TIL therapy for advanced melanoma

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German, Austrian and Swiss Associations for Hematology and Medical Oncology
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Disclosure Information

I have the following financial relationships to disclose:

- **I have provided consultation, attended advisory boards, and/or provided lectures for: Agenus, AZ, BMS, CureVac, GSK, Imcyse, Iovance Bio, Immunocore, Ipsen, Merck Serono, MSD, Molecular Partners, Novartis, Orgenesis, Pfizer, Roche/Genentech, Sanofi, Third Rock Ventures**

- **I participated in the SAB of Achilles Tx, BioNTech, Instil Bio, PokeAcell, T-Knife, Scenic and Neogene Therapeutics (AZ)**

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- **I am Editor-in-Chief of ESMO IOTECH**

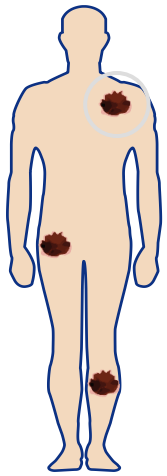
Background treatment landscape melanoma

- Immune checkpoint inhibitors and targeted therapies have dramatically improved the outcome of patients with advanced melanoma
- Treatment with anti-PD-1 antibodies (nivolumab or pembrolizumab) is frequently used as a first-line treatment in this patient population[1-4]
- Adjuvant anti-PD-1 (1 year) is standard of care for patients with stage III melanoma[5,6]
- However, approximately 50% of patients still dies from their disease within 5 years from diagnosis of stage IV disease[7,8]
- Thus, there is a great unmet need for additional effective treatment options in this patient population

[1]Hamid, O. et al., Ann Oncol 2019; [2]Robert, C. et al., J Clin Oncol 2020; [3]Robert, C. et al., Lancet Oncol 2019; [4]Michielin, O. et al., Ann Oncol 2019; [5]Eggermont, A.M.M. et al., N Engl J Med. 2018; [6]Ascierto, P.A. et al., Lancet Oncol. 2020; [7]Larkin, J. et al., NEJM 2019; [8]Hodi, F.S. et al., JCO 2022, presented at ASCO 2022

Tumor-infiltrating lymphocytes (TIL)

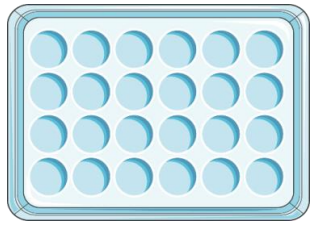
Preparation and treatment



Surgical removal of melanoma lesion

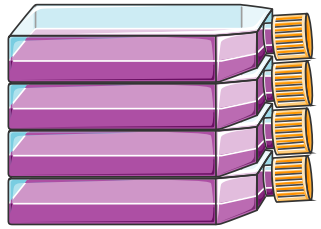
Addition of interleukin -2 (IL-2)

Tumor digest/fragments put into culture plates



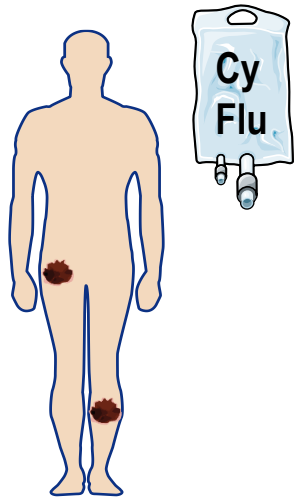
Initial outgrowth

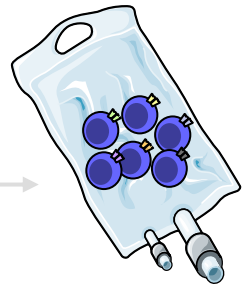
Addition of:
- Anti-CD3
- Feeder cells
- IL-2



Rapid expansion protocol (“REP”)

Non-myeloablative, lymphodepleting chemotherapy prior to TIL infusion

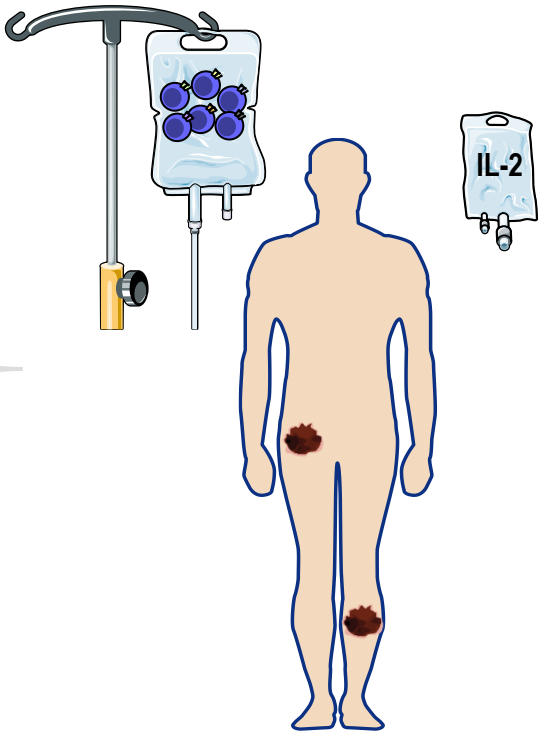




Expanded TIL pooled in one infusion bag

Single infusion of TIL

Administration of high-dose IL-2

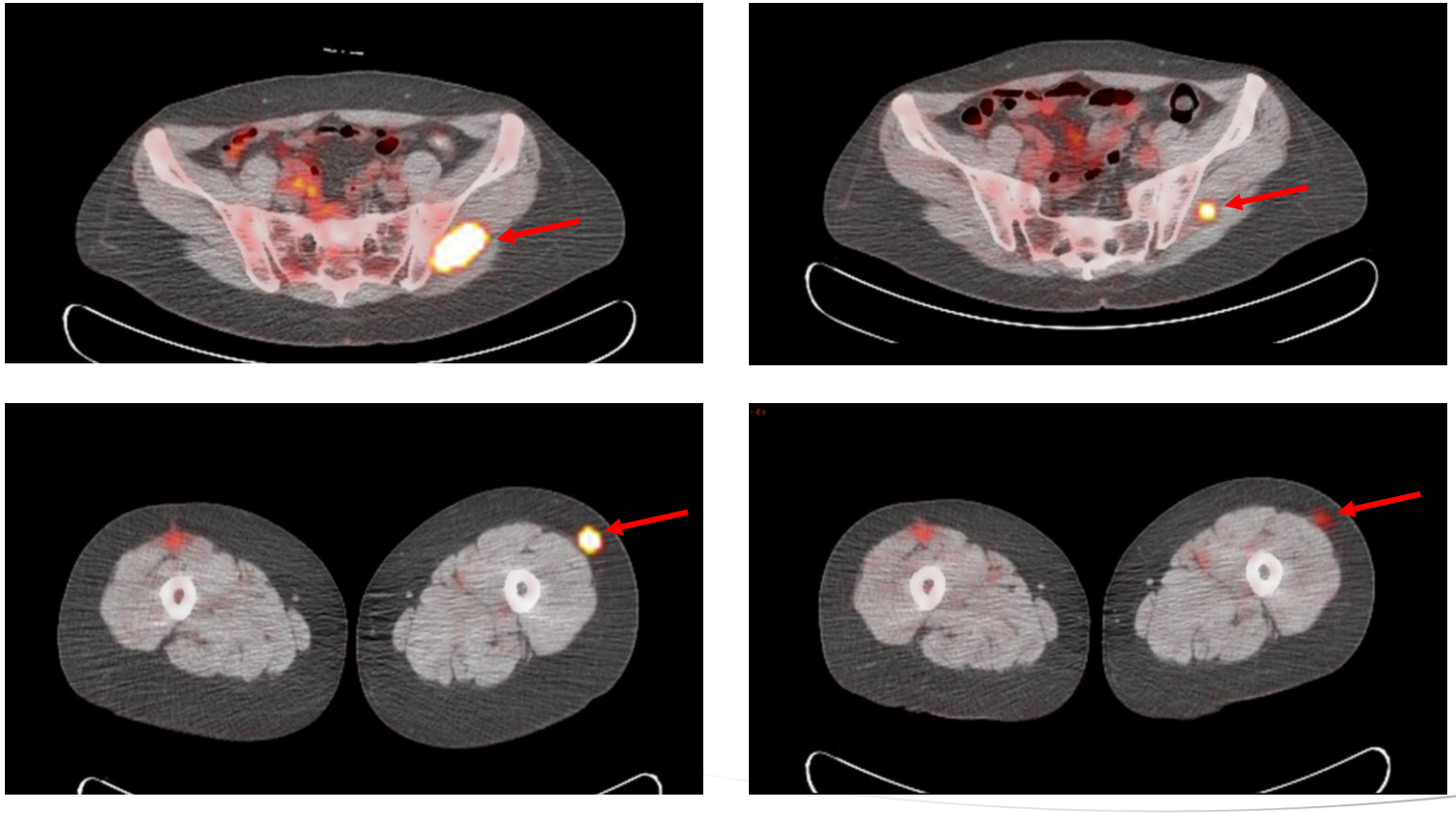


Examples of clinical activity in phase I/II trial

Clinical data N10TIL005: PR (6 months)

Prior to TIL

3 months post TIL



Days -7 to -1: Nonmyeloablative chemotherapy with cyclophosphamide and fludarabin

Day 0: 1.9 x 10^{11} TIL (unselected 'young' TIL)

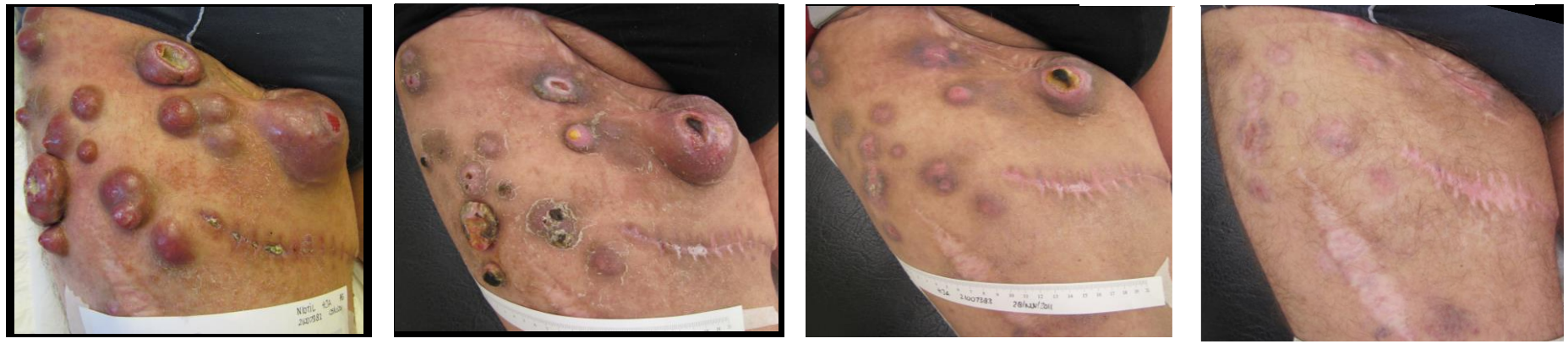
Days 0 – 3: high dose bolus IL-2 (2 in total)

Van den Berg et al. JITC 2020

Examples of clinical activity in phase I/II trial

Clinical data N10TIL003 patient: CR at 20 weeks

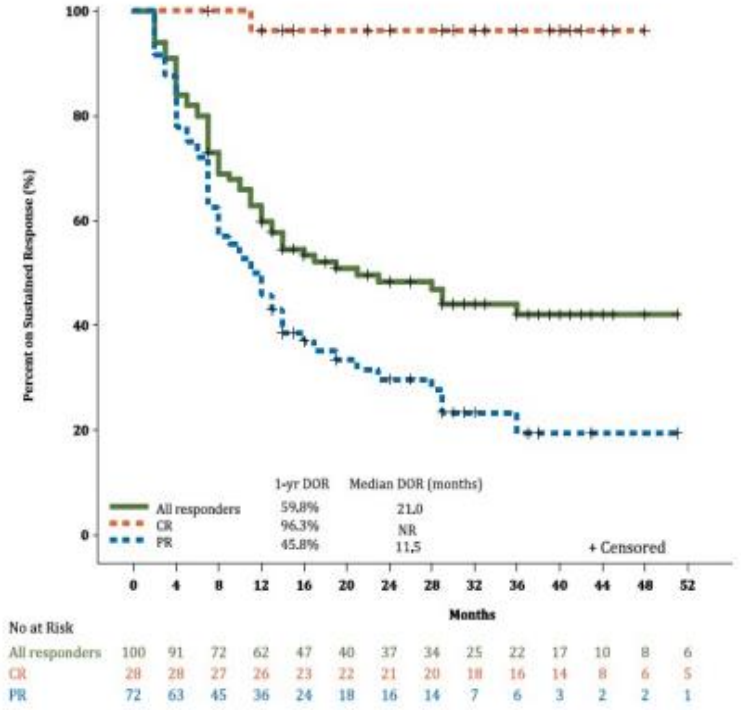
Prior to TIL | 3 wks after TIL | 8 wks after TIL | 20 wks after TIL



Days -7 to -1: Nonmyeloablative chemotherapy with Cyclophosphamide and fludarabin
Day 0: 2 x 10^{11} TIL (unselected 'young' TIL)
Days 0 – 3: high dose bolus IL-2 (4 in total)

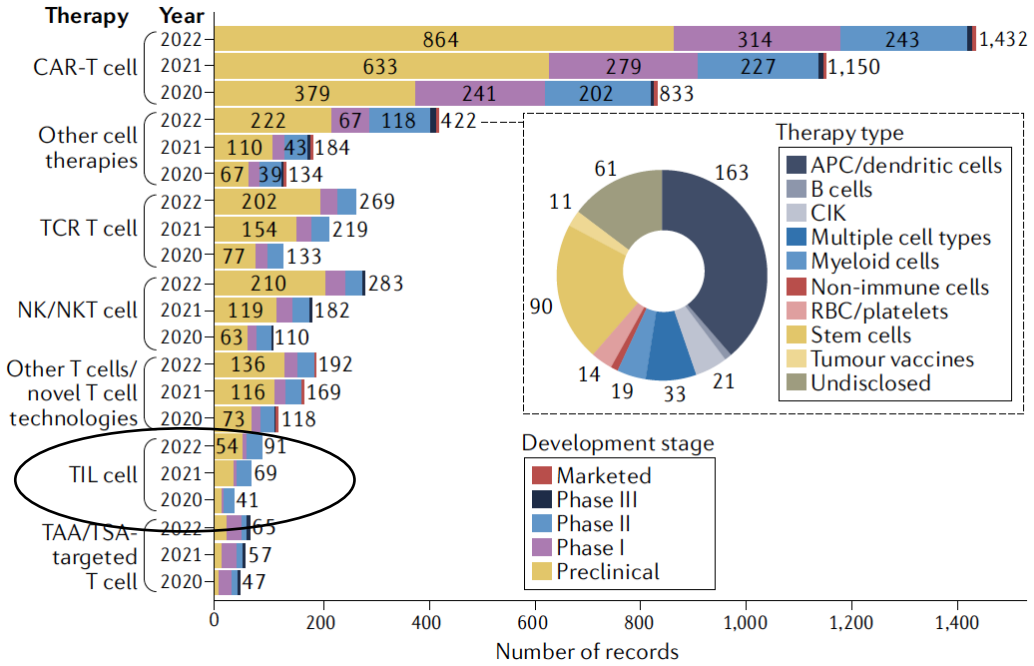
Van den Berg et al. JITC 2020

Meta-analysis of academic phase I/II trials with TIL in melanoma



CR= complete response
PR= partial response

Dafni et al., Ann Oncol 2019



Saez-Ibañez et al., Nat Rev Drug Disc 2022

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Commercial TIL products show efficacy in heavily pretreated melanoma patients

Lifileucel, a Tumor-Infiltrating Lymphocyte Therapy, in Metastatic Melanoma

Amod A. Sarnaik, MD[1]; Omid Hamid, MD[2]; Nikhil I. Khushalani, MD[1]; Karl D. Lewis, MD[3]; Theresa Medina, MD[3]; Harriet M. Kluger, MD[4]; Sajeve S. Thomas, MD[5]; Evidio Domingo-Musibay, MD[6]; Anna C. Pavlick, DO, MBA[7]; Eric D. Whitman, MD[8]; Salvador Martin-Algarra, MD, PhD[9]; Pippa Corrie, PhD, FRCP[10]; Brendan D. Curti, MD[11]; Judit Oláh, MD, DSc[12]; Jose Lutzky, MD[13]; Jeffrey S. Weber, MD, PhD[7]; James M. G. Larkin, MD, PhD[14]; Wen Shi, MD, PhD[15]; Toshimi Takamura, BA, BS[15]; Madan Jagasia, MD[15]; Harry Qin, PhD[15]; Xiao Wu, PhD[15]; Cecile Chartier, PhD[15]; Friedrich Graf Finckenstein, MD[15]; Maria Fardis, PhD, MBA[15]; John M. Kirkwood, MD[16]; and Jason A. Chesney, MD, PhD[17]

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Journal for ImmunoTherapy of Cancer

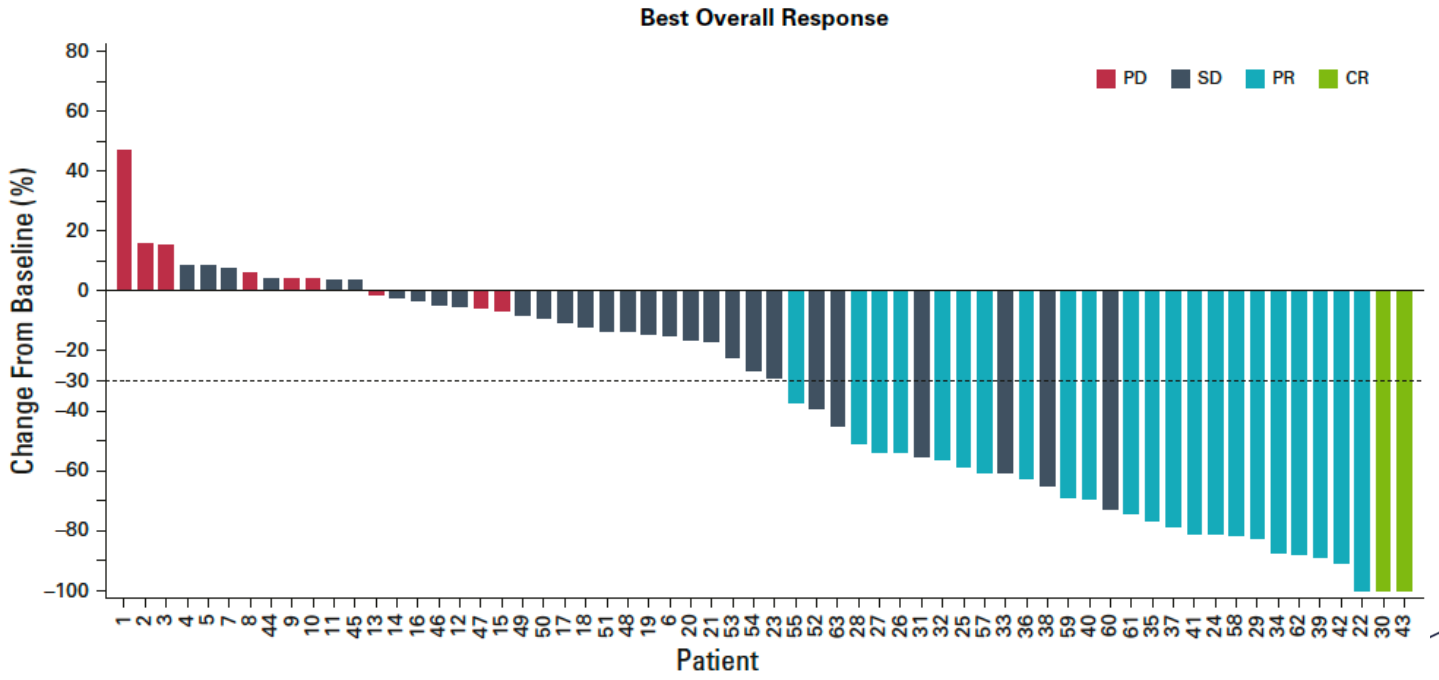
Efficacy and safety of lifileucel, a one-time autologous tumor-infiltrating lymphocyte (TIL) cell therapy, in patients with advanced melanoma after progression on immune checkpoint inhibitors and targeted therapies: pooled analysis of consecutive cohorts of the C-144-01 study

Jason Chesney,[1] Karl D Lewis,[2] Harriet Kluger,[3] Omid Hamid,[4] Eric Whitman [5] Sajeve Thomas,[6] Martin Wermke,[7] Mike Cusnir,[8] Evidio Domingo-Musibay [9] Giao Q Phan,[10] John M Kirkwood,[11] Jessica C Hassel [12] Marlana Orloff,[13] James Larkin,[14] Jeffrey Weber [15] Andrew J S Furness,[14] Nikhil I Khushalani [16] Theresa Medina,[2] Michael E Egger,[1] Friedrich Graf Finckenstein,[17] Madan Jagasia,[17] Parameswaran Hari,[17] Giri Sulur,[17] Wen Shi,[17] Xiao Wu,[17] Amod Sarnaik [16]

Samaik et al., J Clin Oncol 2021; Chesney et al., JiTC 2022

Outcome of the treatment with lifileucel

Response (RECIST v1.1)	Cohort 2 (N = 66)
ORR, No. (%) (95% CI)	24 (36) (25 to 49)
DCR, No. (%) (95% CI)	53 (80) (69 to 89)
Best overall response, No. (%)	
CR	2 (3)
PR	22 (33)
SD	29 (44)
PD	9 (14)
Nonevaluable	4 (6)
Median DOR, months (range)	Not reached (2.2-26.9+)



Samaik et al., J Clin Oncol 2021

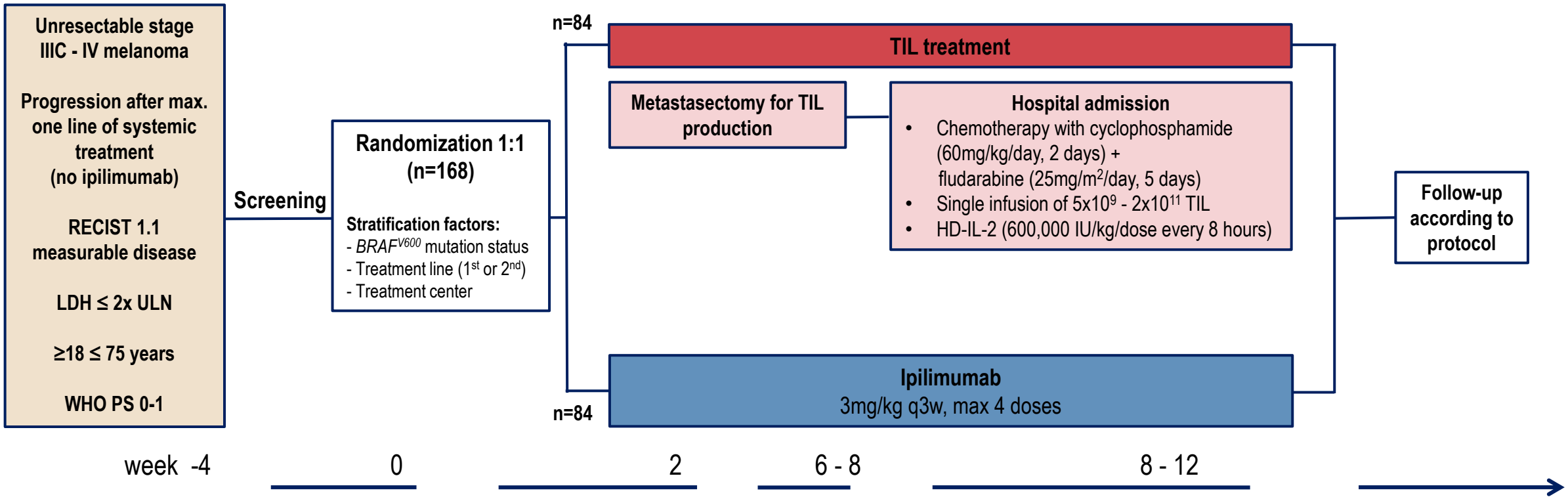
Status of TIL therapy in melanoma <2022

- Since 2002, TIL therapy has been studied in several academic phase I/II clinical trials with consistent clinical activity[1,2,3,4]
- Interest from commercial entities in TIL in melanoma (Iovance Bio, Instil Bio, Achilles Tx etc), illustrating clinical efficacy in heavily pretreated melanoma patients[5,6]
- Meta-analysis showing the survival benefit for melanoma patients responding to TIL therapy[7]

Results from a randomized controlled trial comparing TIL to SOC in immune checkpoint inhibition refractory patients was lacking…

[1]Dudley, M.E. et al., Science 2002; [2]Dudley, M.E. et al., J Clin Oncol 2008; [3]van den Berg, J.H. et al., J Immunother Cancer 2020; [4]Andersen, R. et al., Clin Cancer Res 2016; [5]Sarnaik, A.A. et al., J Clin Oncol 2021, [6]Chelsey et al., JITC 2022, [7]Dafni et al., Ann Oncol 2019

Trial design



Primary endpoint: Progression-free survival (PFS) according to RECIST 1.1 per investigator review in the intention-to-treat population (ITT)*

*Using the stratified (unweighted) log-rank test and the stratified cox regression model. The study was considered to be positive when PFS after TIL is significantly longer than ipilimumab, based on the log-rank test with a two-sided p-value below 0.05.

Statistical design

- The sample size was calculated based on a comparison of the PFS rates at six months.
- It was expected that the PFS rate at six months in the ipilimumab arm would be 20-25%.
- To detect an improvement of the PFS rate at six months in the TIL arm up to 45% (odds ratio 3.27) with 90% power, using a two-group continuity corrected chi-squared test with a 0.05 two-sided significance level, at least 80 patients should be randomized in each group (160 patients in total). With this, a difference of 25-50% (odds ratio 3.0) absolute PFS could be detected with 88% power.
- Considering the possibility that 5-10% of patients randomized to TIL would not receive the intended treatment, the total sample size was calculated to comprise 168-176 patients.

Patient disposition

199 patients with unresectable stage IIIC - IV melanoma were assessed for eligibility

31 patients did not meet eligibility criteria
- Rapidly progressive disease/new CNS metastases (n=17)
- Unfeasible surgery (n=5)
- Inadequate organ function (n=4)
- Late response to prior therapy (n=3)
- Positive viral serology (n=1)
- Resection + adjuvant ICI (n=1)

168 patients randomized 1:1 from Sept 2014 to Mar 2022

TIL treatment

- **84 assigned to TIL treatment (intention-to-treat)**
- **80 received infusion of TIL (safety analysis)**
- 4 did not receive treatment
  - 1 patient decision*
  - 1 late response upon prior treatment
  - 1 insufficient TIL outgrowth*
  - 1 rapid clinical decline

Ipilimumab

- **84 assigned to ipilimumab (intention-to-treat)**
- **82 received at least one cycle (safety analysis)**
- 2 did not receive treatment
  - 1 patient decision*
  - 1 rapid progressive disease after randomization*

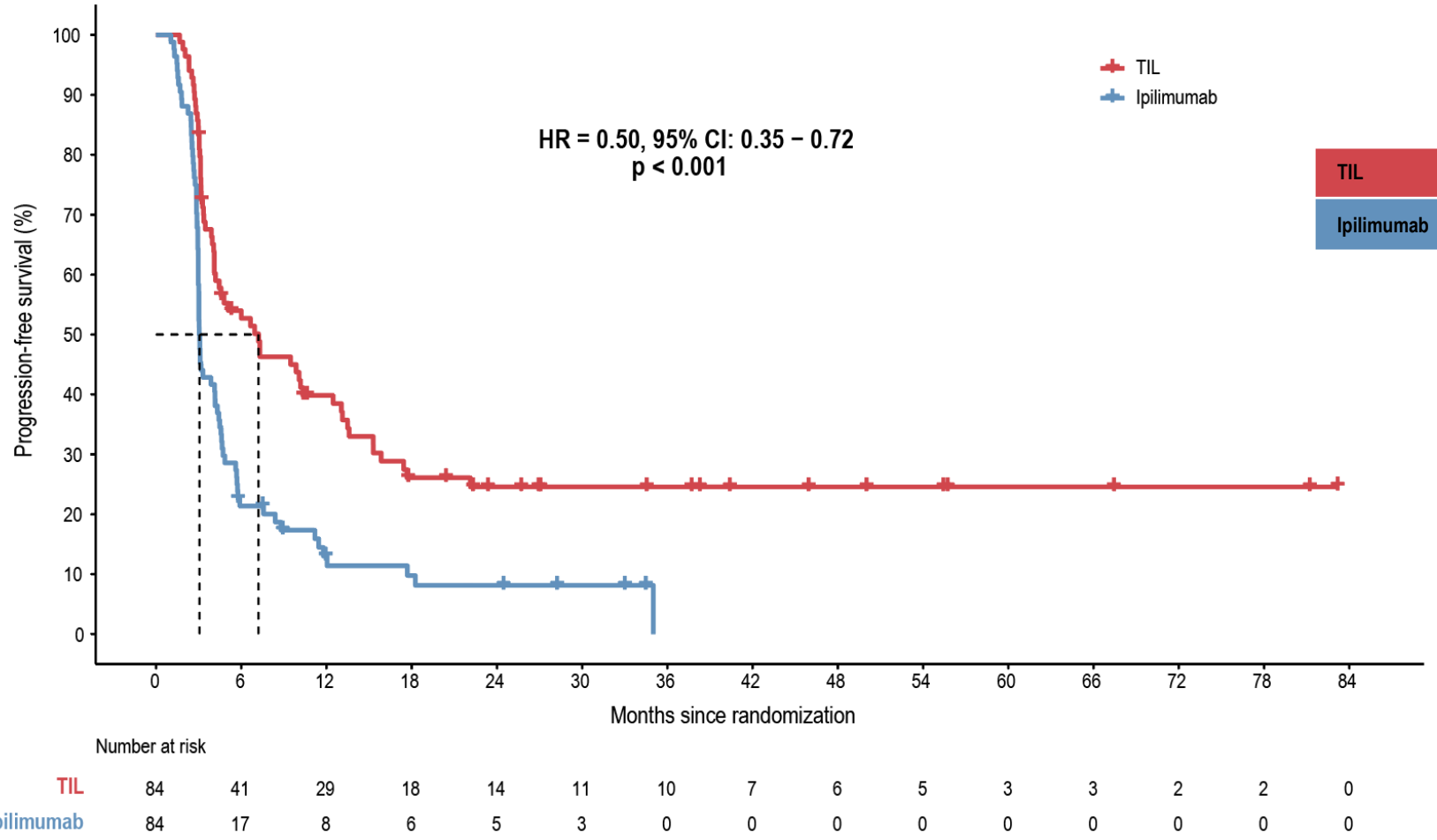
*Patients started subsequent immune checkpoint inhibition or targeted therapy as standard of care

Baseline characteristics

Characteristic	TIL (n=84)	Ipilimumab (n=84)
Gender – n (%)		
Male	47 (56.0)	53 (63.1)
Female	37 (44.1)	31 (36.9)
Age, years		
Median (range)	59 (26 - 74)	58 (30 - 77)*
WHO performance status – n (%)		
0	69 (82.1)	70 (83.3)
1	15 (17.9)	14 (16.7)
***BRAF* mutation status – n (%)**		
V600 mutation	37 (44.1)	36 (42.9)
Wild type	47 (56.0)	48 (57.1)
Treatment Center – n (%)		
NKI	66 (78.6)	66 (78.6)
CCIT	18 (21.4)	18 (21.4)
Disease stage at study entry – n (%)		
Unresectable stage IIIC	2 (2.4)	2 (2.4)
Stage IV	82 (97.6)	82 (97.6)
CNS metastases	6 (7.1)	7 (8.3)
Liver metastases	20 (23.8)	9 (10.7)
LDH – n (%)		
≤ ULN	67 (79.8)	70 (83.3)
1-2 x ULN	17 (20.2)	14 (16.7)
Prior systemic therapy – n (%)		
None	9 (10.7)	10 (11.9)
Adjuvant anti-PD-1	17 (20.2)	23 (27.4)
First-line anti-PD-1	56 (66.7)	49 (58.3)
Other	2 (2.4)	2 (2.4)

*Two patients ≥75 years were included in the trial, as these patients were deemed in excellent clinical condition by the principal investigator

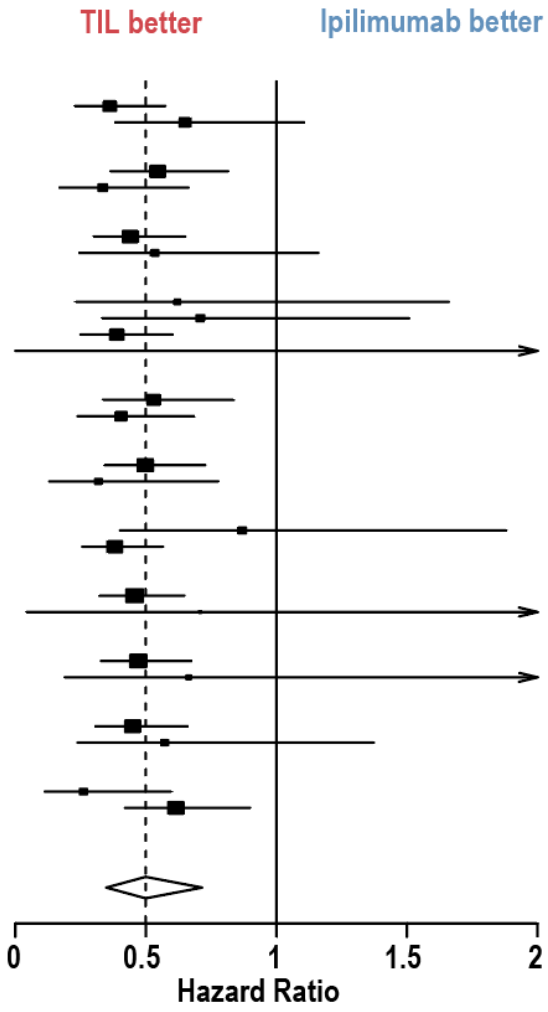
Progression-free survival according to RECIST 1.1 in the ITT population



	Median follow-up (months)	Median PFS (months)	95% CI	6 month PFS (%)	95% CI
TIL	33.5	7.2	4.2 - 13.1	52.7	42.9 - 64.7
Ipilimumab	33.0	3.1	3.0 - 4.3	21.4	14.2 - 32.2

Progression-free survival subgroup analysis

Subgroup	TIL Events/N	Ipilimumab Events/N	HR (95% CI)
Gender			
Male	31/47	49/53	0.36 (0.23 – 0.57)
Female	29/37	27/31	0.65 (0.38 – 1.11)
Age			
≤65 years	47/62	51/58	0.55 (0.36 – 0.81)
>65 years	13/22	25/26	0.33 (0.17 – 0.66)
Site			
NKI	48/66	62/66	0.44 (0.30 – 0.65)
CCIT	12/18	14/18	0.53 (0.25 – 1.16)
Prior systemic therapy			
None	7/9	10/10	0.62 (0.23 – 1.66)
Adjuvant anti-PD-1	11/17	18/23	0.71 (0.34 – 1.51)
First-line anti-PD-1	41/56	46/49	0.39 (0.26 – 0.61)
Other	1/2	2/2	0.00 (0.00 – Inf)
BRAF mutation			
No	33/47	44/48	0.53 (0.34 – 0.84)
Yes	27/37	32/36	0.40 (0.24 – 0.69)
WHO performance status			
0	50/69	63/70	0.50 (0.34 – 0.73)
1	10/15	13/14	0.32 (0.13 – 0.78)
LDH (<ULN)			
No	15/17	12/14	0.87 (0.40 – 1.88)
Yes	45/67	64/70	0.38 (0.26 – 0.57)
Disease stage			
IV	59/82	75/82	0.46 (0.32 – 0.65)
Unresectable IIIc	1/2	1/2	0.71 (0.04 – 1.79)
Brain metastases			
No	55/78	69/77	0.47 (0.33 – 0.67)
Yes	5/6	7/7	0.66 (0.19 – 2.32)
Liver metastases			
No	46/64	68/75	0.45 (0.31 – 0.66)
Yes	14/20	8/9	0.57 (0.24 – 1.37)
Follow-up systemic therapy			
No	9/32	15/22	0.26 (0.11 – 0.60)
Yes	51/52	61/62	0.61 (0.42 – 0.90)
Overall result	**60/84**	**76/84**	**0.50 (0.35 – 0.72)**

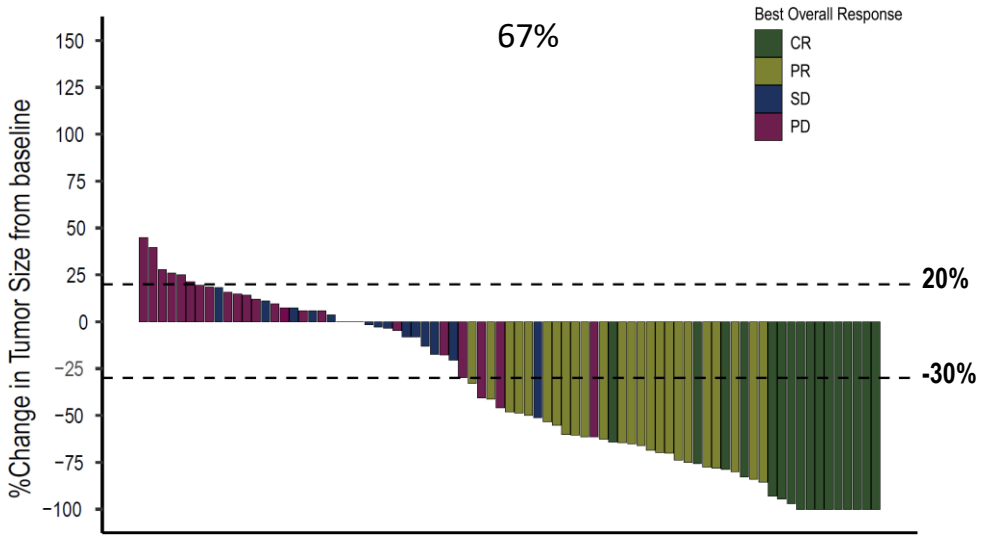


Best overall response according to RECIST 1.1*

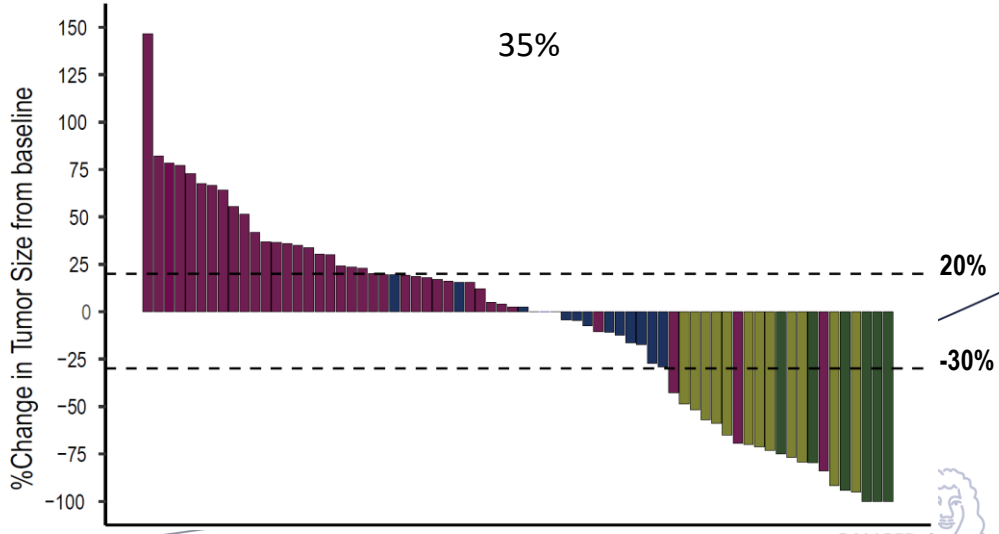
	TIL (n=84)	Ipilimumab (n=84)
Best overall response	**n (%)**	**n (%)**
Complete response	17 (20.2)	6 (7.1)
Partial response	24 (28.6)	12 (14.3)
Stable disease	16 (19.1)	15 (17.9)
Progressive disease	24 (28.6)	40 (47.6)
Not evaluable/done#	3 (3.6)	11 (13.1)
Overall response†	41 (48.8)	18 (21.4)
Clinical benefit‡	57 (67.9)	33 (39.3)

*In the intention-to-treat population. #In 3 (3.6%) and 11 (13.1%) of TIL and ipilimumab treated patients, respectively, best radiologic response could not be evaluated or was not done due to an event (death or need to start subsequent anticancer therapy) before the moment of first response evaluation or due to unevaluable target lesions in follow-up. †Defined as CR plus PR and ‡CR, PR plus SD according to RECIST 1.1.

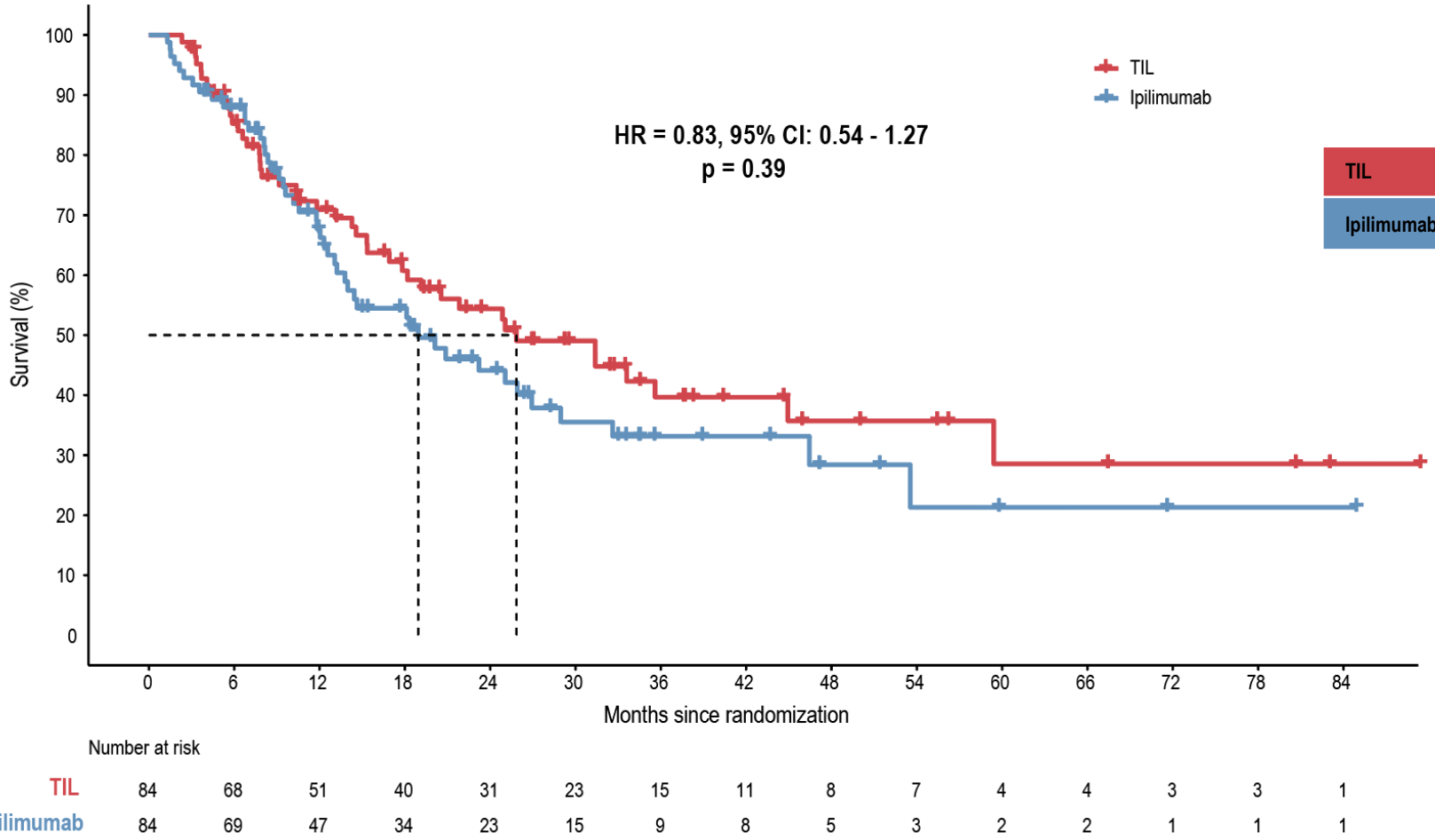
TIL treatment



Ipilimumab treatment



Overall survival in the ITT population



	Median overall survival (months)	95% CI	2 year overall survival (%)	95% CI
TIL	25.8	18.2 – NR	54.3	43.9 – 67.2
Ipilimumab	18.9	13.8 – 32.6	44.1	33.6 – 57.8

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Safety with grade ≥ 3 treatment-related adverse events according to CTCAEv4.03*

TIL (n=80)

Chemotherapy	
Adverse event	**n (%)**
Total	**80 (100)**
Neutropenia	80 (100)
Thrombocytopenia	71 (88.8)
Febrile neutropenia	67 (83.8)
Lymphopenia	57 (71.3)
Hypophosphatemia	20 (25.0)
Anemia	16 (20.0)
Elevated ALT	7 (8.8)
GGT increased	6 (7.5)
Elevated AST	4 (5.0)
Fatigue	4 (5.0)

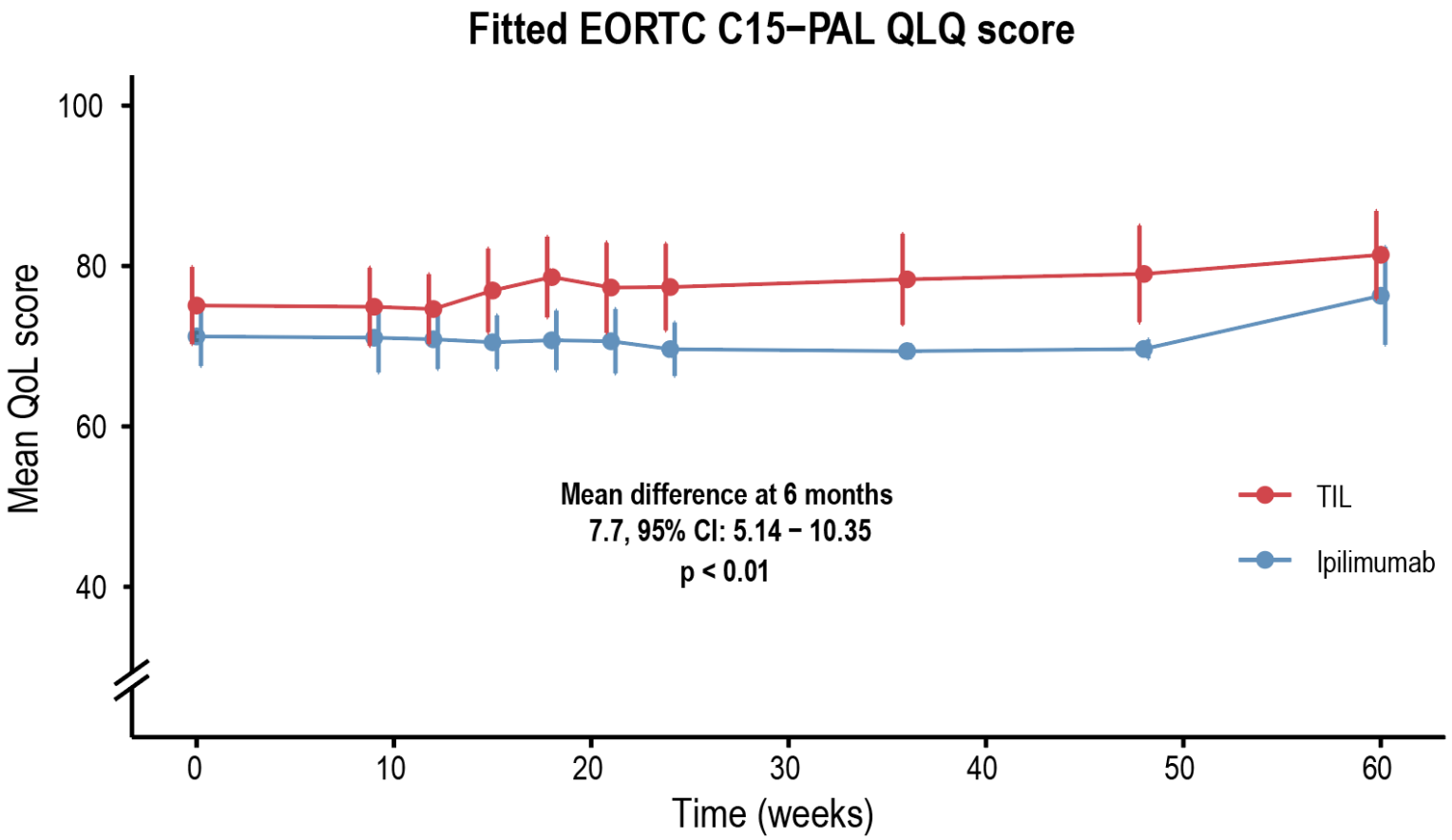
TIL plus IL-2	
Adverse event	**n (%)**
Total	**77 (96.3)**
Febrile neutropenia	58 (72.5)
Hypophosphatemia	48 (60.0)
Fever	36 (45.0)
Dyspnea	15 (18.8)
Hypertension	11 (13.8)
CPK increased	9 (11.3)
Rash	9 (11.3)
Elevated ALT	8 (10.0)
Elevated AST	8 (10.0)
Fatigue	7 (8.8)
Chills	6 (7.5)
GGT increased	6 (7.5)
Hypotension	6 (7.5)
Hypoxia	5 (6.3)

Ipilimumab (n=82)

Adverse event	**n (%)**
Total	**47 (57.3)**
Colitis	16 (19.5)
Diarrhea	12 (14.6)
Elevated ALT	8 (9.8)
Elevated AST	7 (8.5)
GGT increased	7 (8.5)

*Most common grade ≥ 3 treatment-related adverse according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.03 that occurred in ≥5% of patients receiving at least one dose of treatment (safety analysis set), per treatment arm. More than one adverse event could occur in the same patient.

Overall Health-related Quality of Life



Summary

- This multicenter, phase 3 trial is the **first randomized trial investigating T cell therapy in solid tumors**, comparing TIL to ipilimumab, a second-line standard of care option in metastatic melanoma
- **TIL significantly improved PFS** compared to ipilimumab in patients with advanced melanoma as first- or **second-line** treatment in anti-PD-1 refractory patients, with a HR: 0.5 and $p<0.001$
- **TIL resulted in a 49% ORR and 20% CR rate** compared to 21% and 7% for ipilimumab respectively
- **No new safety issues** were observed
- **Health-related quality of life scores were higher** in patients treated with TIL
- **TIL** could become a **possible new treatment** option for patients with advanced melanoma

Clinical implementation of TIL for melanoma

- TIL treatment has now been approved and is being reimbursed in Denmark and the Netherlands (2nd line treatment after failure of adjuvant anti-PD-1, or anti-PD-1 or ipilimumab/nivolumab in 1st line setting for stage IV disease

- It is expected that based on lifileucel data in melanoma, TIL will soon be approved as well in US (early 2024)

- We have started the route to EMA registration based on the phase III TIL trial

Acknowledgements

- **Patients and their families**

- Contributing team from the Netherlands Cancer Institute and Sanquin, Amsterdam, The Netherlands

- Contributing team from National Center for Cancer Immune Therapy and Department of Oncology, Copenhagen University Hospital, Herlev, Denmark

- Referring centers from The Netherlands and Denmark

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