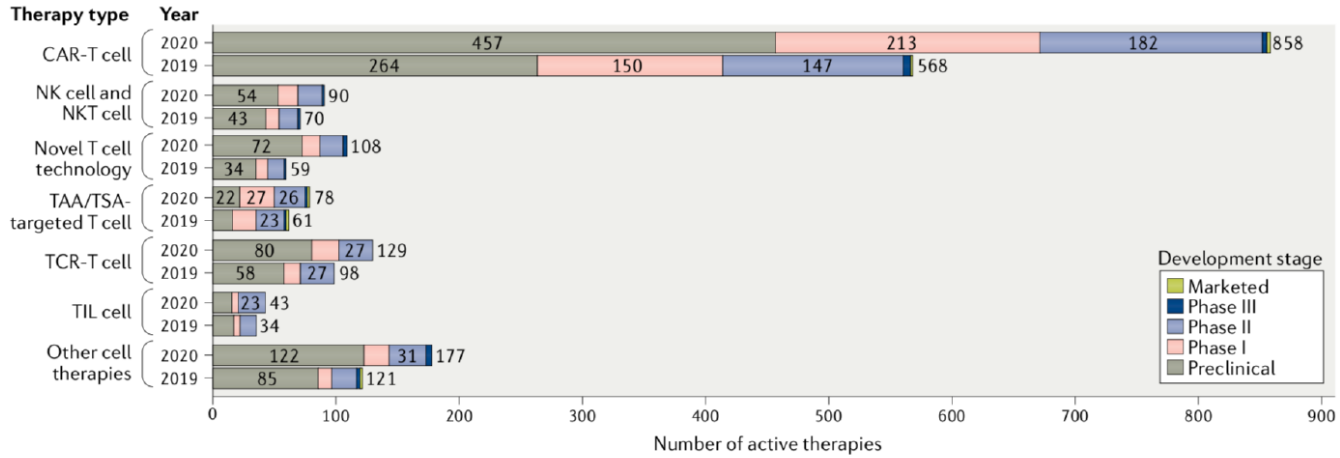
- Research: Novartis / Roche / Thermo Fisher / AstraZeneca / Taiho / BeiGene
- Consultant/Advisor: Roche/Genentech - F.Hoffmann/La Roche - Ellipses Pharma - Neomed Therapeutics1 Inc - Boehringer Ingelheim - Janssen Global Services – SeaGen – TFS – Alkermes – Thermo Fisher - Bristol-Mayers Squibb – MabDiscovery – Anaveon – F-Star Therapeutics
- Speakers Bureau: Merck Sharp & Dohme / Roche / Thermo Fisher / Lilly
- Clinical Trials PI or Co-PI (Institution): Affimed Gmbh - Amgen SA – Anaveon AG – AstraZeneca AB – Biontech Gmbh – Catalym Gmbh - Cytomx - F.Hoffmann La Roche Ltd – F-Star Beta Limited - Genentech Inc - Genmab B.V. – Hutchison Medipharma Limited – Icon - Imcheck Therapeutics – Immunocore Ltd - Janssen-Cilag SA – Medimmune Llc – Merck Kgga - Novartis Farmacéutica, S.A – Peptomyc – Ribon Therapeutics – Roche Farma SA – Seattle Genetics Inc – Symphogen A/S – Taiho Pharma Usa Inc

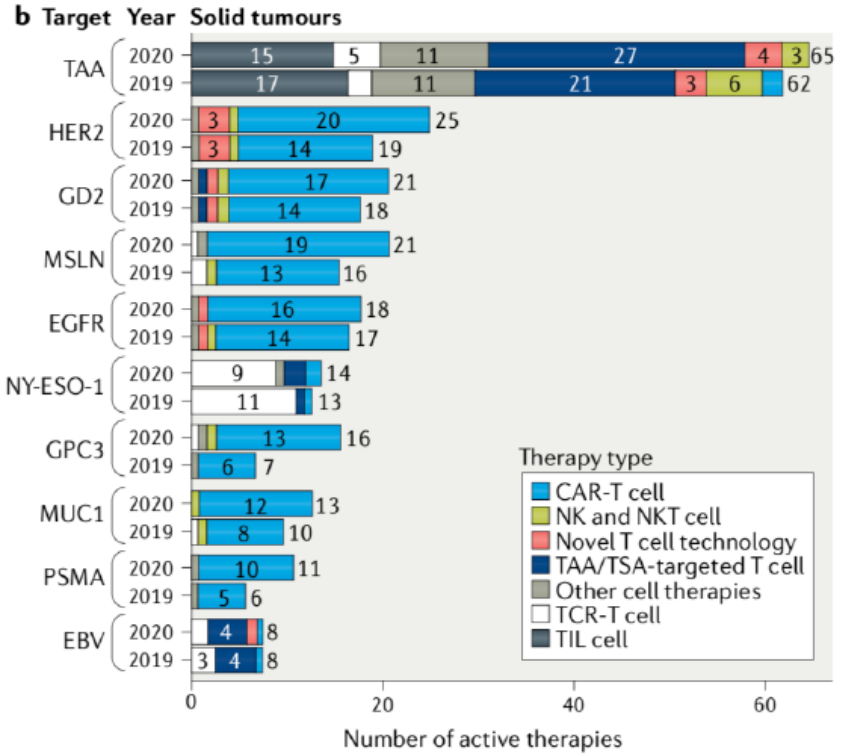
Growth in Adoptive Cellular Therapies (ACT) for Cancer



Yu et al. Nature Drugs Discovery 2019

Cancer cell therapies: the clinical trial landscape



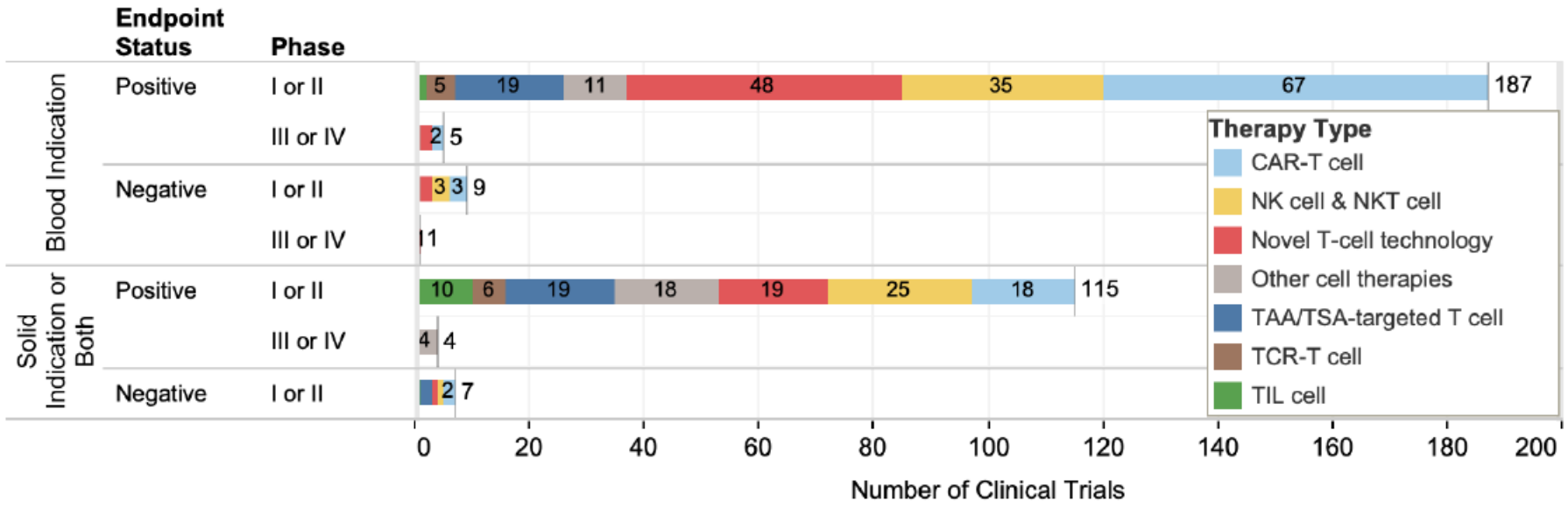


CANCER RESEARCH INSTITUTE The Anna-Maria Kellen Clinical Accelerator

Trends in the cancer cell therapy pipeline. Comparison of the pipeline in March 2019 and March 2020 (data on analysis included in the Supplementary file). TAA, tumour-associated antigen; TCR, T cell receptor; TIL, tumour-infiltrating lymphocyte; TSA, tumour-specific antigen.

Yu et al. Nature Reviews Drug Discovery. May 2020.

Cancer cell therapies: the clinical trial landscape

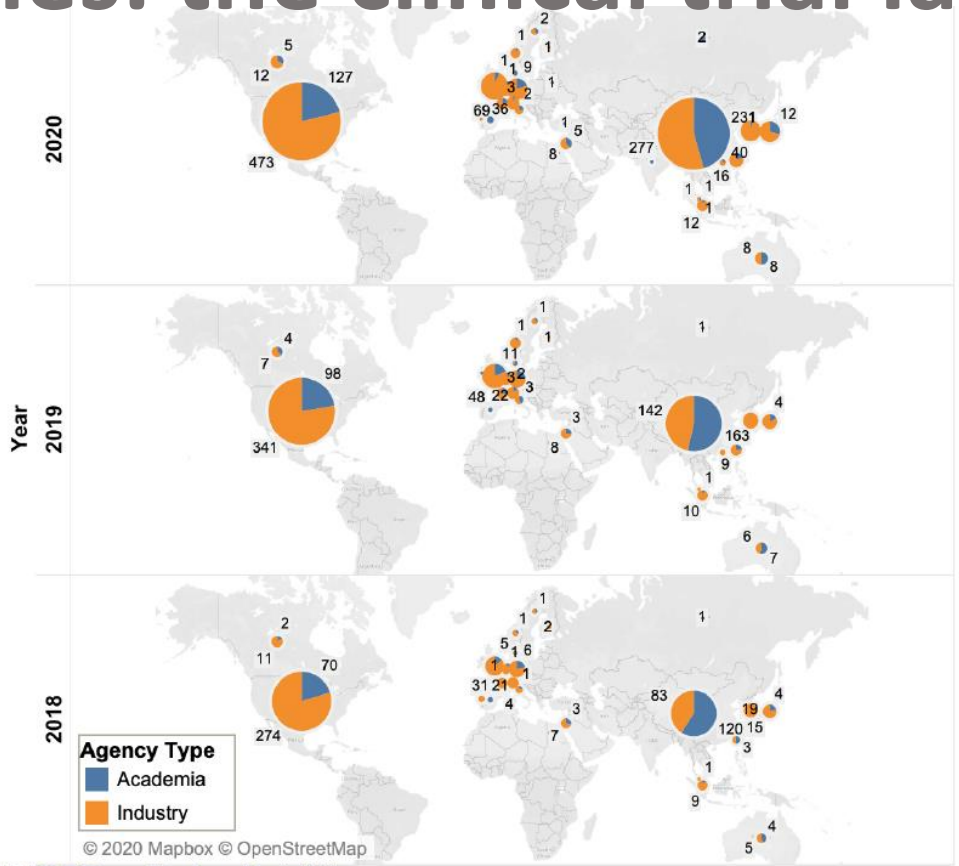


CANCER RESEARCH INSTITUTE The Anna-Maria Kellen Clinical Accelerator

Comparison of endpoint status of trials with published results by cancer types, therapy types, and phases. (Positive = Fully/Partially Achieved Endpoints, Negative = Did not achieve endpoints)

Yu et al. Nature Reviews Drug Discovery. May 2020.

Cancer cell therapies: the clinical trial landscape



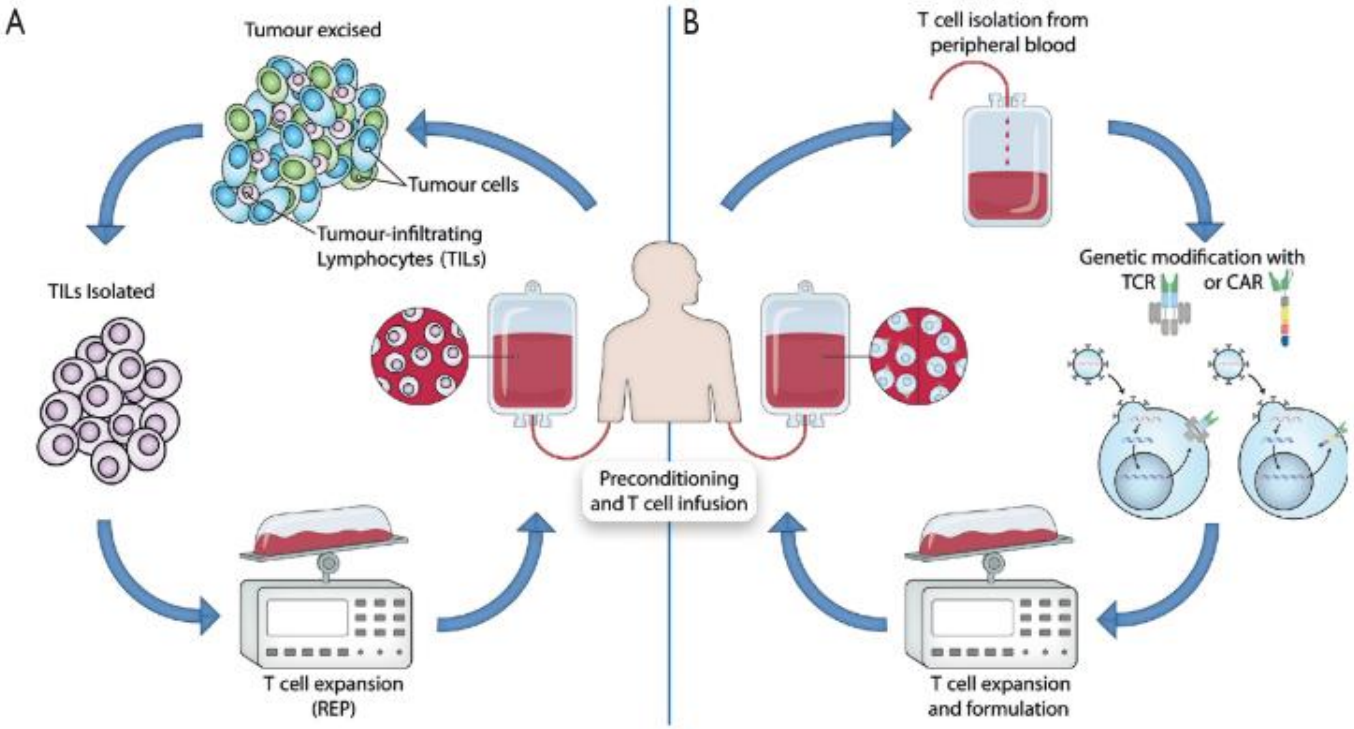
CANCER RESEARCH INSTITUTE The Anna-Maria Kellen Clinical Accelerator

Comparison of active cancer cellular immunotherapy pipeline from update year 2018 to 2020 by ownership type.

Yu et al. Nature Reviews Drug Discovery. May 2020.

Adoptive Cell Therapy

Figure 1 Different adoptive T cell transfer approaches to harness the immune system in cancer therapy.



(A) Adoptive transfer of anti-tumour T cells isolated from within a patient's tumour. TILs are extracted from surgically resected tumour samples, then expanded *in vitro*, followed by re-infusion into the lymphodepleted patient.
(B) T cells from patient peripheral blood are isolated and expanded in culture, and genetically modified to express either a TCR or a CAR that confers the ability to specifically recognise and destroy tumour cells when re-infused into the lymphodepleted patient.

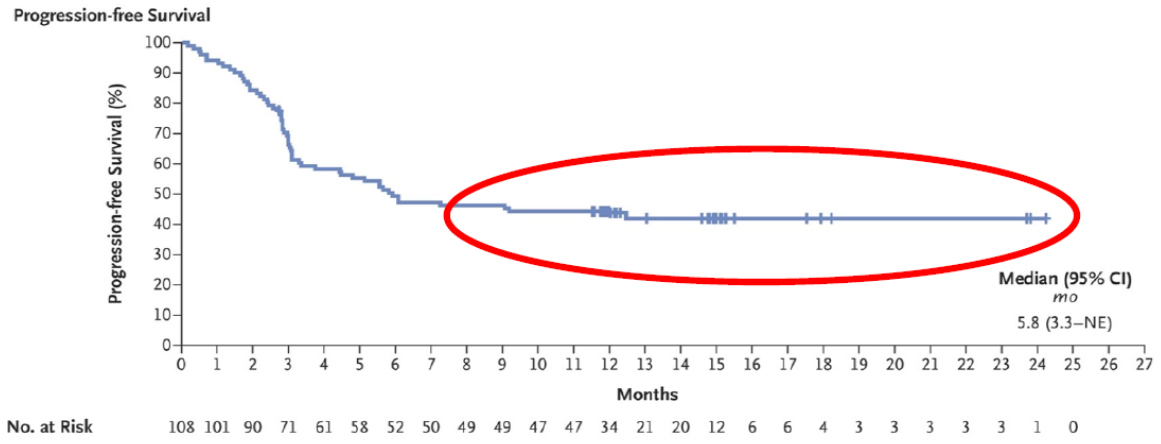
Abbreviations: CAR, chimeric antigen receptor; REP, rapid expansion protocol; TCR, T cell receptor; TIL, tumour infiltrating lymphocyte.

Haanen, J. B. A. G., Califano, R., Lugowska, I., & Garassino, M. C. (218AD). *ESMO Handbook of immuno-oncology*.

Advantages ACT

- **Induce Long Remisions**

CD19 CAR-T in large B cell lymphoma



Neelapu et al. NEJM 2017

- Living platform
- T cells can be selected in vitro or genetically modified to enhance tumor reactivity
- Manipulated ex vivo to overcome impediments of T cell therapy
- Possibility to modify the host prior to the cell transfer.

Efficacy data: melanoma

Succesfull expansion of 24 out of 25 samples
Melanoma (6), sarcoma (10), adenocarcinomas (8)
Enzymatic digestion → cell suspension + IL-2
Lymphocytes population: 3-74%
Rate of expansion: 2.9 to 9.1×10^8 fold (14 – 100 days)
9 cultures lysed fresh autologous tumor
Large-scale expansion ($>10^{10}$) in 5 out of 8

ELSEVIER
Journal of Immunological Methods
Volume 102, Issue 1, 24 August 1987, Pages 127-141

Expansion of human tumor infiltrating lymphocytes for use in immunotherapy trials

Suzanne L. Topalian [1], Linda M. Muul [1], Diane Solomon [2], Steven A. Rosenberg [1]

Immunotherapy of Patients With Advanced Cancer Using Tumor-Infiltrating Lymphocytes and Recombinant Interleukin-2: A Pilot Study

By Suzanne L. Topalian, Diane Solomon, Frederick P. Avis, Alfred E. Chang, Deborah L. Freerksen, W. Marston Linehan, Michael T. Lotze, Cary N. Robertson, Claudia A. Seipp, Paul Simon, Colleen G. Simpson, and Steven A. Rosenberg

Table 5. Therapy and Results

Patient No.	Diagnosis	Dates of Treatment	CPM (mg/kg)	TIL (No. Cells)	rIL-2 (10^{-3} U/kg)	rIL-2 (No. Doses)	rIL-2 (Cum Dose U/kg × 10^{-3})	Result
1	Melanoma	11/20-11/27/86	50	1.9×10^{10}	100	16	1,600	Progression; resection solitary lung met 4 mo; NED 7 mo
2	Melanoma	12/14-12/19/86	50	1.7×10^{10}	100	15	1,500	Progression; DOD 4 mo
3	Breast carcinoma	2/24-3/3/87	25	5.4×10^{10}	100	14	1,400	PR for <1 mo; DOD 4 mo
4	Colon carcinoma	3/11-3/17/87	25	2.8×10^{10}	100	8	800	Progression; DOD 3 mo
5	Renal cell carcinoma	3/18-3/22/87	25	5.2×10^{10}	100	9	900	PR for 3 mo in lymph node met, lung met stable; AWD 4 mo
6	Melanoma	4/8-4/11/87	0	1.6×10^{10}	100	8	800	Progression; AWD 4 mo
7	Renal cell carcinoma	4/15-4/17/87	0	7.2×10^{10}	30	7	210	Progression; AWD 3 mo
8	Renal cell carcinoma	4/23-4/25/87	0	5.9×10^{10}	30	7	210	Progression; DOD 3 mo
9	Melanoma	5/11-5/20/87	0	8.9×10^{10}	10	27	270	Progression; DOD 2 mo
10	Melanoma	5/14-5/17/87	25	1.9×10^{10}	30;10	1;1	40	Progression; DOD 1.5 mo
11	Melanoma	5/20-5/25/87	25	2.3×10^{11}	100	11	1,100	PR for 3 mo; new cerebral mets
12	Renal cell carcinoma	5/27-6/2/87	25	8.0×10^{9}	100	11	1,100	Progression; AWD 2 mo

Abbreviations: met, metastasis; NED, no evidence of disease; DOD, dead of disease; AWD, alive with disease.

Journal of Clinical Oncology, Vol 6, No 5 (May), 1988: pp 839-853

SPECIAL REPORT

USE OF TUMOR-INFILTRATING LYMPHOCYTES AND INTERLEUKIN-2 IN THE IMMUNOTHERAPY OF PATIENTS WITH METASTATIC MELANOMA

A Preliminary Report

Table 1. Characteristics of Therapy in 20 Patients Treated with TIL.*

Patient No.	Sex/Age	Tumor Harvest	Tumor-Infiltrating Lymphocytes*					Doses of IL-2†	Response		
		Site	% Lympho-cytes	Days in Culture	Lymphocyte Expansion Index	Cells Infused ($\times 10^{-10}$)	CD3/CD4/CD8 (%)		Type	Site	Duration (mo)
1	F/46	Subcutaneous	15	27	330	23	95/6/93	11	Partial	Lung	3
2	M/56	Subcutaneous	70	29	300	3	74/4/64	12	Complete	Subcutaneous	>13
3	F/42	Subcutaneous	6	27	4,633	25	97/83/12	7	Partial	Lung, subcutaneous, nodal	3
4	F/38	Subcutaneous	6	24, 38	27,100	30	98/82/20	7	Partial	Lung, subcutaneous	4
5	M/37	Lymph node	16	29	585	9	98/81/7	7	Partial	Subcutaneous	7
6	M/21	Subcutaneous	28	34	2,423	23	83/93/10	13	Partial	Liver, spleen, nodal, subcutaneous	7
7	M/58	Lymph node	41	39	588	1.3	99/98/<3	12	None	—	—
8	M/25	Lymph node	4	42	44,450	19	97/19/>90	13	Partial	Lung, liver, nodal, subcutaneous	9 4
9	M/58	Liver	24	26	2,317	75	98/88/<3	7	Partial	Lung, liver	—
10	F/45	Lymph node	50	56	1,802	12	93/87/3	10	Mixed	Liver responded (brain metastases)	—
11	F/28	Subcutaneous	6	29	4,867	35	99/93/3	14	None	—	—
12	M/59	Soft tissue	6	53	2,623	17	96/67/2	9	None	—	—
13	M/50	Soft tissue	7	44	2,443	43	76/73/11	6	None	—	—
14	M/35	Bone and soft tissue	6	33	32,017	29	95/80/14	10	Partial	Lung, bone, subcutaneous	4
15	F/50	Lymph node	84	30	17,544	22	100/50/50	7	None	—	—
16‡	M/32	Lymph node	15	49	45,597,875	10	95/20/70	4	None	—	—
17‡	M/41	Subcutaneous	58	37	7,062	15	95/2/80	3	None	—	—
18‡	F/39	Subcutaneous	10	39	39,827	19	100/15/85	11	Partial	Subcutaneous	2
19‡	F/35	Lung	15	36	8,938	34	98/72/16	8	None	—	—
20‡	F/58	Lymph node	21	31	45,670	17	100/98/4	3	Partial	Nodal	6

*Before treatment with TIL, all patients received 25 mg of cyclophosphamide per kilogram.
†Doses of 100,000 units per kilogram every eight hours. Patient 16 received three of the four doses at 30,000 units per kilogram; Patient 17 received all three doses at 30,000 units per kilogram.
‡Previous treatment with interleukin-2 alone or interleukin-2 plus LAK cells had failed.

ORR: 60% (IL-2 naive)

ORR: 40%

- Phase 2, single center study
- 20 Patients (brain metastasis excluded)
  - 18: surgical excision
  - 5: chemotherapy
  - 3: radiotherapy
  - 5 received IL-2
  - 1: α-IFN

Rosenberg et al. N Engl J Med 1988

REVIEW

Efficacy of adoptive therapy with tumor-infiltrating lymphocytes and recombinant interleukin-2 in advanced cutaneous melanoma: a systematic review and meta-analysis

U. Dafni[1,2†], O. Michielin[1†], S. Martin Lluesma[1,3], Z. Tsourti[4], V. Polydoropoulou[4], D. Karlis[5], M. J. Besser[6,7], J. Haanen[8], I.-M. Svane[9], P. S. Ohashi[10], U. S. Kammula[11], A. Orcurto[1], S. Zimmermann[1], L. Trueb[1], C. A. Klebanoff[12,13,14], M. T. Lotze[15], L. E. Kandalaft[1,3‡] & G. Coukos[1,3*,‡]

PubMed electronic database (inclusions to 17 December 2018)

NMA + TIL + IL-2 (HD or LD)

Primary endpoint: ORR / Secondary: CRR, OS, DOR

1211 records screened → **13 studies (published 1988-2016)**

410 heavily pretreated patients: 332 received HD-IL-2 and 78 LD-IL-2.

Annals of Oncology 30: 1902–1913, 2019

Table 1. Characteristics of studies included in the meta-analysis, along with information on primary outcome

IL-2 dose	Study year	Type of TILs administrated	Stage (AJCC/ WHO)	Age in years (median/ range)	Performance status	Pts with brain metastasis	Response determination criteria	*N* = 410 Included in the meta-analysis	CR	PR	*N* with TIL expansion failures	*N* with TIL expansion failures, refusals and failures to receive treatment
Low (<720 000 IU/kg)	Topalian-1988[a] [10]	Traditional	NA	41 (35–50)	NA	No	WHO	4[b]	0	1	–	–
	Rosenberg-1988[a] [11]	Traditional	NA	41.5 (21–59)	NA	No	WHO	20	1	10	30	37
	Ellebaek-2012[a] [23]	Traditional	M1a & c	53.5 (36–62)	0	Yes	RECIST 1.0	6	2	0	7	11
	Ullenhag-2012[a,c] [39]	Traditional	IV	55.5 (17–73)	0–3	Yes	RECIST 1.1	24	1	4	–	–
	Andersen-2016[a] [28]	Young	M1a-c	51.5 (25–68)	0–3	Yes	RECIST 1.0	24	3	7	–	25
High (≥720 000 IU/kg)	Dudley-2005 [44]	Traditional	IV	≥18	0–1	Yes	WHO	35	15	3	–	–
	Dudley-2010 [22]	Young	M1a-c	≥18	Good clinical performance	No	RECIST	33[d,e]	3	16	–	–
	Rosenberg-2011 [45]	Traditional	M1a-c	≥18	0–1	Yes	RECIST	43[d]	5	16	–	–
	Pilon-Thomas-2012[a] [40]	Traditional	M1b-c	49 (25–67)	0–1	Unknown	RECIST 1.1	13	2	3	14	–19
	Radvanyi-2012[a] [24]	Traditional	IIIc–IV	≥15	NA	Yes	irRC	31	2	11	–	–
	Besser-2013 [25]	Young	M1a-c	Mean age 54	0–1	Yes	RECIST 1.0	57	5	18	65	80
	Dudley-2013 [26]	Young	M1a-c	≥18	0–1	Yes	RECIST 1.0	69	5	14	86	101
	Goff-2016 [29]	Traditional	M1a-c	45	0–1	Unknown	RECIST 1.0	51[d,e]	12	11	–	–

[a]Information on number of cells infused available at patient level.
[b]Patients with renal, breast or colon cancer excluded.
[c]Related comment in 'Svane, I.M. Cancer Immunol Immunother (2012) 61: 747'.
[d]Patients treated with combination of NMA and TBI are excluded.
[e]There are patients without prior treatment that cannot be excluded from analysis, since they cannot be separated regarding response outcome from the other participants, $n = 8$ for Dudley-2010 and $n = 14$ for Goff-2016.
NA, not available.

Dafni et al. Annals of Oncology, 2019

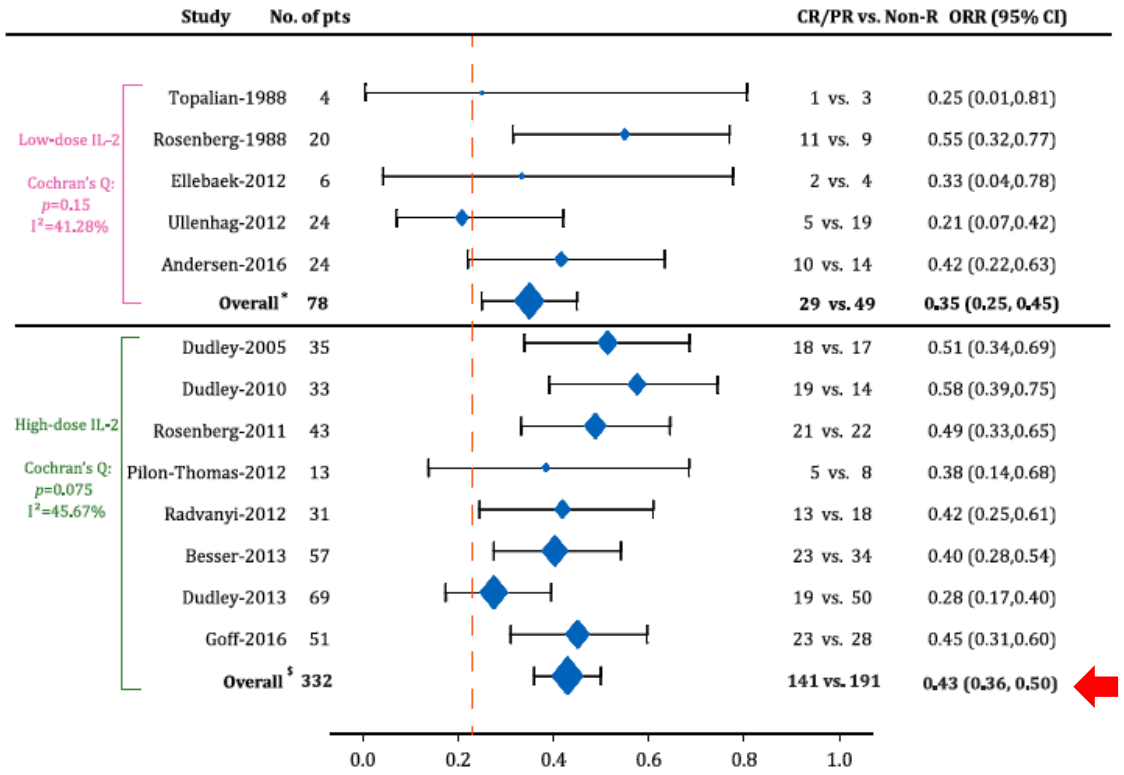


Figure 2. Forest plot for ORRs, by IL-2 dose level. Overall pooled ORR (irrespective of IL-2 dose level): 41%, with 95% CI 35% to 48% (random effects model; Cochran's Q $P = 0.049$; $I^2 = 43.10\%$). Reference line – – –: Zimmer et al. [42], ORR, 95% CI 23% [9% to 44%]. REM estimate for ORR for the LD-IL-2 group: 36%, 95% CI 22% to 50% (*estimate and 95% CI derived from a fixed effect model; $estimate and 95% CI derived from a random effects model; CR: complete response, PR: partial response, Non-R: non-response). Effect of IL-2 dose level $P = 0.32$ (random effects model; Cochran's Q $P = 0.050$; $I^2 = 44.15\%$).

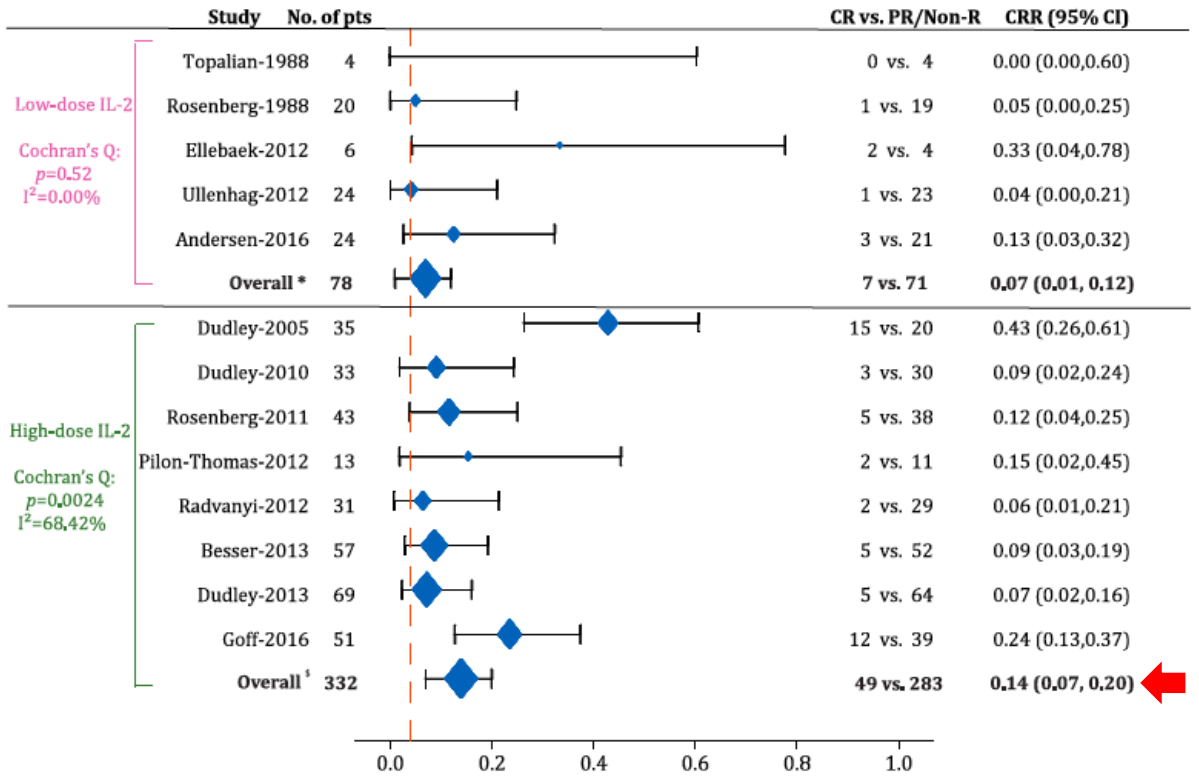


Figure 3. Forest plot for CRRs, by IL-2 dose level Overall pooled CRR (irrespective of IL-2 dose level: 12%, 95% CI 7% to 16%; REM; Cochran's Q $P = 0.0070$; $I^2 = 56.01\%$). Reference line – – –: Zimmer et al. [42] ORR, 95% CI 4% [0% to 20%]. REM estimate for CRR for the LD-IL-2 group: 7%, 95% CI 1% to 12% (*estimate and 95% CI derived from a fixed effect model; $estimate and 95% CI derived from a random effects model; CR: complete response; PR: partial response; Non-R: non-response). Effect of IL-2 dose level $P = 0.32$ (random effects model; Cochran's Q $P = 0.008$; $I^2 = 56.68\%$).

Dafni et al. Annals of Oncology, 2019

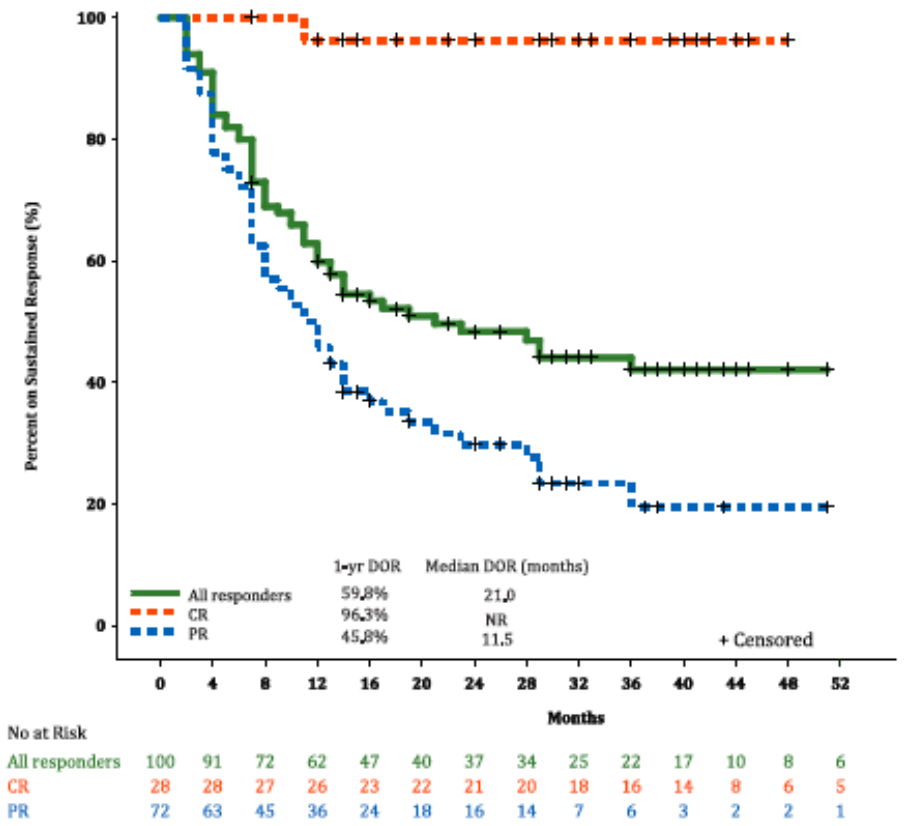


Figure 4. Kaplan–Meier plot for duration of response by type of response, HD-IL-2 studies only (complete versus partial). Data for KM plot derived from Dudley et al. [22, 26, 44], Rosenberg et al. [45], and Goff et al. [29] studies. KM plot lines for complete and partial responders are presented only for illustrative purposes (CR: complete response; PR: partial response).

Dafni et al. Annals of Oncology, 2019

SMR ANNUAL MEETING, NOVEMBER 20-23, 2019 | SALT LAKE CITY, UTAH, USA

Lifileucel, a Potential Therapy for Metastatic Melanoma Patients who are Primary Refractory to Prior Anti-PD-1 Therapy

Lifileucel (a cryopreserved autologous tumor infiltrating lymphocyte therapy) produces durable responses at one-year median study follow-up in patients with advanced metastatic melanoma primary refractory to/ previously progressed on multiple prior therapies including anti-PD-1

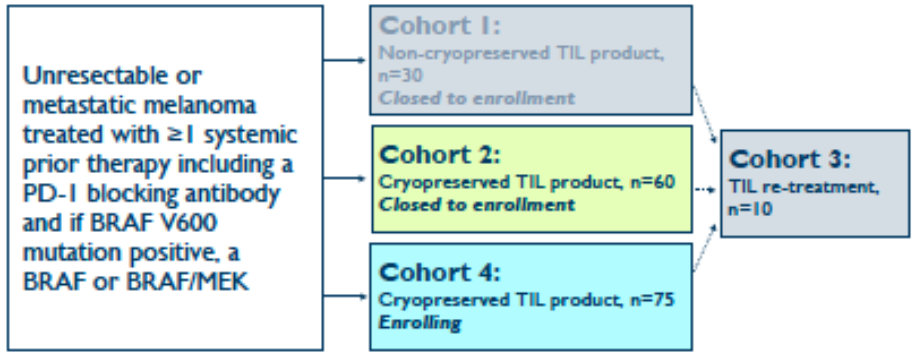
Amod Sarnaik, MD[1], Nikhil I. Khushalani, MD[1], Jason Alan Chesney, MD, PhD[2], Harriet M. Kluger, MD[3], Karl D. Lewis, MD[4], Theresa Medina, MD[4], Evidio Domingo-Musibay, MD[5], Anna C. Pavlick, MD, MBA[6], Eric D. Whitman, MD[7], Salvador Algarra[8], Pippa Corrie, PhD, BMBCh, FRCP[9], Omid Hamid, MD[10], Jose Lutzky, MD[11], Judit Oláh, MD, DSc[12], Jeffrey S. Weber, MD, PhD[6], James M. G. Larkin, MD, PhD[13], Wen Shi, MD, PhD[14], Kelly DiTrapani, RN, BSN, BA[14], Harry Qin, PhD[14], Renee Wu, PhD[14], Friedrich Graf Finckenstein, MD[14], Maria Fardis, PhD, MBA[14], John M. Kirkwood, MD[15]

[1] H. Lee Moffitt Cancer Center, Tampa, FL, USA
[2] James Graham Brown Cancer Center, University of Louisville, Louisville, KY, USA
[3] Yale University School of Medicine, Smilow Cancer Center, New Haven Hospital, New Haven, CT, USA
[4] University of Colorado Cancer Center – Anschutz Medical Campus, Aurora, CO, USA
[5] University of Minnesota, Masonic Cancer Center, Minneapolis, MN, USA
[6] Laura and Isaac Perlmutter Cancer Center, NYU Langone Medical Center, New York, NY, USA
[7] Atlantic Health System Cancer Care, Morristown, NJ, USA
[8] Clínica Universidad de Navarra, Pamplona, Spain
[9] Cambridge University Hospitals NHS Foundation Trust – Addenbrooke's Hospital, Cambridge, UK
[10] The Angeles Clinic and Research Institute, Los Angeles, CA, USA
[11] Mount Sinai Comprehensive Cancer Center, Miami, FL, USA
[12] University of Szeged – Albert Szent-Györgyi Health Center, Szeged, Hungary
[13] Royal Marsden NHS Foundation Trust, London, UK
[14] Iovance Biotherapeutics, Inc. San Carlos, CA, USA
[15] Hillman Cancer Center – University of Pittsburgh Medical Center, Pittsburgh, PA, USA

For more information, please contact: publications@iovance.com

Figure 2. C-144-01 Study Design: Iovance C-144-01 Phase 2 Trial in Metastatic Melanoma

Phase 2, multicenter study to assess the efficacy and safety of autologous Tumor Infiltrating Lymphocytes (LN-144) for treatment of patients with metastatic melanoma (**NCT02360579**)



Cohort 2 Endpoints:

- Primary: Efficacy defined as investigator assessed Objective Response Rate (ORR)
- Secondary: Safety, efficacy, ORR by independent review committee (IRC)

Study Updates:

- Cohort 2 safety and Investigator assessed efficacy for the subpopulation with BOR of PD to first Anti-PD-1/L1 presented here (n=42, Data extract as of 24 Sept 2019)
- Cohort 4 in C-144-01 is ongoing in support of lifileucel registration with the primary endpoint of ORR by IRC

Table 1. Cohort 2 Patient Characteristics

- In n=42 patients primary refractory to Anti-PD-1/L1, defined as BOR of PD to the earliest anti-PD-1/L1 treatment:
  - Mean duration on first anti-PD-1/L1 was 3.1 months
  - 57% PD-L1 High/Positive (TPS ≥ 1%)

CHARACTERISTIC	n=42 (%)
Gender	
Male	26 (62)
Female	16 (38)
Age	
Median	56
Min, Max	20, 77
Prior therapies, n (%)	
Mean # prior therapies	3.3
Anti-CTLA-4	33 (79)
Anti-PD-1	42 (100)
BRAF/MEK	9 (21)
Progressive Disease (PD) for at least 1 prior therapy	
Anti-CTLA-4	29 (88)*
Anti-PD-1	42 (100)
Baseline ECOG score, n (%)	
0	25 (60)
1	17 (40)

CHARACTERISTIC	n=42 (%)
BRAF Status	
Mutated V600	11 (26)
Wild Type	29 (69)
Unknown	2(5)
Baseline LDH (U/L)	
Median	259
1-2 times ULN	10 (24)
> 2 times ULN	5 (12)
Target Lesion Sum of Diameter (mm)	
Mean (SD)	114 (78)
Min, Max	17, 343
Number of Target & Non-Target Lesions (at Baseline)	
>3	35 (83)
Mean	6
Patients with Baseline Liver and/or Brain Lesions	21 (50)

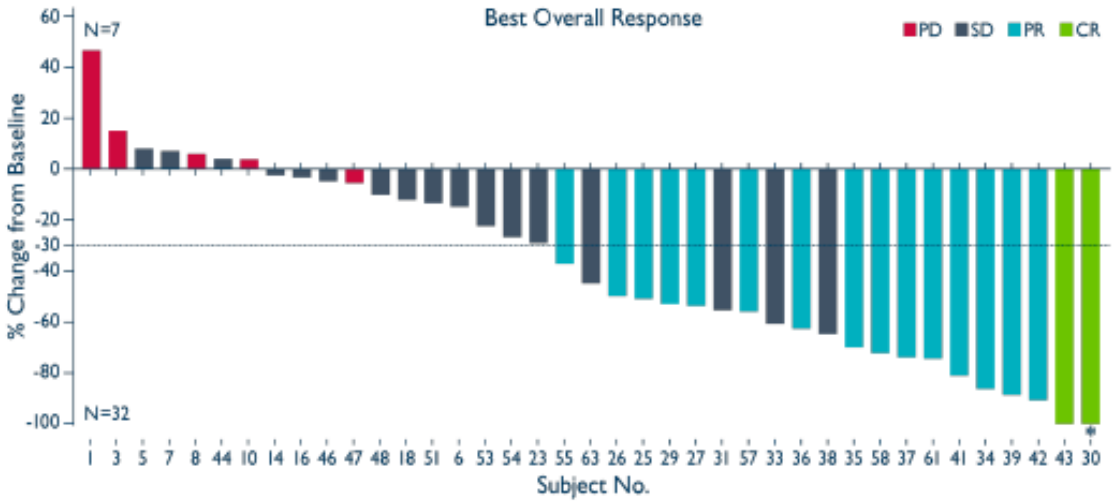
*% is calculated based on number of patients received prior anti-CTLA4.

Table 3. Efficacy Assessed by Investigator

- In n=42 patients primary refractory to Anti-PD-1/L1:
  - Median DOR has not been reached at median 12.0 months study follow up
  - ORR was notable in this sub-group at 40.5%

RESPONSE (RECIST v1.1)	COHORT 2 FULL ANALYSIS SET N=66 (%)	COHORT 2 PATIENTS PRIMARY REFRACTORY TO ANTI-PD-1/L1 n=42 (%)
Objective Response Rate (ORR)	**24 (36.4)**	**17 (40.5)**
Complete Response (CR)	2 (3.0)	2 (4.8)
Partial Response (PR)	22 (33.3)	15 (35.7)
Stable Disease (SD)	29 (43.9)	17 (40.5)
Progressive Disease (PD)	9 (13.6)	5 (11.9)
Non-Evaluable	4 (6.1)	3 (7.1)
Disease Control Rate (DCR)	53 (80.3)	34 (81.0)
Median Duration of Response (DOR)	**Not Reached**	**Not Reached**
Min, Max	2.2, 21.2+	2.8+, 21.2+

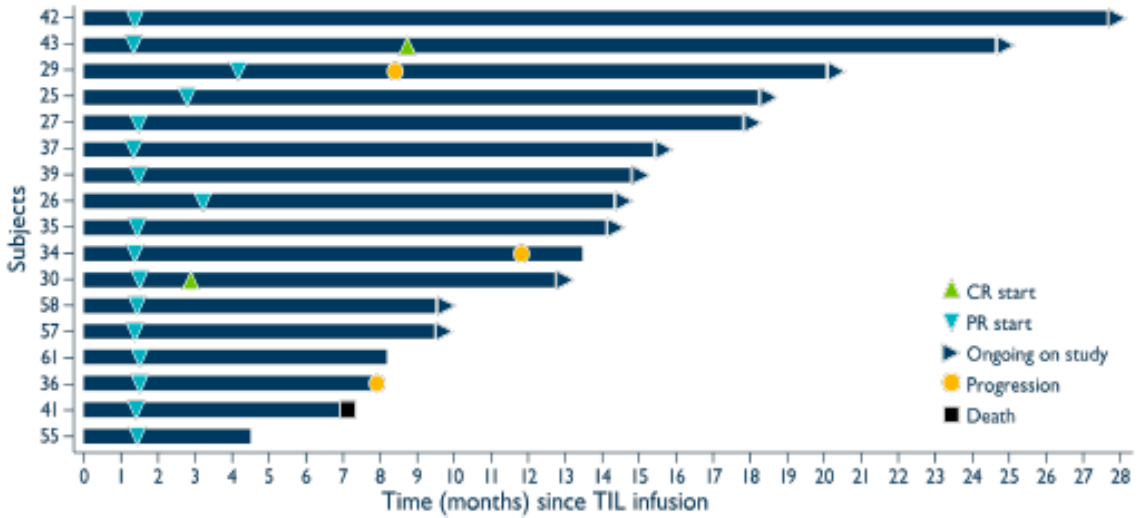
Figure 4. Efficacy: Best Overall Response



Two patients had no post-TIL assessments due to early death.
One patient had no post-TIL assessment due to start of new anti-cancer therapy prior to day 42.
**-100% change from baseline is displayed for the CR visit involved lymph nodes.*

Figure 5. Efficacy: Time to Response (PR or Better)

- 71% of the responders are ongoing on study



CONCLUSIONS

- Relapsed and refractory metastatic melanoma presents a high unmet medical need with low survival rates and with limited treatment options
- Lifileucel treatment resulted in 36.4% investigator assessed ORR in heavily pretreated metastatic melanoma patients with high baseline disease burden
- Lifileucel was equally efficacious in patients who were primary refractory to prior anti PD-1/L1 ICI therapy:
  - 40.5% ORR in patients who were primary refractory to Anti PD-1/L1
  - 71% of responders who were primary refractory to Anti PD-1/L1 remain on study
- At 12 months of study follow up, median DOR has still not been reached for primary refractory or the full population of the cohort

Treatment with tumor-infiltrating lymphocytes in the changing treatment landscape of metastatic melanoma.

Troels Borch, Rikke Andersen, Eva Ellebaek, Özcan Met, Marco Donia, Inge Marie Svane

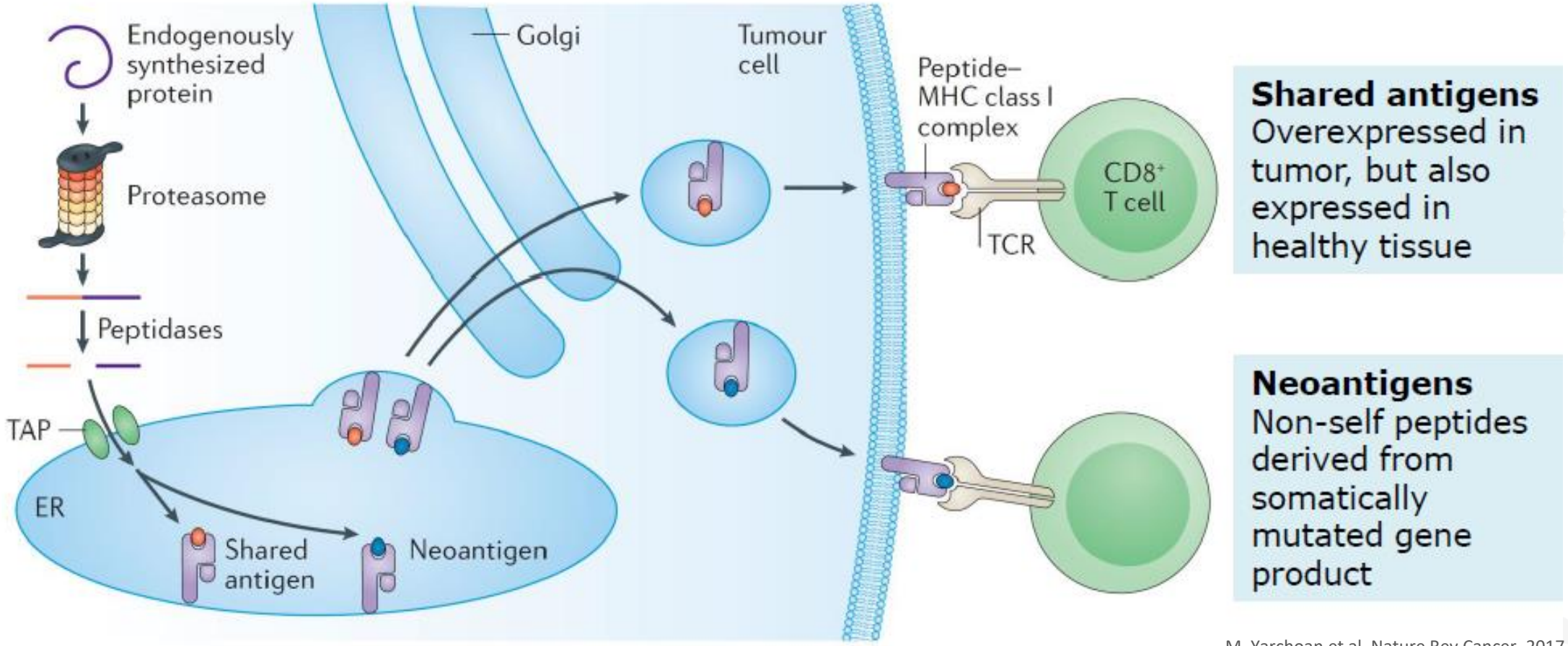
Show Less

Center for Cancer Immune Therapy, Department of Hematology and Department of Oncology, Herlev Hospital, University of Copenhagen, Herlev, Denmark; Department of Oncology and Center for Cancer ImmuneTherapy, Department of Hematology, Copenhagen University Hospital Herlev, Herlev, Denmark

Data from 3 clinical trials: 55 treated patients
OS: 15.9m; PFS: 3.7m (follow-up 40m)
ORR: 37% (PR: 26%, CR: 11% - 4/6 ongoing)
No prior anti-PD-1: 42%/ prior anti-PD-1: 32% (p=0,06)

Journal of Clinical Oncology 37, no. 15_suppl_e14024.May 26, 2019

Clonal Neoantigens as targets for adoptive cell therapy



M. Yarchoan et al. Nature Rev Cancer, 2017

VII SIMPOSIO GETTHI

Sesión 3: Vías de desarrollo de la oncología transversal (I)

MENU

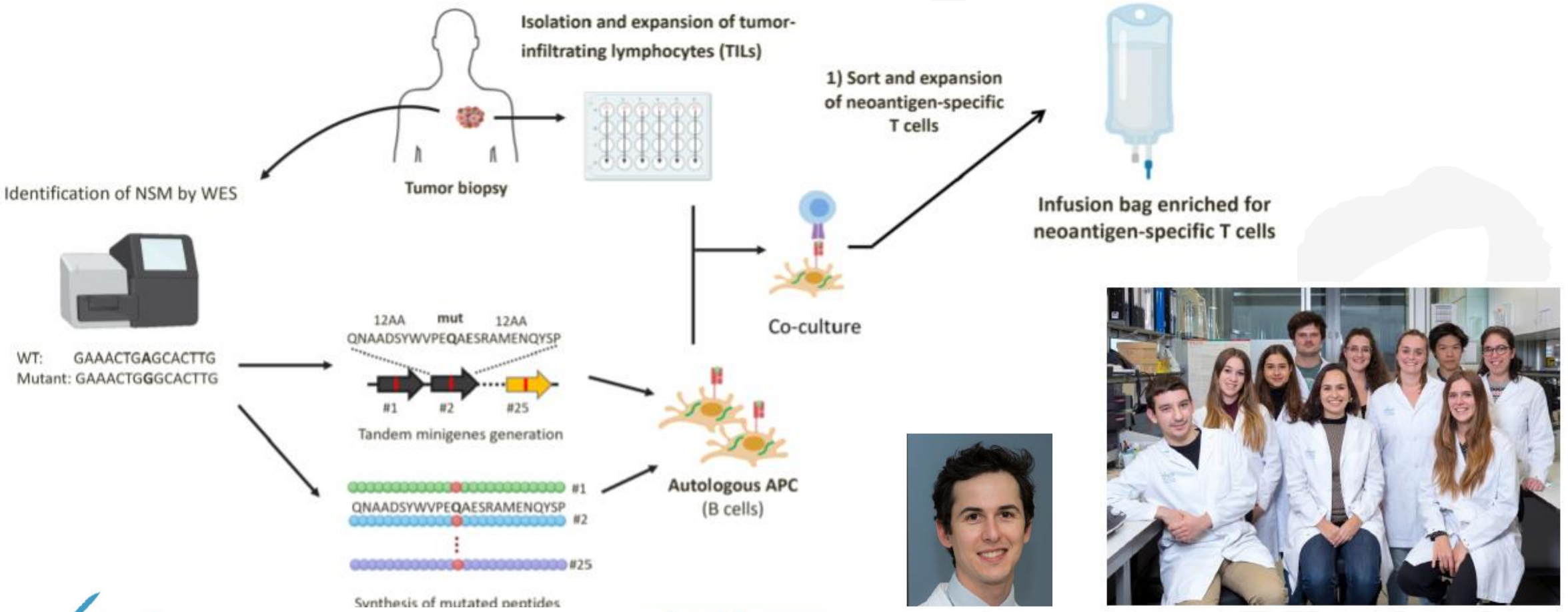
nature medicine

Letter | Published: 04 June 2018

Immune recognition of somatic mutations leading to complete durable regression in metastatic breast cancer

Nikolaos Zacharakis, Harshini Chinnasamy, Mary Black, Hui Xu, Yong-Chen Lu, Zhili Zheng, Anna Pasetto, Michelle Langhan, Thomas Shelton, Todd Prickett, Jared Gartner, Li Jia, Katarzyna Trebska-McGowan, Robert P. Somerville, Paul F. Robbins, Steven A. Rosenberg ✉, Stephanie L. Goff & Steven A. Feldman

NEXTGEN-TIL: Neoantigen selection



Vladimir Galvao

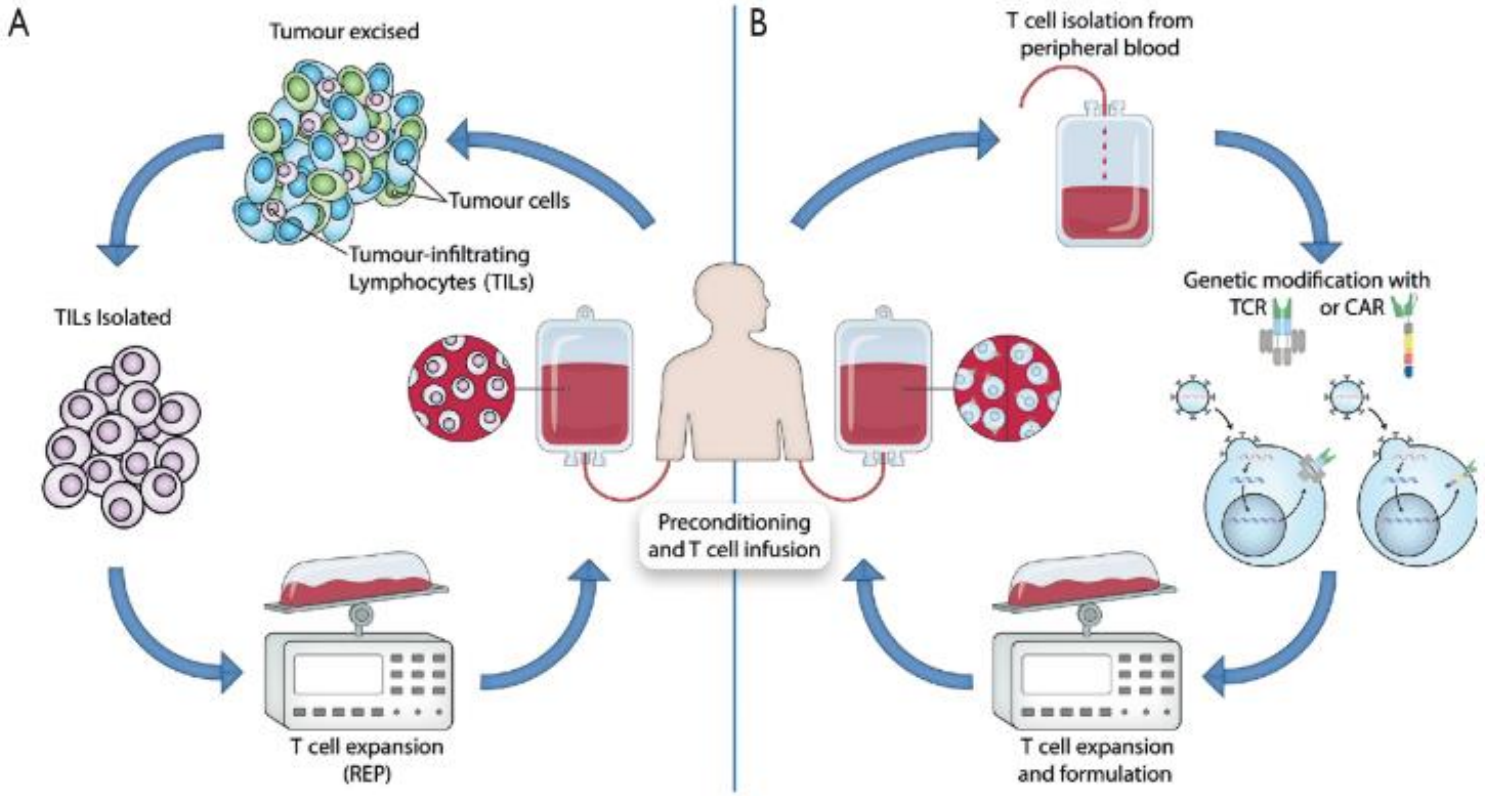
Alena Gros

Terapia NEXTGEN-TIL: TILs seleccionados contra NeoAg

1. **Menos invasiva:** generación de TIL a partir de biopsias en lugar de resecciones tumorales
2. **Segura:** Los neoantígenos se expresan exclusivamente en células tumorales
3. **Potente:** Los TCR dirigidos a los neoantígenos no se agotan como resultado de la tolerancia central
4. **TILs diversos y heterogéneos** dirigidos a múltiples neoantígenos

Adoptive Cell Therapy

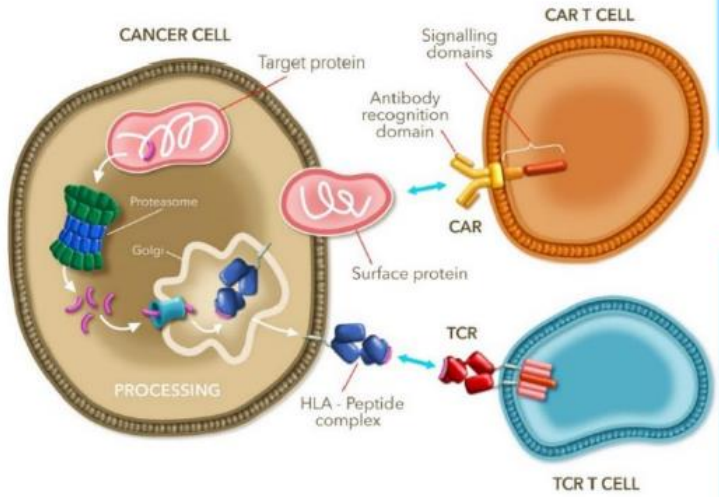
Figure 1 Different adoptive T cell transfer approaches to harness the immune system in cancer therapy.



(A) Adoptive transfer of anti-tumour T cells isolated from within a patient's tumour. TILs are extracted from surgically resected tumour samples, then expanded *in vitro*, followed by re-infusion into the lymphodepleted patient.
(B) T cells from patient peripheral blood are isolated and expanded in culture, and genetically modified to express

Haanen, J. B. A. G., Califano, R., Lugowska, I., & Garassino, M. C. (218AD). *ESMO Handbook of immuno-oncology*.

ACT: CAR-T vs TCR



CAR-T	Very few targets; limited to extracellular
	Chimeric antigen receptor; not dependent on recognition an HLA peptide
TCRs	Access to extra- and intracellular proteins
	Affinity enhanced TCRs overcome naturally low affinity target expression
	Requires MHC-I expression and HLA matching

Fiona Thistlethwaite. ESMO Advanced Course on Car-T. 2021

CAR-T

Brain	EGFRvIII, HER2, IL-13RA
Head and Neck	ERBB family
Lung	CEA, HER2, MSLN
Pleura	FAP, MSLN
Breast	CEA, cMet, HER2, MSLN
Gastric	CEA, HER2
Liver	GPC3
Colon	CEA
Pancreas	CEA, MSLN
Renal	VEGFR2
Ovarian	FR, HER2, MSLN, MUC16
Prostate	PSMA
Skin	GD2, VEGFR2
Bone	GD2, HER2
Soft Tissue	GD2, HER2
Neural	GD2, L1-CAM

Morello et al. Cancer Discovery (2016)

VII SIMPOSIO GETTHI

Sesión 3: Vías de desarrollo de la oncología transversal (I)

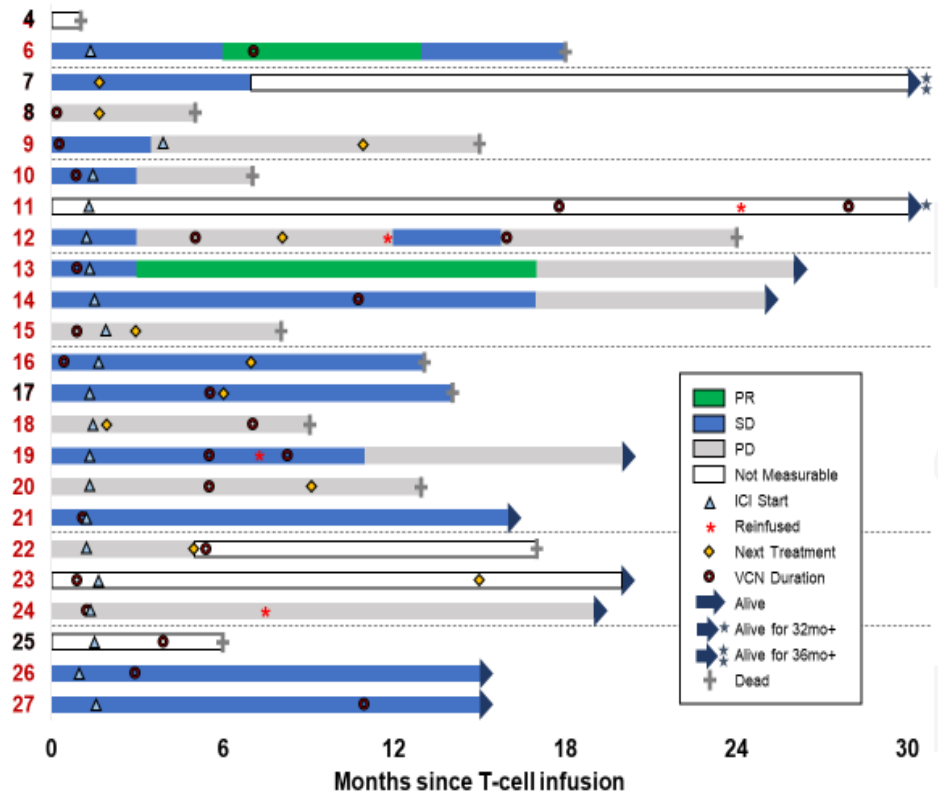
CANCER DISCOVERY 10

Home About Articles For Authors Alerts News COVID-19 Webinars 10th Anniversary Search

Research Article

A phase I trial of regional mesothelin-targeted CAR T-cell therapy in patients with malignant pleural disease, in combination with the anti-PD-1 agent pembrolizumab

Prasad S Adusumilli, Marjorie G Zauderer, Isabelle Riviere, Stephen B Solomon, Valerie W Rusch, Roisin E O'Cearbhaill, Amy Zhu, Waseem Cheema, Navin K Chintala, Elizabeth Halton, John Pineda, Rocio Perez-Johnston, Kay See Tan, Bobby Daly, Jose A Araujo Filho, Daniel Ngai, Erin McGee, Alain Vincent, Claudia Diamonte, Jennifer L Sauter, Shanu Modi, Devanjan Sikder, Brigitte Senechal, Xiuyan Wang, William D Travis, Mithat Gonen, Charles M Rudin, Renier J Brentjens, David R. Jones, and Michel Sadelain



- 35 patients
- 27 pts received an intrapleural mesothelin targeted CAR-T
- 2 PR
- mOS 23 MPM patients was 17.7 months
- mOs 18 pts received also pembro 23.9 months (reverts CAR-T cell exhaustion preclinically)
  - Ipi + nivo phase 3 trial approved with mOS of 18 months in the frontline setting

Adusumili et al. Cancer Discovery 2021

VII SIMPOSIO GETTHI

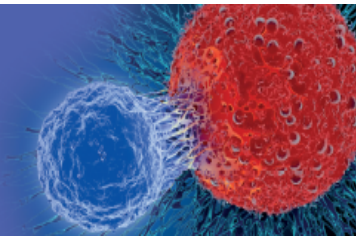
Sesión 3: Vías de desarrollo de la oncología transversal (I)

TCR

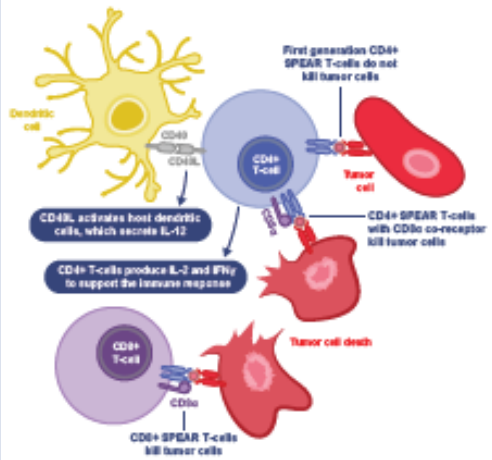
Safety and Efficacy From the SURPASS Trial With ADP-A2M4CD8, a SPEAR T-cell Therapy Incorporating a CD8α Co-receptor and an Affinity Optimized TCR Targeting MAGE-A4

David S. Hong[1], Jeffrey M. Clarke[2], Adam Asch[3], John Charlson[4], Tanner M. Johanns[5], Emiliano Calvo[6], Valentina Boni[6], María de Miguel[6], Victor Moreno[7], Donald P. Lawrence[8], Marcus O. Butler[9], Jon Zugazagoitia[10], Mariela A. Blum Murphy[1], Partow Kebriaei[1], George R. Blumenschein Jr[1], Hassan Danesi[11], Quan Lin[11], Elliot Norry[11]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Duke Cancer Center, Durham, NC, USA; [3]OU Health Stephenson Cancer Center, Oklahoma City, OK, USA; [4]Cancer Center-Froedtert Hospital, Medical College of Wisconsin, Milwaukee, WI, USA; [5]Washington University School of Medicine, St. Louis, MO, USA; [6]START Madrid-CIOCC, Centro Integral Oncológico Clara Campal, Madrid, Spain; [7]START Madrid-FJD, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain [8]Massachusetts General Hospital, Boston MA, USA; [9]Princess Margaret Cancer Centre, Toronto, Ontario, Canada; [10]Hospital Universitario 12 de Octubre, Madrid, Spain; [11]Adaptimmune, Philadelphia, PA, USA



ADP-A2M4CD8 next-generation SPEAR T-cells



- SPEAR T-cells are a mix of CD4+ and CD8+ T-cells engineered with a TCR recognizing an intracellular tumor antigen in an HLA-restricted fashion
- ADP-A2M4CD8 are next-generation SPEAR T-cells targeting MAGE-A4 with a CD8α co-receptor introduced into T-cells alongside the TCR
- The co-expression of CD8α adds CD8+ killer cell capability to CD4+ helper cells, while also maintaining/enhancing their helper cell capabilities
- The enhanced TCR interaction results in a more potent response because the ADP-A2M4CD8 next-generation CD4+ SPEAR T-cells can now both kill tumor cells as well as engage the broader immune system, including dendritic cell activation

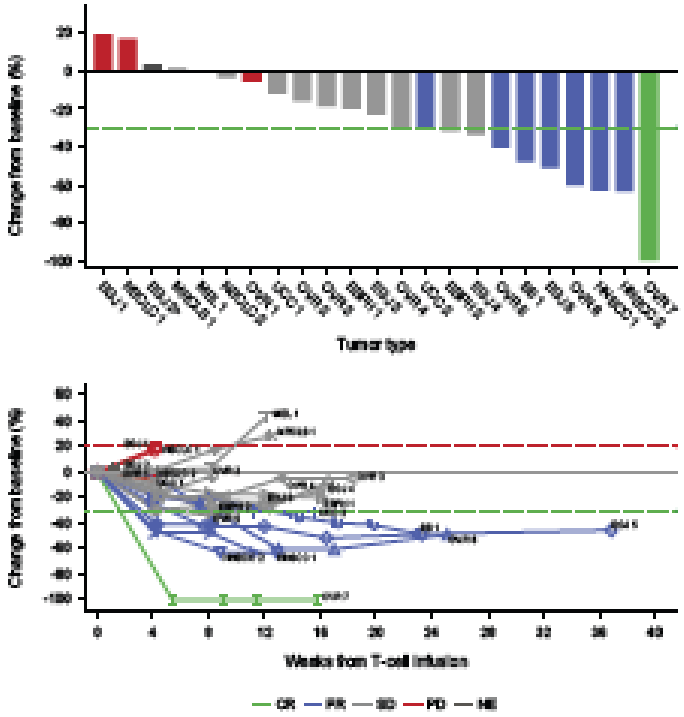
Key Eligibility Criteria and Patient Characteristics

- Advanced gastric, esophageal, EGJ, UCC, NSCLC, or HNSCC cancers
- HLA-A*02 and MAGE-A4 positive
- Aged between 18 and 75 years
- Measurable disease per RECIST v1.1
- ECOG performance status ≤1
- Adequate organ function
- No active autoimmune or immune-mediated disease
- No leptomeningeal disease, carcinomatous meningitis, or symptomatic CNS metastases
- No active infection

Table 4. Best overall response among 22 evaluable patients across treatment groups

Best overall response (N=22[a])	Overall, n (%)	Indication (n=1 unless otherwise indicated)
CR	1 (4.5)	Ovarian cancer
PR	7 (31.8)	Ovarian cancer (2), HNSCC (2), synovial sarcoma, EGJ cancer, UCC
SD	11 (50.0)	Ovarian cancer (3), EGJ cancer (2), esophageal cancer (2), NSCLC, MRCLS, melanoma, UCC
PD	3 (13.6)	EGJ cancer, NSCLC, ovarian cancer

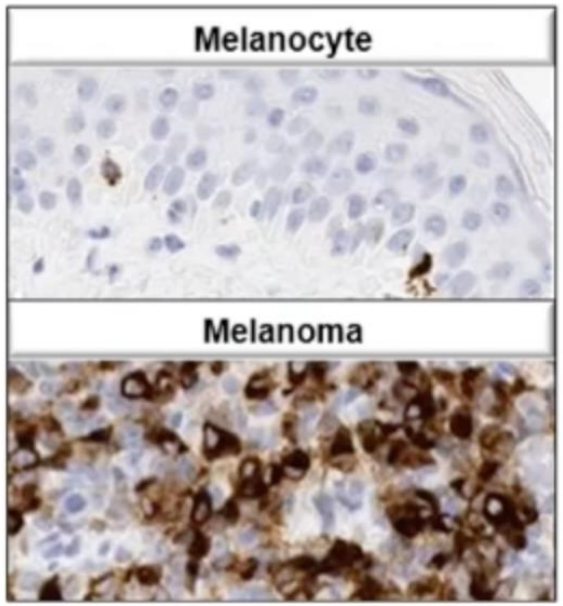
Figure 1. Tumor shrinkage seen in 18 patients with 8 responses

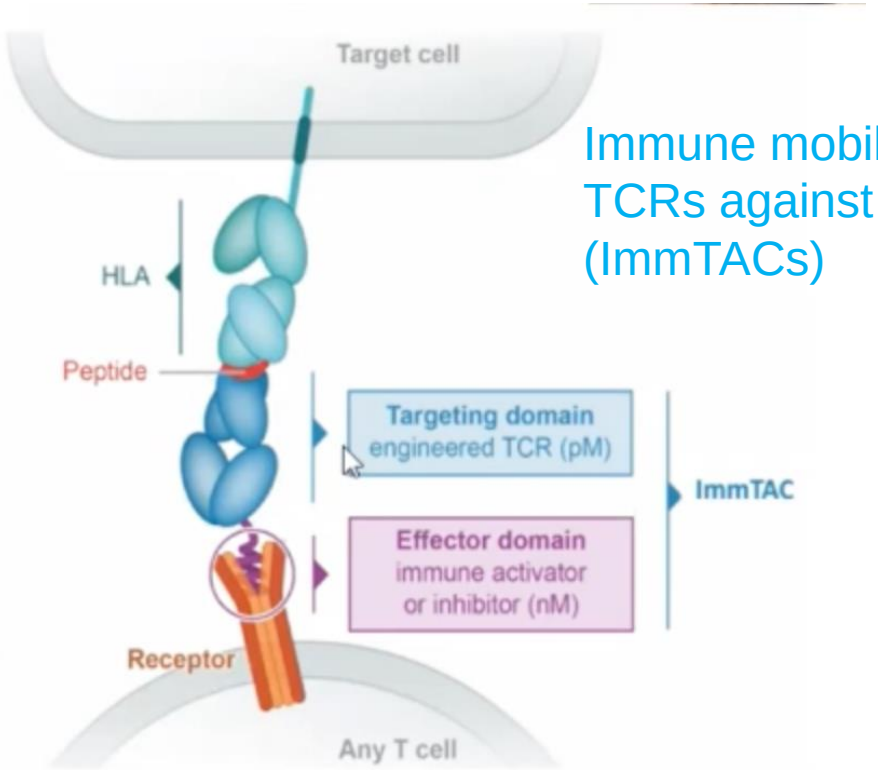


Tebentafusp (bispecific fusion protein) – uveal melanoma

Uveal Melanoma (UM)

- Rare melanoma type with low mutational burden
- Frequent liver metastases; poor benefit from IO
- No standard of care once metastatic
- 12-mo OS up to 52% in first line clinical trials[1,2,3]
- Commonly expresses gp100 (melanocytic protein)





Immune mobilizing TCRs against cancer (ImmTACs)

Tebentafusp

- Bispecific, soluble TCR therapeutic
- Affinity-enhanced TCR fused to anti-CD3
- Designed to redirect T cells to gp100+ melanocytic cells

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

1. Piulats JM, et al. *J Clin Oncol* 2021;39(6):586–98; 2. Rantala ES, et al. *Melanoma Res* 2019;29(6):561–8;
3. Khoja L, et al. *Ann Oncol* 2019;30(8):1370–80

Neumann et al. AACR 2021

Tebentafusp - uveal melanoma

Advanced UM:

- HLA-A*0201+
- No prior systemic therapy in the advanced setting
- No prior liver-directed therapy, except surgery
- Any LDH

Randomized 2:1

Stratification by LDH level (>ULN vs ≤ULN)

Tebentafusp:

- 20 mcg C1D1
- 30 mcg C1D8
- 68 mcg C1D15+

Investigator's Choice (IC):

- Pembrolizumab 2 mg/kg Q3W
- Ipilimumab 3 mg/kg Q3W
- Dacarbazine 1000 mg/m^2 Q3W

Co-primary endpoints

- **OS in randomized patients to tebentafusp vs IC treatment (ITT)**
- OS in randomized patients to tebentafusp with rash during Wk 1 vs IC treatment

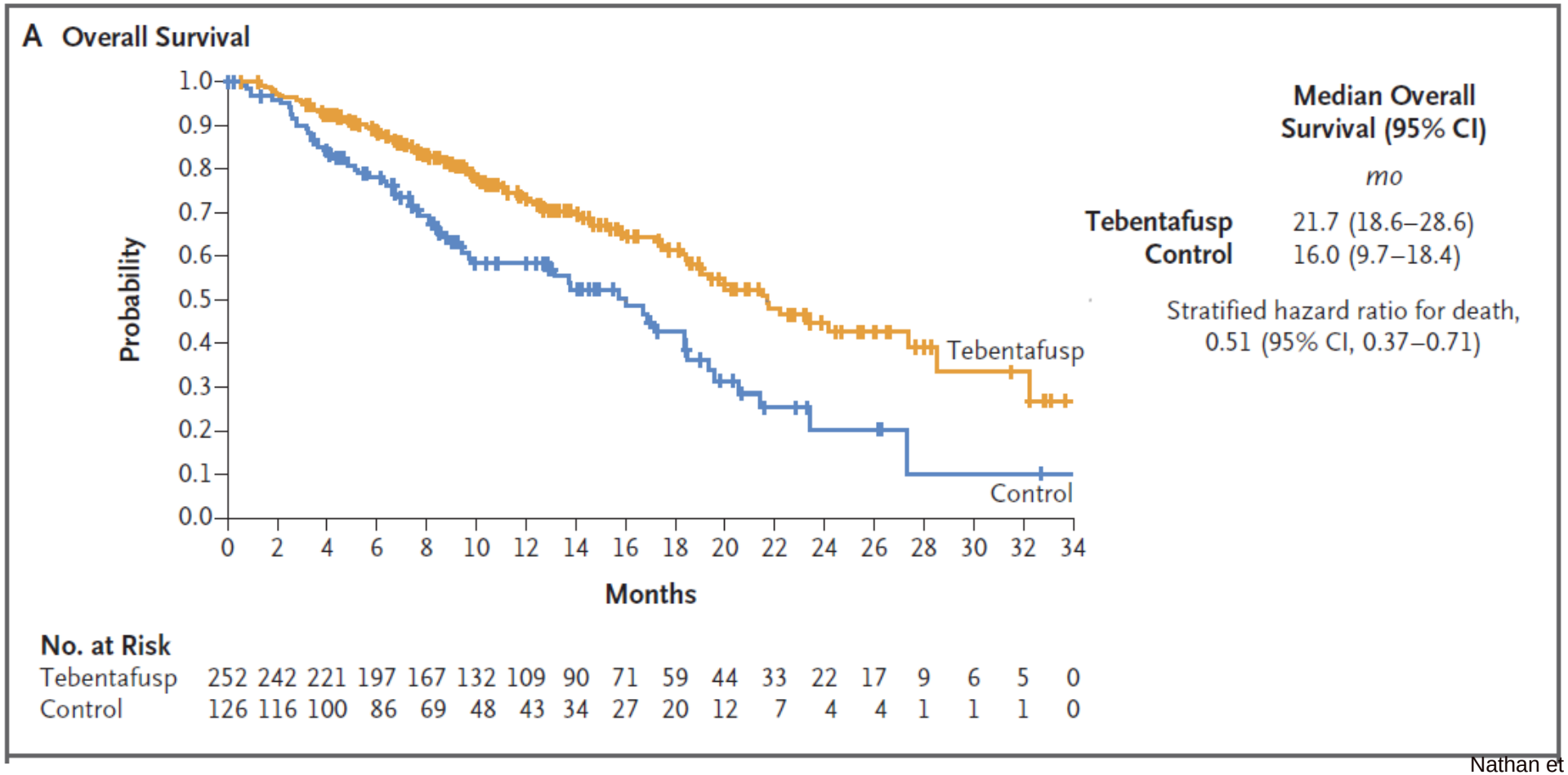
Key secondary endpoints

- **ORR and PFS by investigator assessment**

Data cut-off date: October 13, 2020; data snapshot date: January 22, 2021.
ITT, intent-to-treat; ORR, overall response rate; PFS, progression free survival.

Neumann et al. AACR 2021

Tebentafusp - uveal melanoma - overall survival



Nathan et al- NEJM 2021

Conclusions

- ACT is a powerfull treatment strategy offering the chance of cure for patients with cancer
- TILS in melanoma have shown remarkable responses but there are still multiple challenges for clinical delivery that need to be addressed.
- Promising techniques to identify mutation reactive T cells and potentially improve results of unselected TIL therapy.
- ACT is potentially aplicable across a wide range of tumor types
- Areas of active investigation: Identification of suitable antigens, management of toxicities, overcaming IO suppressive tumor microenviroments.
- Other ACT strategies: ie. NK cells.

Acknowledgements

PHASE I Unit

- **Josep Tabernero**
- **Vladimir Galvao**
- Irene Braña
- Maria Vieito
- Omar Saavedra
- Guzman Alonso
- H. K. Oberoi
- Julia Lostes
- Katerin Rojas
- All Clinical Investigators
- Study Nurses
- Study Coordinators

VHIO Investigators

- **Alena Gros**
- **Pere Barba**
- Joaquin Arribas
- Eva Muñoz

BST Team

- Sergi Querol
- Luciano Rodriguez

VHIO Projects office

- **Susana Muñoz**
- **Xenia Villalobos**
- **Silvia Martin Luesma**
- Neus Bayo
- Alex Piris

Others

- Patients
- Families
- Funding Entities

CANCER RESEARCH UK

Fundación BBVA

Roche

Instituto de Salud Carlos III

aecc Contra el Cáncer

fundación fero

Obra Social "la Caixa"

imi innovative medicines initiative

ImmuneImageO

European Union's Horizon 2020 research and innovation programme

VII SIMPOSIO GETTHI

Sesión 3: Vías de desarrollo de la oncología transversal (I)

GETTHI
Grupo Español de Oncología Transversal y Tumores Huérfanos e Infrecuentes

2 de diciembre de 2021 - *Formato virtual*

¡Gracias!

Terapia Celular en tumores sólidos.

Elena Garralda, MD MSc
egarralda@vhio.net