2024 ASCO® ANNUAL MEETING

Towards Real-World Experience in Unmodified Tumor-Infiltrating Lymphocytes Therapy

TIL: a new standard of care for melanoma

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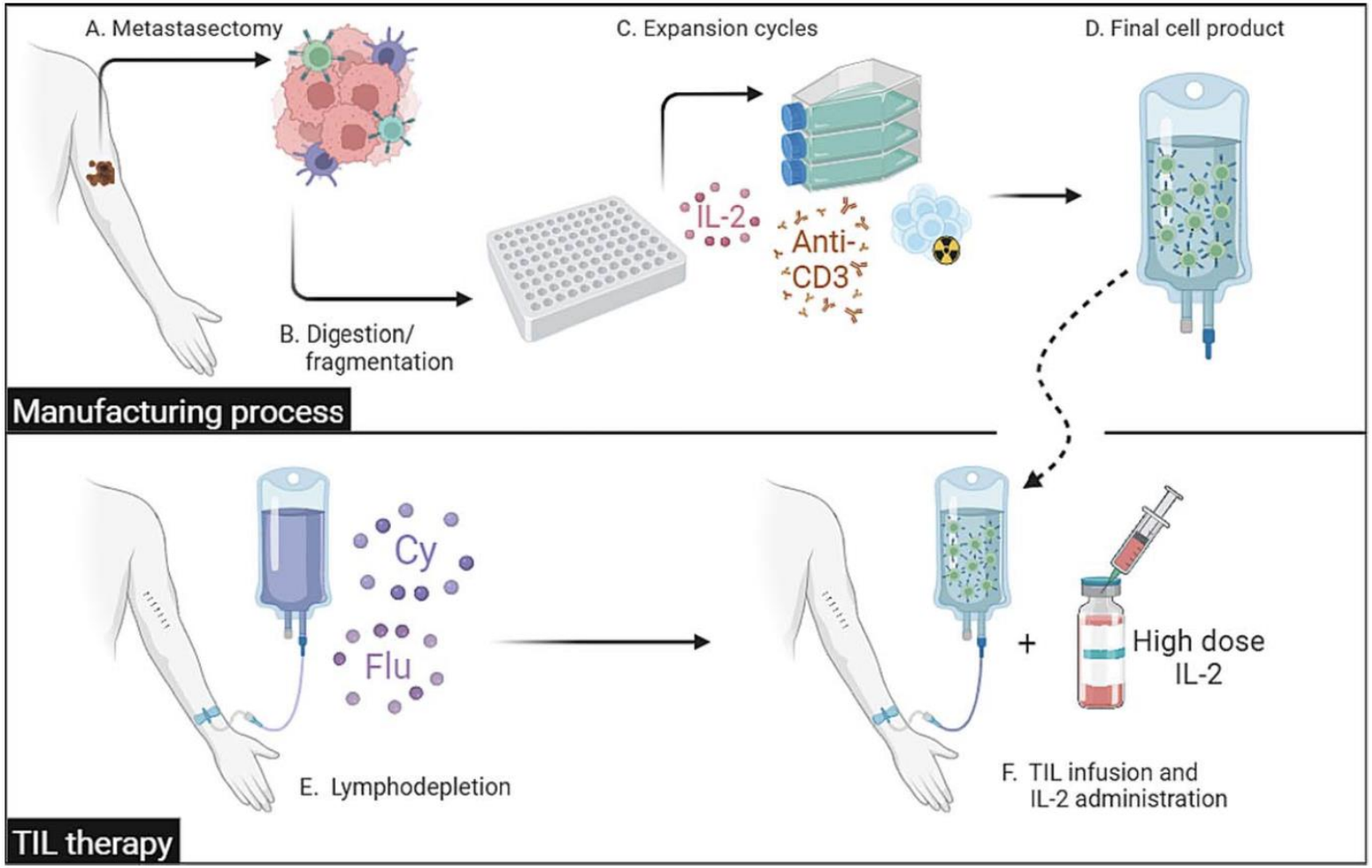
Learning objectives

- Understanding TIL
- What are the data that led to FDA approval or use as SOC?
- Which patients can be treated with TIL?
- Where should TIL be given?

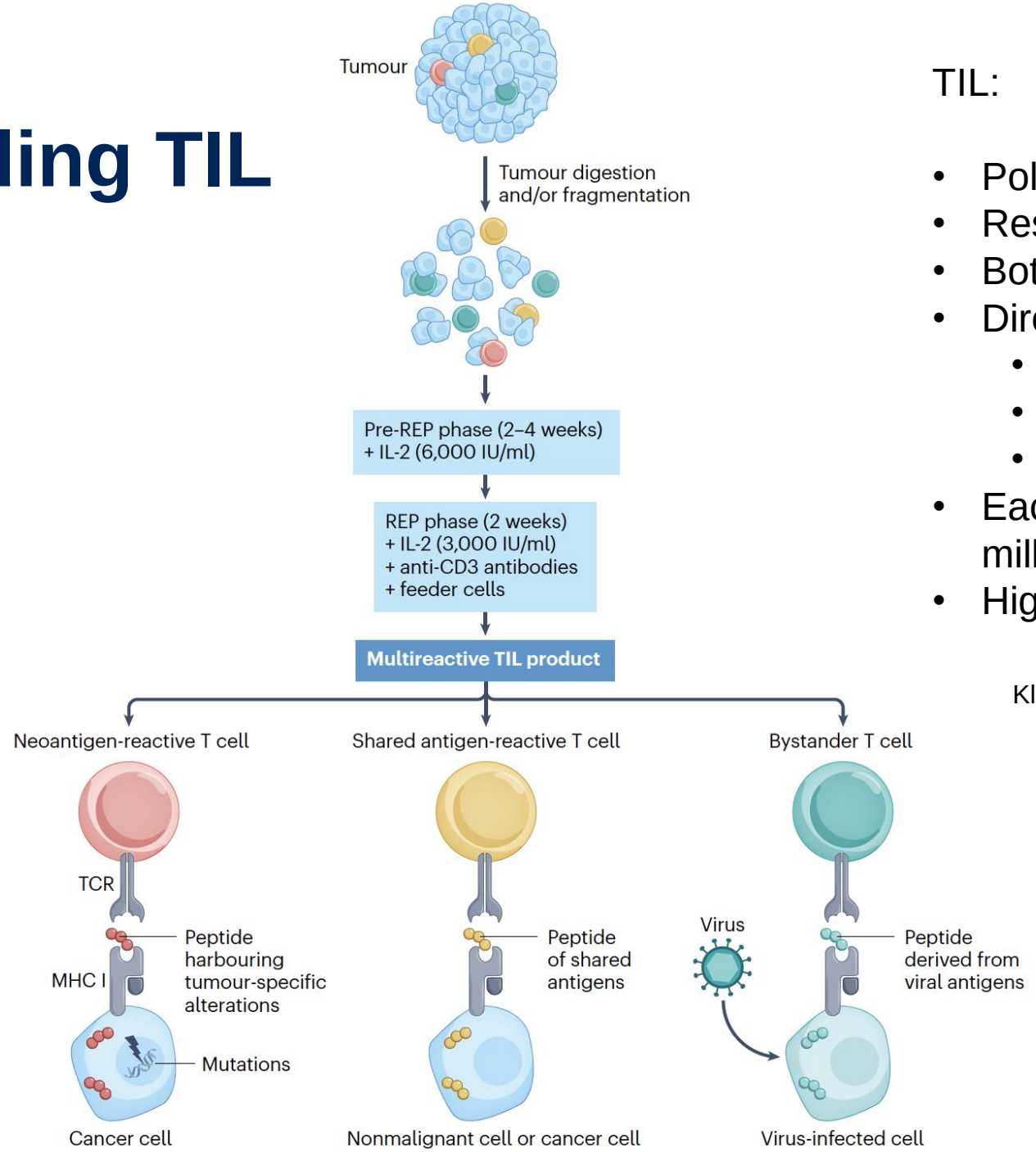
Understanding Tumor Infiltrating Lymphocyte (TIL) treatment



Los et al., The Cancer Journal 2024

- Metastasectomy
- Chemotherapy
- TIL product infusion
- HD IL-2

Understanding TIL



TIL:

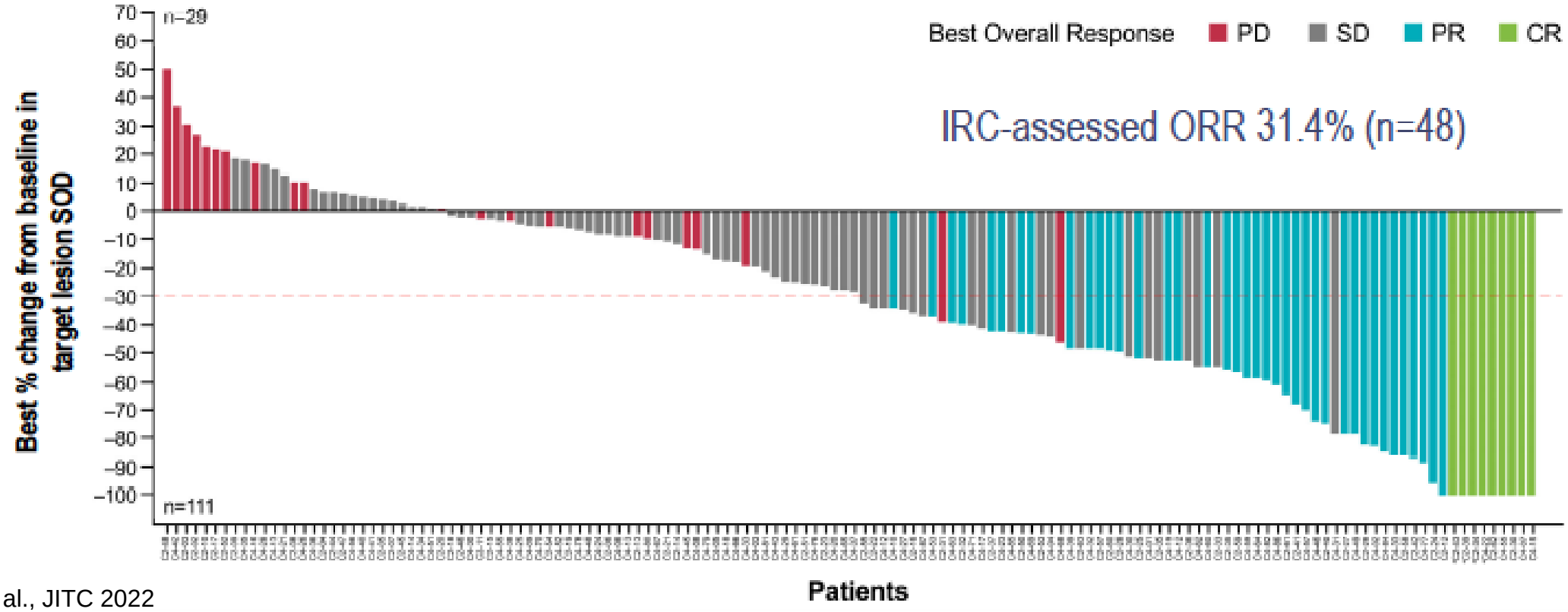
- Polyclonal population of T cells
- Residing in malignant tumor
- Both CD4 and CD8 T cells
- Directed at multiple antigen types
  - Neoantigens
  - Shared antigens
  - Viral antigens
- Each category consisting of millions of T cells
- Highly individualized product

Klobuch et al., Nat Rev Clin Oncol 2023

What is the current status of TIL for melanoma?

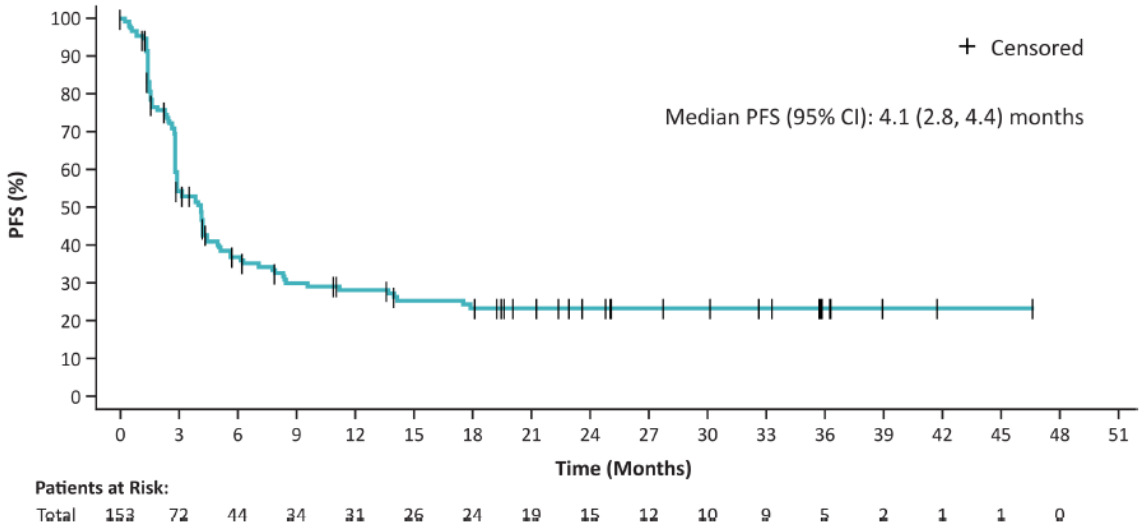
- Lifileucel/LN-144 (Amtagvi®): a commercial FDA approved cryopreserved autologous TIL product for the treatment of stage IV melanoma following PD on standard of care
- TM001: non-commercial fresh autologous TIL product (NKI, CCIT), reimbursed under hospital exemption, in Netherlands and Denmark for the treatment of irresectable stage III/IV melanoma with PD following anti-PD-1 based therapies. An application for Marketing Authorization by EMA is in development.

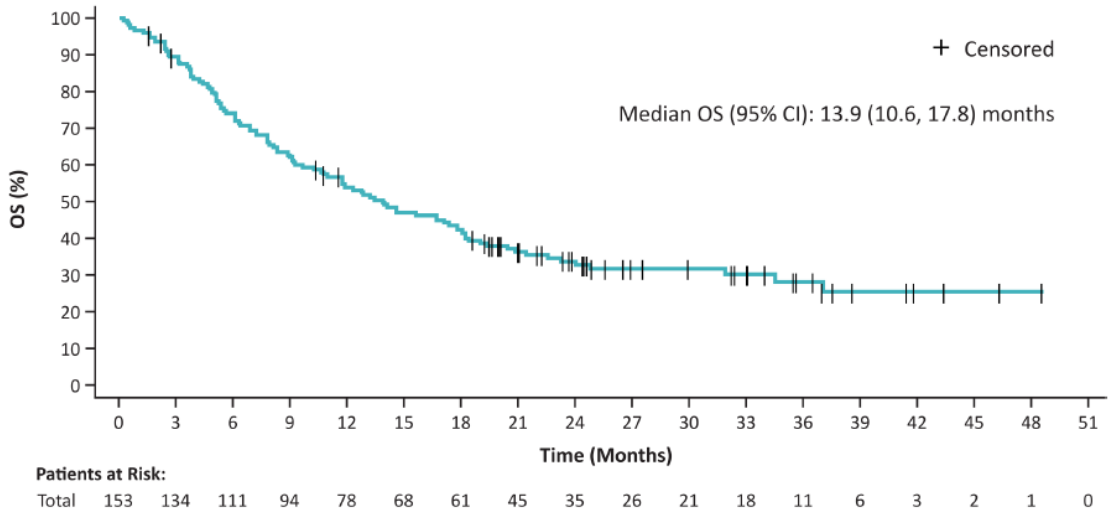
Data leading to FDA approval of lifileucel/LN-144



Chesney et al., JITC 2022

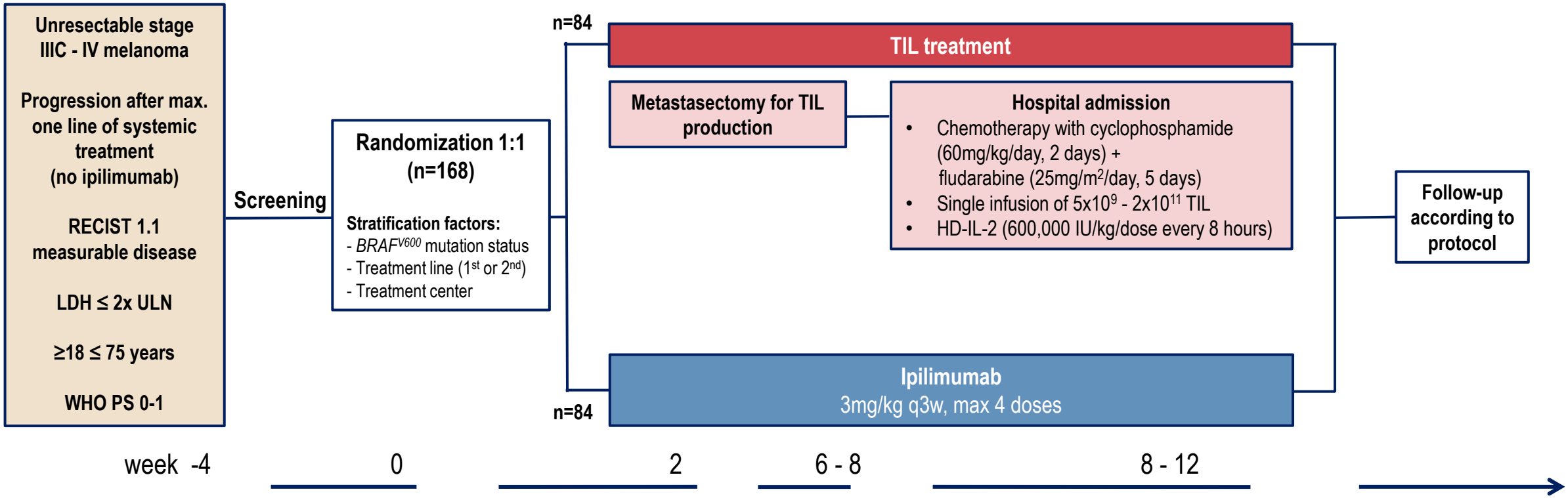
Data leading to FDA approval of lifileucel/LN-144





Chesney et al., JITC 2022

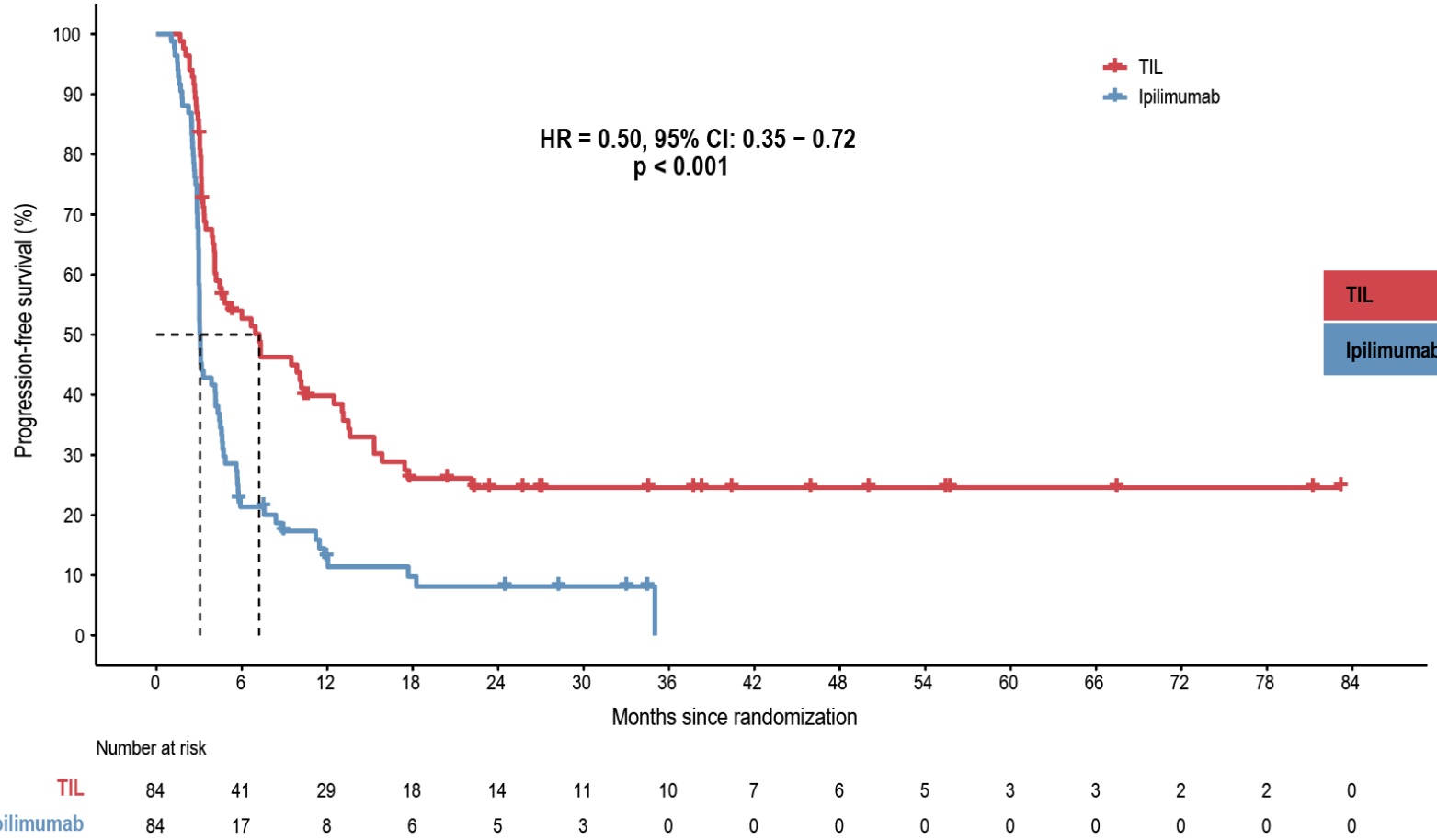
Data leading to TM001 reimbursement



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

Rohaan et al., NEJM 2022

Data leading to TM001 reimbursement



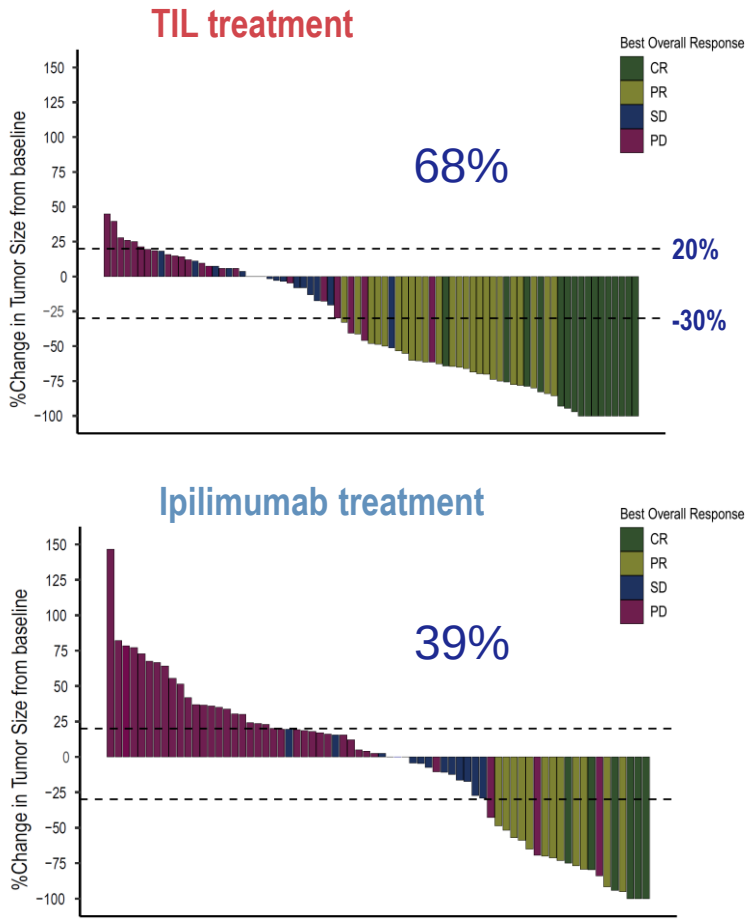
	Median follow-up (months)	Median PFS (months)	95% CI	6 month PFS (%)	95% CI
TIL	33.5	7.2	4.2 - 13.1	52.7	42.9 - 64.7
Ipilimumab	33.0	3.1	3.0 - 4.3	21.4	14.2 - 32.2

Rohaan et al., NEJM 2022

Data leading to TM001 reimbursement

	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)

Rohaan et al., NEJM 2022



Which patients should be treated with TIL?

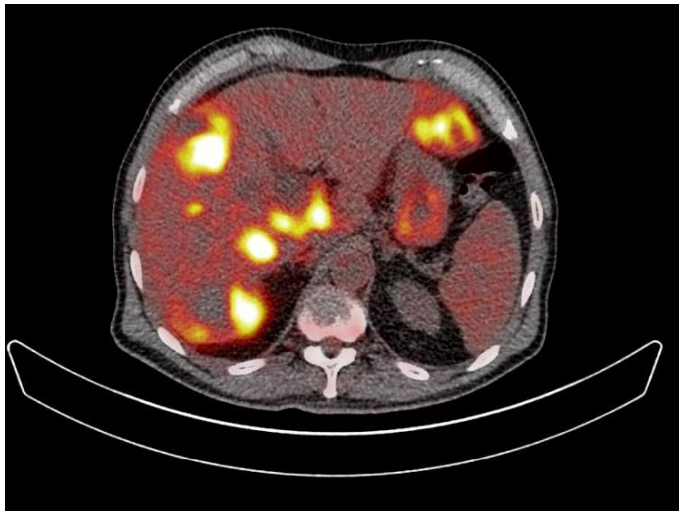
Lifileucel cohorts 2 & 4 (n=153)

- Median age: 56 years
- 93% stage IV disease
- 68% PS 0
- ~ 80% cutaneous melanoma
- 46% normal LDH / 19% > 2xULN
- 46% M1a disease
- Median number of prior Tx: 3

RCT TIL trial (n=80)

- Median age: 56 years
- 98% stage IV disease
- 82% PS 0
- 100% cutaneous melanoma
- 80% normal LDH / 0% > 2x ULN
- 67% M1c disease (24% liver metastases)
- Median number of prior Tx: 1

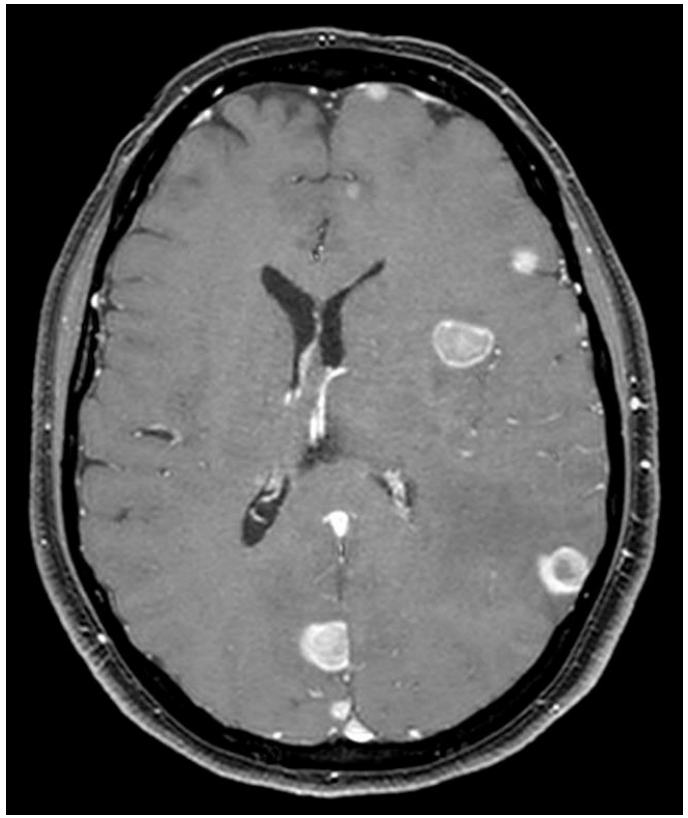
Eligible for TIL?



- Case 1:
  - 71 year old male stage IV BRAF V600E mutated melanoma patient
  - In remission after BRAF/MEK inhibitors. Stopped because of SJS
  - Prior lines: anti-PD-1 (PD), TVEC (PD), surgery (PD)
  - Sept 2022: presented with abdominal discomfort, malaise, fatigue and loss of appetite
  - PS WHO 2
  - Normal PET in May 2022
  - On physical exam: enlarged liver, no ascites
  - Lab: AP: 270 U/L; AST: 76 U/L; ALT: 77 U/L; LDH 660 U/L

Eligible for TIL?

- Case
  - 41 year old female st IV melanoma patient, BRAF wt
  - PD under ipilimumab + nivolumab
  - More than 50 brain metastases, at least 20 were treated with γ-knife RT
  - Also extensive extracranial disease
  - On low dose dexamethasone



Who are not eligible for TIL?

- Patients with symptomatic active brain metastases (requiring CS)
- Patients with LM disease, extensive (asymptomatic) brain metastases
- Patients with poor performance status (ECOG ≥ 2), high LDH (>2x ULN), rapidly progressing disease
- Patients older than 75 years unless extremely fit
- Patients with severe COPD (Gold stage III/IV)
- Patients with LVEF < 45% or (instable) AP
- Patients with CKI (GFR<40 ml/min)

Reminder

TIL = high-dose LD chemo + TIL infusion + HD bolus IL-2

So, patients who can only tolerate LD chemo + TIL **or** TIL + IL-2 are NOT eligible!

Patients rapidly progressing while waiting for TIL growth should NOT be treated

Experience with high dose cyclophosphamide/fludarabine is necessary!

(cyclophosphamide 60 mg/kg x 2 days / fludarabine 25 mg/m2 for 5 days)

Experience with high-dose IL-2 is necessary!

(IL-2 at 600,000 – 720.000 IU/kg per i.v. bolus every 8-12 hrs for max 6 boluses)

Adoptive TIL therapy is team effort!

- Dedicated surgeon(s) should be involved
- Medical oncology/(hematology) team experienced with non-myeloablative chemotherapy and management of high dose IL-2
- Logistics of surgical specimen to Iovance Bio and return to pharmacy to release to patient should be in place
- SOPs of all steps of TIL therapy must be present and easily available
- Possibility for ICU admission (ICU should know what to do in case of IL-2 toxicity (no steroids, no tocilizumab!)

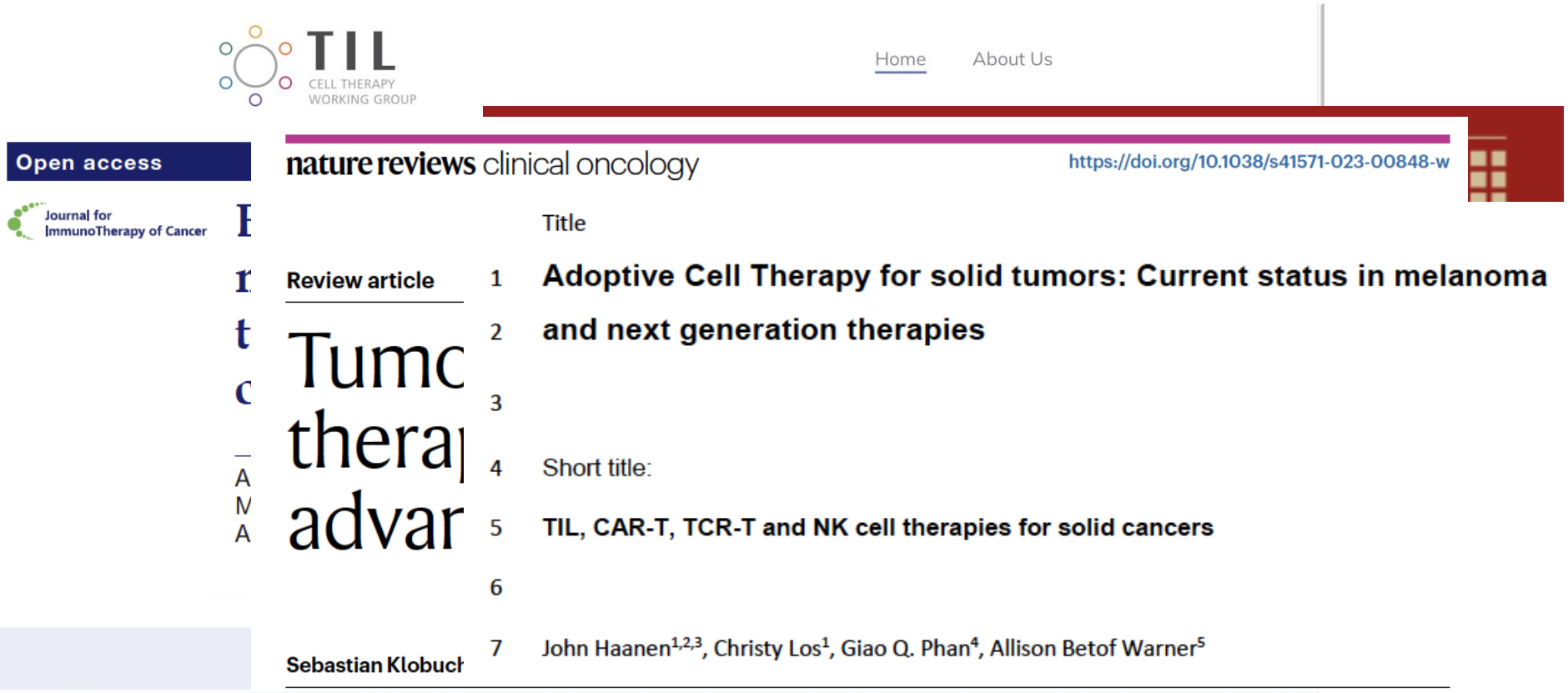
Where should TIL be given?

- @ any site fulfilling these criteria.
- Get training from experienced sites
- Hire doctors with TIL experience
- Make sure to have a back-up as a single doctor cannot give TIL therapy

- Visit: www.tilworkinggroup.com

Important information/literature on TIL therapy

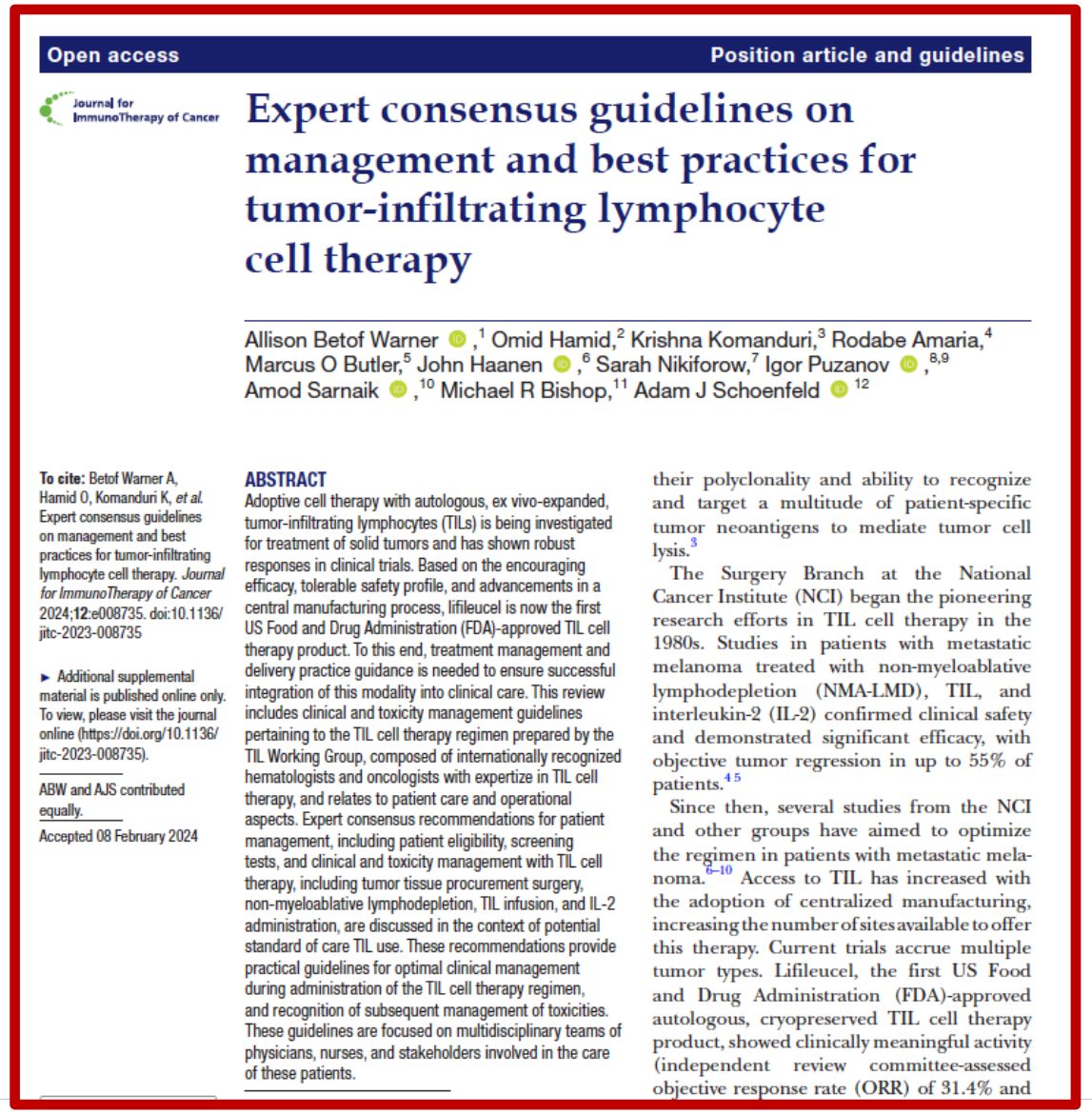
- www.tilworkinggroup.com
- Expert Guide
- Reading mat
  - Los et al., (
  - Klobuch et
  - Haanen, L(



Take home messages

- TIL is a new standard of care for patients with pretreated metastatic melanoma
- TIL therapy requires a solid set-up to deliver it safely
- Work closely together with experienced centers/doctors
- Use same eligibility criteria as those used for trials
- IL-2 toxicity is not the same as a CAR-T CRS and should be treated differently

Consensus Management Guidelines



Open access Position article and guidelines

Journal for ImmunoTherapy of Cancer

Expert consensus guidelines on management and best practices for tumor-infiltrating lymphocyte cell therapy

Allison Betof Warner ,[1] Omid Hamid,[2] Krishna Komanduri,[3] Rodabe Amaria,[4] Marcus O Butler,[5] John Haanen ,[6] Sarah Nikiforow,[7] Igor Puzanov ,[8,9] Amod Sarnaik ,[10] Michael R Bishop,[11] Adam J Schoenfeld [12]

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ABW and AJS contributed equally.

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ABSTRACT

Adoptive cell therapy with autologous, ex vivo-expanded, tumor-infiltrating lymphocytes (TILs) is being investigated for treatment of solid tumors and has shown robust responses in clinical trials. Based on the encouraging efficacy, tolerable safety profile, and advancements in a central manufacturing process, lifileucel is now the first US Food and Drug Administration (FDA)-approved TIL cell therapy product. To this end, treatment management and delivery practice guidance is needed to ensure successful integration of this modality into clinical care. This review includes clinical and toxicity management guidelines pertaining to the TIL cell therapy regimen prepared by the TIL Working Group, composed of internationally recognized hematologists and oncologists with expertize in TIL cell therapy, and relates to patient care and operational aspects. Expert consensus recommendations for patient management, including patient eligibility, screening tests, and clinical and toxicity management with TIL cell therapy, including tumor tissue procurement surgery, non-myeloablative lymphodepletion, TIL infusion, and IL-2 administration, are discussed in the context of potential standard of care TIL use. These recommendations provide practical guidelines for optimal clinical management during administration of the TIL cell therapy regimen, and recognition of subsequent management of toxicities. These guidelines are focused on multidisciplinary teams of physicians, nurses, and stakeholders involved in the care of these patients.

their polyclonality and ability to recognize and target a multitude of patient-specific tumor neoantigens to mediate tumor cell lysis.[3]

The Surgery Branch at the National Cancer Institute (NCI) began the pioneering research efforts in TIL cell therapy in the 1980s. Studies in patients with metastatic melanoma treated with non-myeloablative lymphodepletion (NMA-LMD), TIL, and interleukin-2 (IL-2) confirmed clinical safety and demonstrated significant efficacy, with objective tumor regression in up to 55% of patients.[4 5]

Since then, several studies from the NCI and other groups have aimed to optimize the regimen in patients with metastatic melanoma.[6–10] Access to TIL has increased with the adoption of centralized manufacturing, increasing the number of sites available to offer this therapy. Current trials accrue multiple tumor types. Lifileucel, the first US Food and Drug Administration (FDA)-approved autologous, cryopreserved TIL cell therapy product, showed clinically meaningful activity (independent review committee-assessed objective response rate (ORR) of 31.4% and

TIL CELL THERAPY WORKING GROUP