# A Pilot Trial of Lifileucel for Melanoma Brain Metastases: Feasibility and Safety

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**ClinicalTrials.gov Identifier:** NCT05640193

# Disclosures

**Consulting:** Adaptimmune, Bristol Myers Squibb, BluePath Solutions, Genmab, Immatics, Instil Bio, IO Biotech, Iovance Biotherapeutics, Novartis, Merck, Pfizer, Replimune

**Research Funding (Institutional):** Bristol Myers Squibb, Iovance Biotherapeutics, Lyell Immunopharma, Obsidian Therapeutics

# Background: Melanoma Brain Metastasis (MBM)

- Melanoma is the solid tumor with highest propensity for brain metastasis[1]
- Approximately 40-75% of patients with metastatic melanoma develop MBM[2,3]
- CheckMate 204[4] and the ABC trial[5] established ipilimumab + nivolumab as first-line therapy for patients with asymptomatic untreated MBM
- BRAF + MEK inhibitor targeted therapy can be effective but typically duration of response is short[6,7]

[1] Lamba et al. *Neuro-Oncology* 2021
[2] Sloan et al. *Cancer Control* 2009
[3] Karz et al. *PCMR* 2022
[4] Tawbi et al. *NEJM* 2018
[5] Long et al. *Lancet Oncol* 2018
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[7] Menzies et al. *Neuro-Oncology Advances* 2024

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- BRAF + MEK inhibitor targeted therapy can be effective but typically duration of response is short[6,7]
- **There is an urgent unmet need for trials evaluating therapies for active brain metastasis following PD-1 failure**

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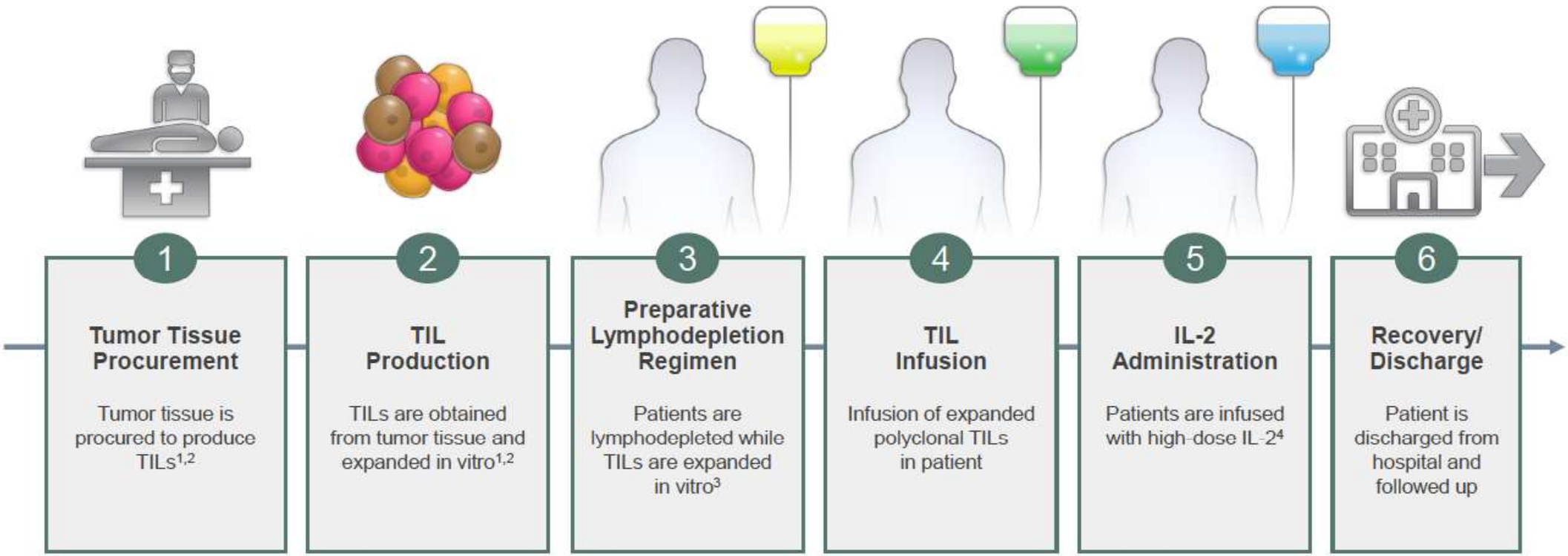
# Background: TIL Therapy for PD-1 Refractory Melanoma




IL, interleukin; TIL, tumor-infiltrating lymphocyte.
1. Itzhaki O, et al. *J Immunother*. 2011;34:212. 2. Dudley ME, et al. *J Immunother*. 2003;26:332. 3. Dudley ME, et al. *J Clin Oncol*. 2008;26:5233. 4. Atkins MB, et al. *J Clin Oncol*. 1999;17:2105.

TIL CELL THERAPY WORKING GROUP

(www.tilworkinggroup.com)

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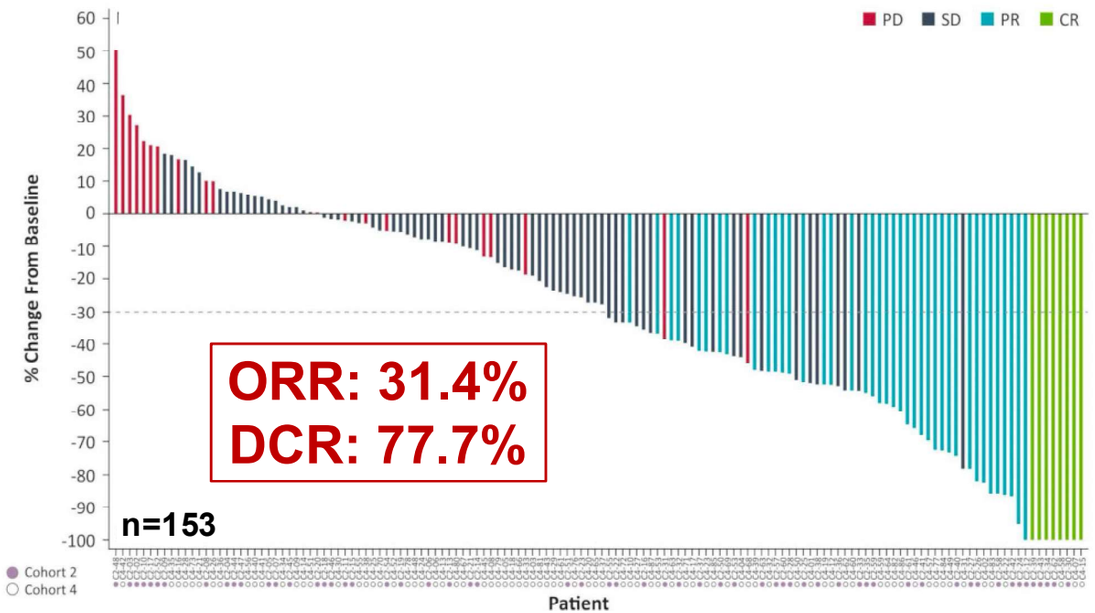


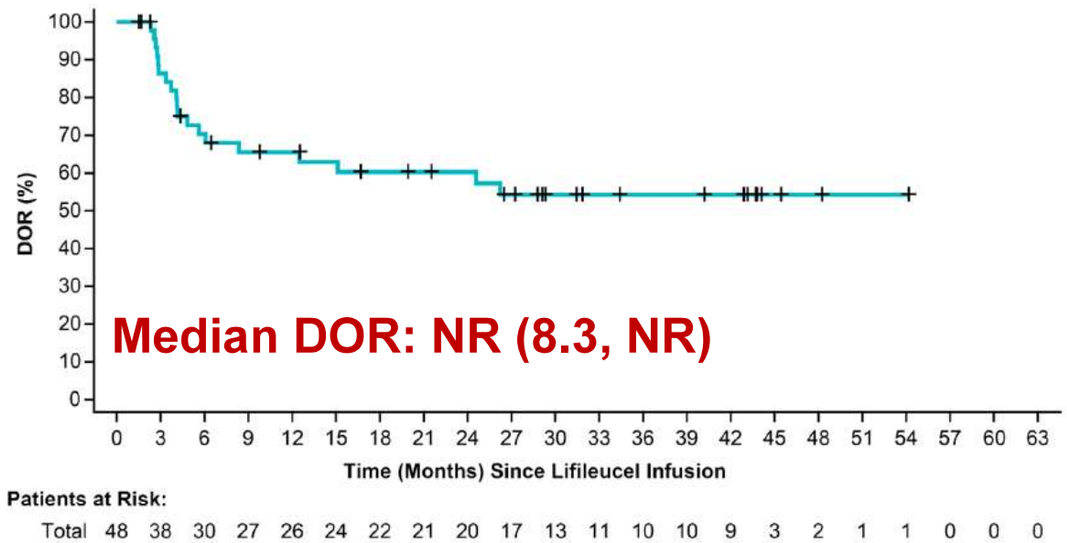


(Chesney et al. *JITC* 2022)

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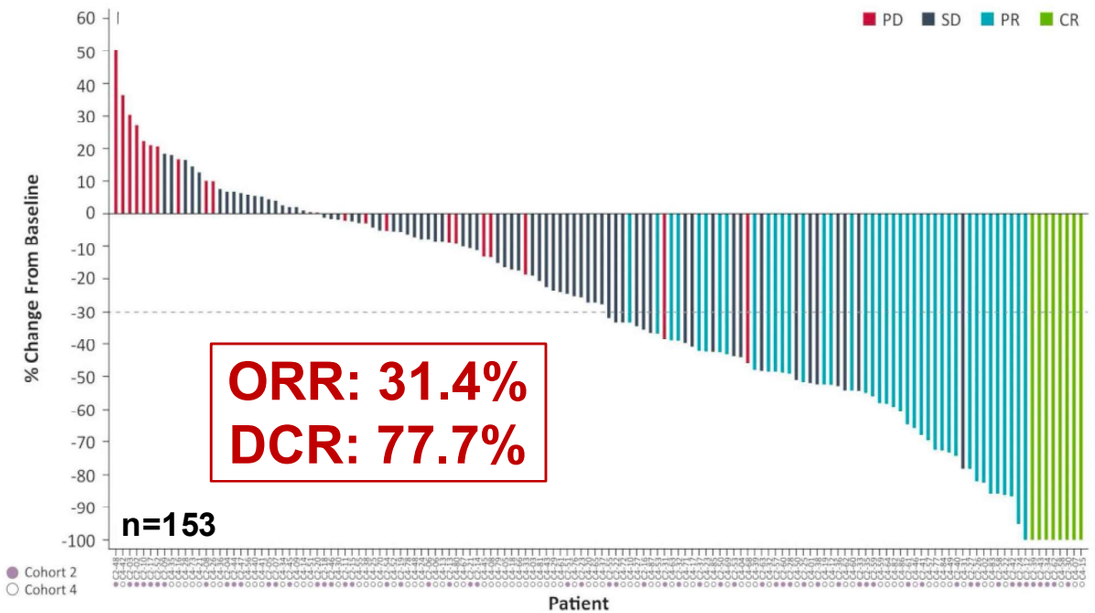
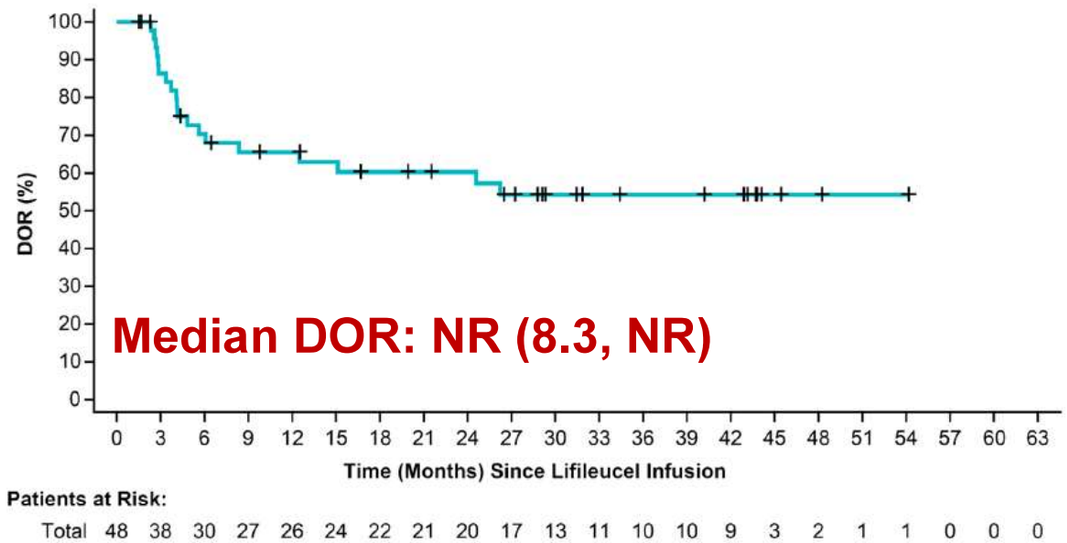


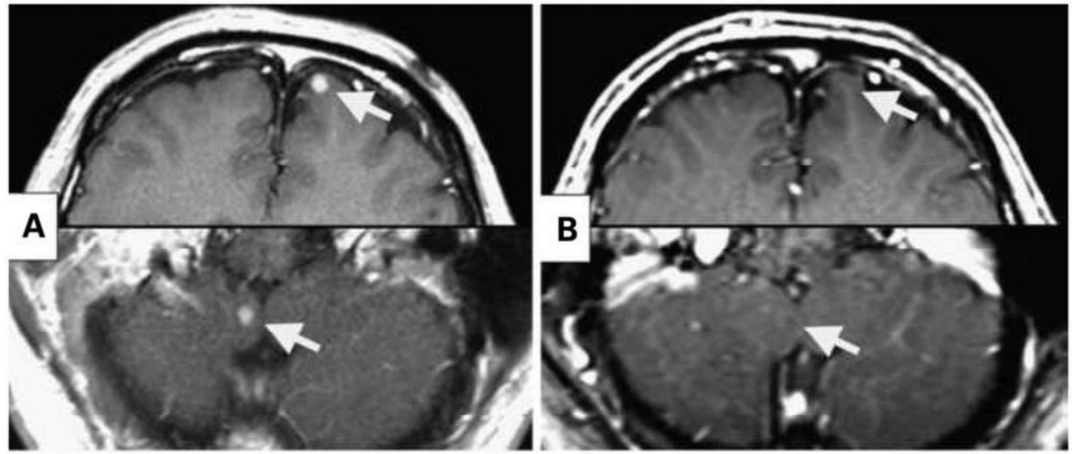

C-144-01 trial: excluded symptomatic and/or untreated brain metastases

M14TIL trial: allowed up to 2 asymptomatic brain metastases of <1 cm with no edema

(Chesney et al. *JITC* 2022)

# Background: TIL for MBM

- NCI Experience[1,2]
  - 18 patients with untreated MBM
  - 4 CR, 1 PR (ORR 28%)
  - 1 symptomatic intracranial hemorrhage

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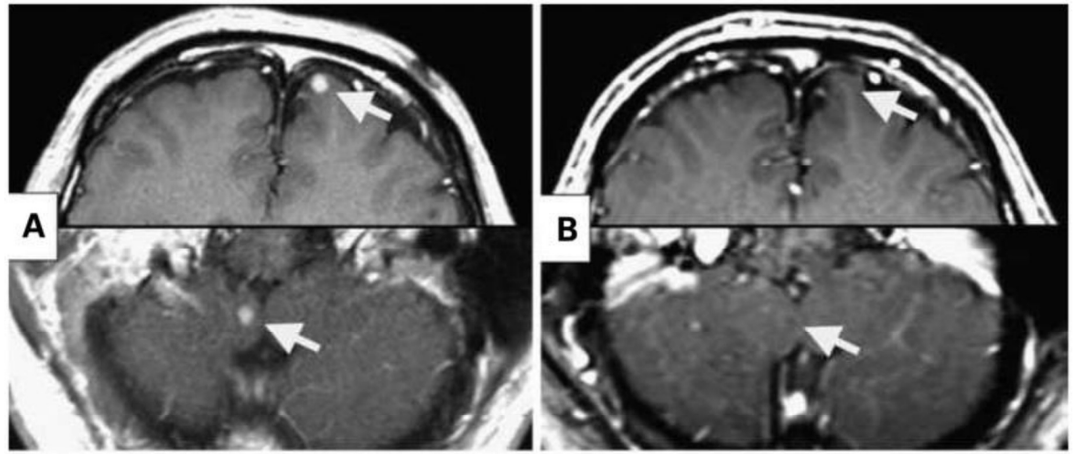


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- AACR Case Report[3]
  - 16M with bulky nodal disease and MBM, progressed s/p ipilimumab and dabrafenib
  - PR at 3 months, CR confirmed at 60 months, ongoing >7 years post-treatment
  - 8 doses of high-dose IL-2, seizure after dose 6

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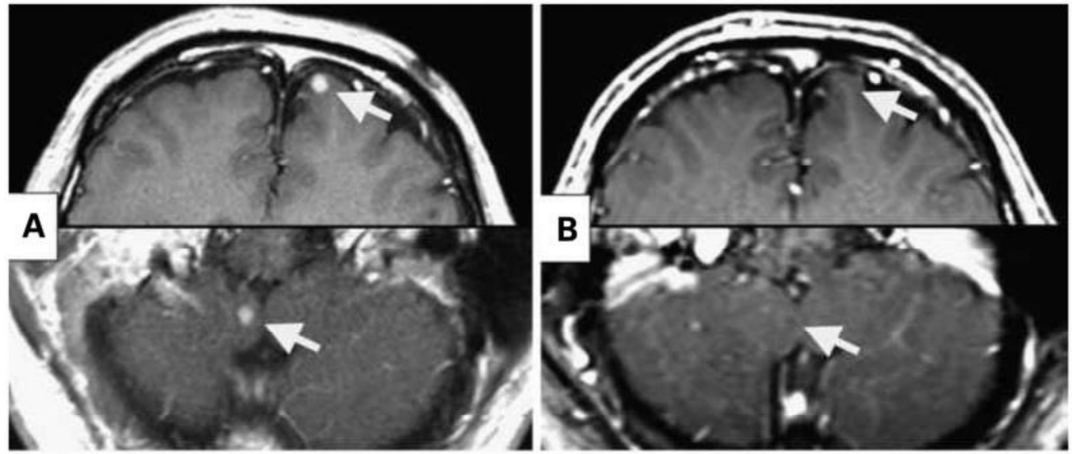


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**Based on these reports, we hypothesized that a modified lifileucel regimen would have clinical activity and be feasible and safe to deliver to patients with MBM.**

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[2] Mehta et al. *J Immunother* 2018
[3] Hawkins et al. AACR 2021

# Pilot Trial of Lifileucel for Patients with Asymptomatic Melanoma Brain Metastases and Progression on Prior PD-1 Therapy

## *Objectives*

**Primary**
- Feasibility of treatment

(≥7/10 patients who undergo tumor harvest receive lifileucel infusion)

**Secondary**
- Manufacturing feasibility
- Safety
- Brain metastasis response rate (mRECIST)

**Exploratory**
- Other markers of efficacy
- OS
- Correlative analyses

**ClinicalTrials.gov Identifier:** NCT05640193

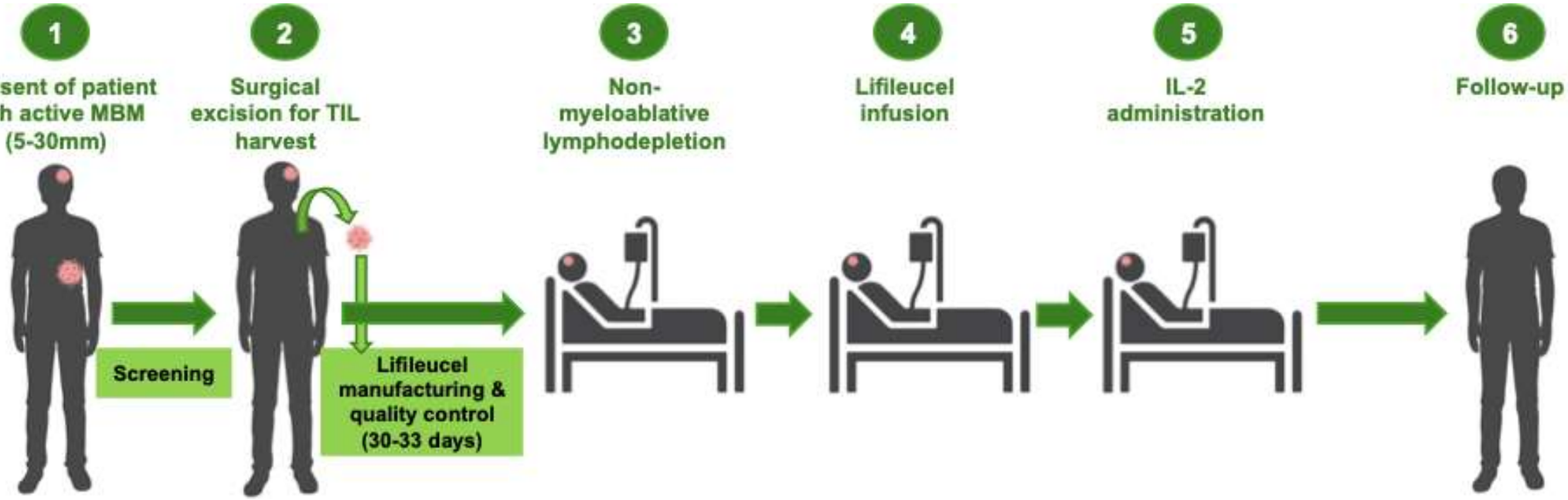
## *Key inclusion criteria*

- Metastatic non-uveal melanoma
- ≥1 **asymptomatic** intracranial lesion 5-30mm
- ≥1 **extracranial** resectable lesion ≥1.5cm diameter for TIL generation
- Prior anti-PD-1(± anti-CTLA-4) for metastatic melanoma with progression. If BRAF V600E/K mutation, must have received prior BRAF+MEK therapy with progression
- ECOG 0-1
- Meet cardiopulmonary requirements for lymphodepleting chemotherapy, cell infusion, and IL-2

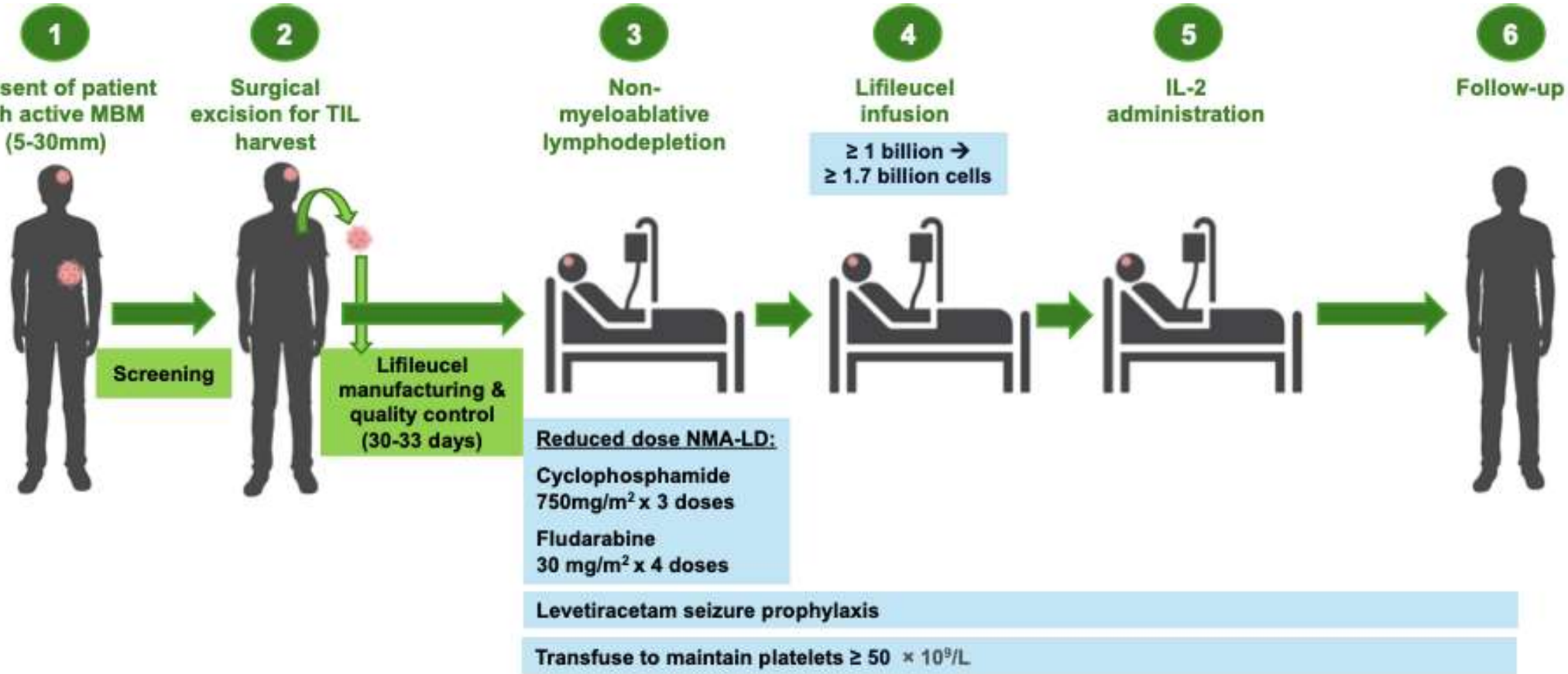
## *Key exclusion criteria*

- Symptomatic brain metastasis of any size or number
- Corticosteroids >10mg prednisone equivalent
- Inability to receive gadolinium-enhanced MRI

# Treatment Schema for TIL Therapy



# Treatment Schema Modified for MBM



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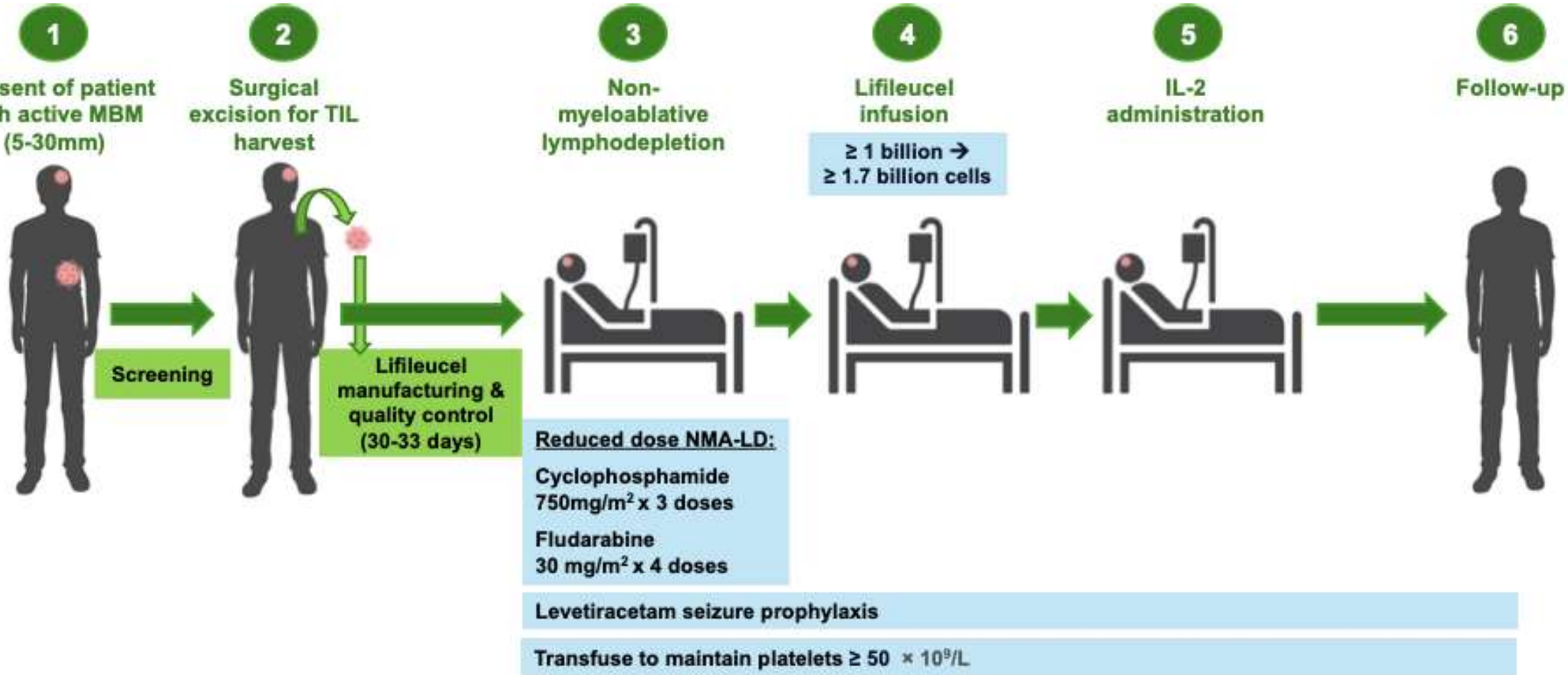


**Imaging:** screening, prior to lymphodepletion, week 6, week 12, week 24, every 3 months starting at month 6
**Research blood collection:** day of tumor harvest, day 1, day 14, day 30, week 6, week 12, week 24, month 12, disease progression
**CSF collection:** prior to lymphodepletion, week 6

# Patient and Disease Characteristics

| Characteristic | All Patients (N=10) |
|---|---|
| Age, yr – median (range) | 43 (32-71) |
| Female – n (%) | 3 (30%) |
| ECOG status 0 – n (%) | 3 (30%) |
| **Melanoma subtype** | |
| Cutaneous – n (%) | 6 (60%) |
| Acral – n (%) | 3 (30%) |
| Mucosal – n (%) | 1 (10%) |
| **Prior systemic therapy** | |
| # lines – median (range) | 2 (1-6) |
| Anti-PD-1 – n (%) | 10 (100%) |
| Anti-CTLA-4 – n (%) | 9 (90%) |
| BRAF+MEK inhibitor – n (%) | 2 (20%) |
| **Screening brain metastasis characteristics** | |
| # brain mets – median (range) | 5 (1 - >40) |
| Largest brain met, mm – median (range) | 10.4 (6.1-25.4) |
| Local brain therapy prior to consent – n (%) | 6 (60%) |
| Radiation therapy | 6 (60%) |
| Surgery | 1 (10%) |

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## Site for TIL Harvest

- Lymph node (n=5)
- Skin/subcutaneous (n=3)
- Lung (n=1)
- Liver (n=1)

## Bridging Therapy

- Brain SRS (n=4)
- WBRT (n=1)
- Systemic therapy (n=3)
  - Chemotherapy (n=2)
  - Nivo/ipi and BRAF+MEKi (n=1)

# Lifileucel infusion was feasible in patients with MBM after progression on anti-PD-1

## Enrolled 10 patients from December 2022 to January 2024

✓ **8/10 patients received lifileucel infusion**

- 2 patients not infused due to clinical progression/rapid deterioration
  - Both received bridging therapy
  - Both had >20 brain metastases at screening
  - 1 patient's product did not not meet specification, underwent re-rep, cell product received after 105 days but patient died prior to infusion

✓ **9/10 patients with successful lifileucel manufacturing**

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✓ **9/10 patients with successful lifileucel manufacturing**

**Days from consent to lifileucel infusion:**
*median (range)* **58 (49-76)**

**Days from TIL harvest surgery to lifileucel infusion:**
*median (range)* **42 (40-49)**

**Number of IL-2 doses:**
*median (range)* **4 (0-5)**

# Safety

| Nonhematologic TEAE in >1 patient[a] N (%) | Any Grade (N=8) | Grade 3/4 (N=8) |
|---|---|---|
| Febrile neutropenia | 5 (63%) | 5 (63%) |
| Chills | 5 (63%) | 0 |
| Fever | 3 (38%) | 0 |
| Fatigue | 3 (38%) | 0 |
| Sinus tachycardia | 3 (38%) | 0 |
| Nausea | 3 (38%) | 0 |
| Diarrhea | 3 (38%) | 0 |
| Hypoxia | 3 (38%) | 0 |
| Infusion reaction | 3 (38%) | 0 |
| Cognitive disturbance | 2 (38%) | 0 |
| Edema | 2 (38%) | 0 |
| Hypotension | 2 (25%) | 0 |
| Urinary incontinence | 2 (25%) | 0 |
| Urinary urgency | 2 (25%) | 0 |

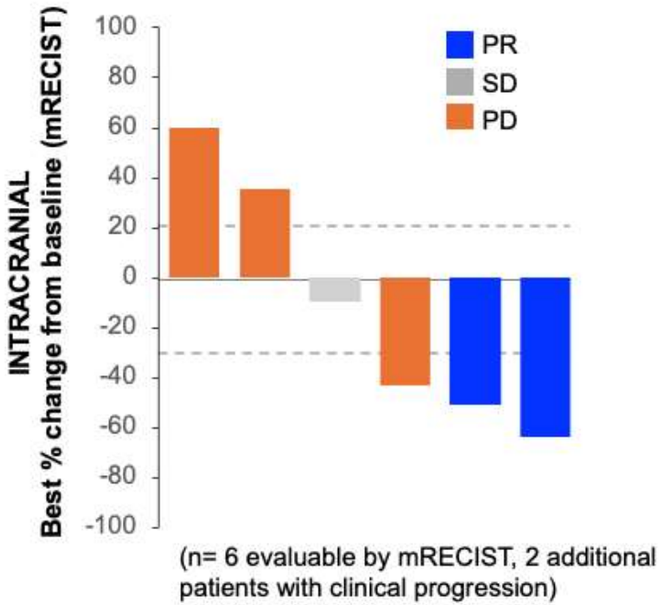
| Grade 3/4 hematologic lab abnormalities[b] N (%) | Grade 3/4 N=8 |
|---|---|
| Neutropenia | 8 (100%) |
| Lymphopenia | 8 (100%) |
| Leukopenia | 8 (100%) |
| Thrombocytopenia | 4 (50%) |
| Anemia | 6 (75%) |

- No treatment-related Grade 5 toxicities
- No unexpected AEs
- No evidence of seizures or intracranial hemorrhage
- **Safety was consistent with underlying disease and known safety profiles of NMA-LD, lifileucel, and IL-2**

[a]TEAEs refer to adverse events that occur from the first dose of NMA-LD up to 30 days after lifileucel infusion or up to the start of a new anticancer therapy
[b]Grade 3/4 hematologic laboratory toxicity during the period from the start of NMA-LD to 30 days after lifileucel infusion
AE, adverse event; IL-2, interleukin-2; NMA-LD, nonmyeloablative lymphodepletion; TEAE, treatment-emergent adverse event

# Lifileucel can produce extracranial and intracranial responses after progression on anti-PD-1

## Intracranial BOR




(n= 6 evaluable by mRECIST, 2 additional patients with clinical progression)

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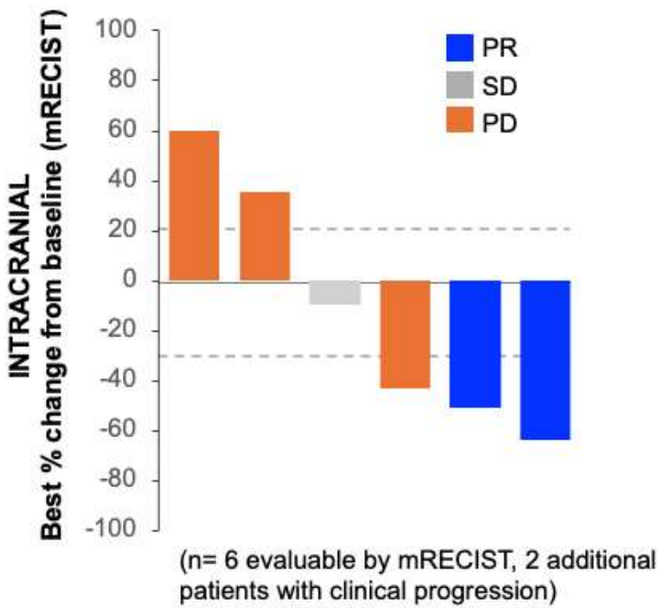


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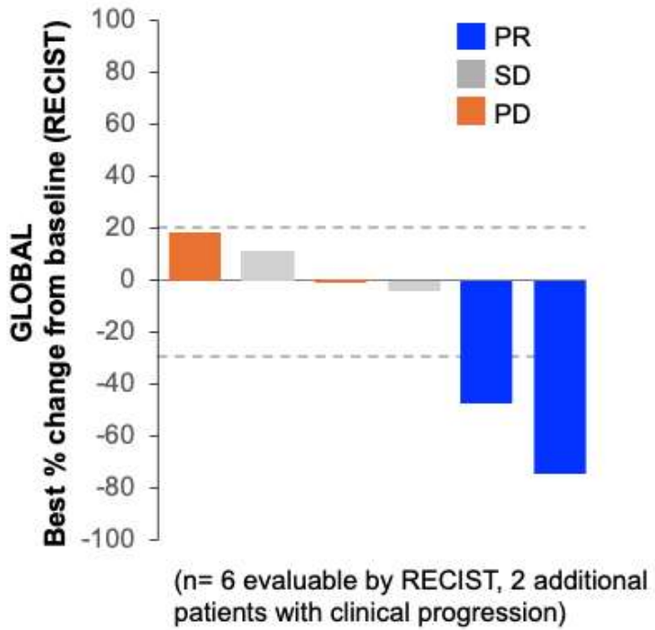
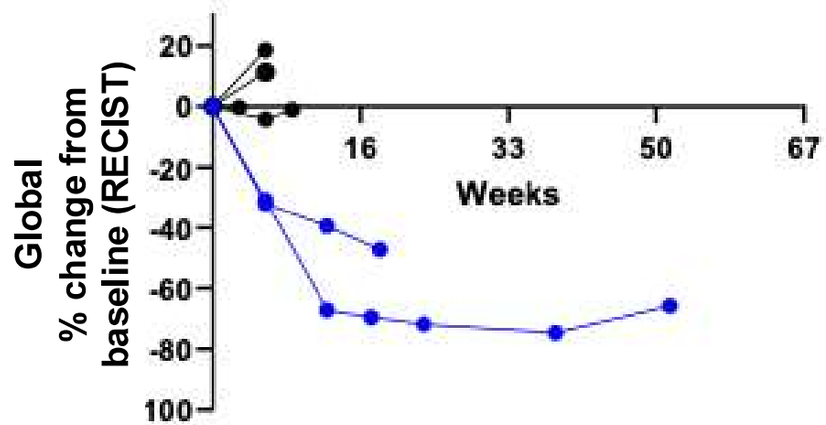
## Global BOR




(n= 6 evaluable by RECIST, 2 additional patients with clinical progression)

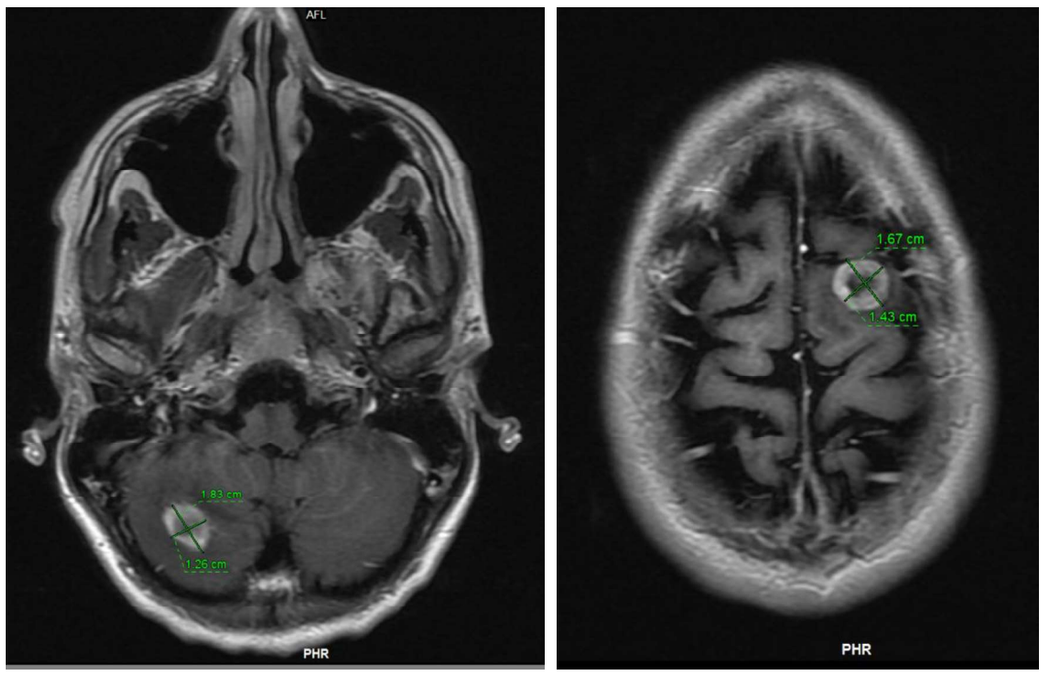
| Best Overall Response (RECIST) | Efficacy Cohort (n=8) |
|---|---|
| **Objective response rate, n (%)** | |
| Partial response | 2 (25%) |
| Stable disease | 2 (25%) |
| Progressive disease | 4 (50%) |
| Disease control rate,* n (%) | 4 (50%) |

*Defined as PR + SD



# Patient Case

**40 year old man with BRAF wildtype cutaneous melanoma with disease progression following treatment with nivolumab and ipilimumab+pembrolizumab. Cerebellar metastasis previously treated with SRS then progressed.**




**Baseline**

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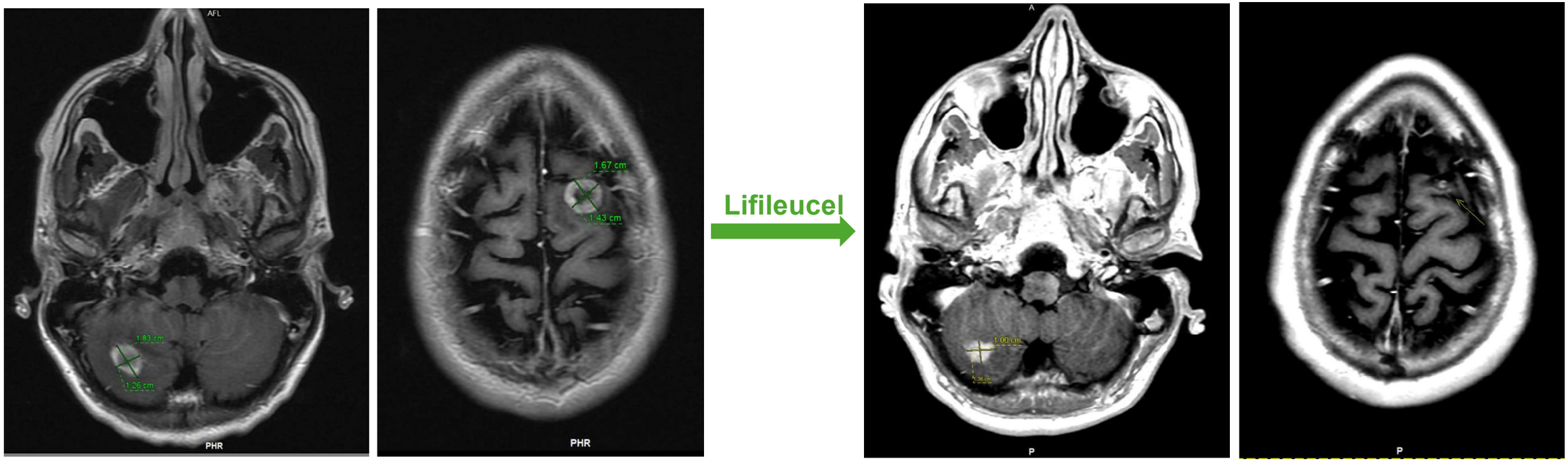


**Baseline** **Month 9**

# Patient Case

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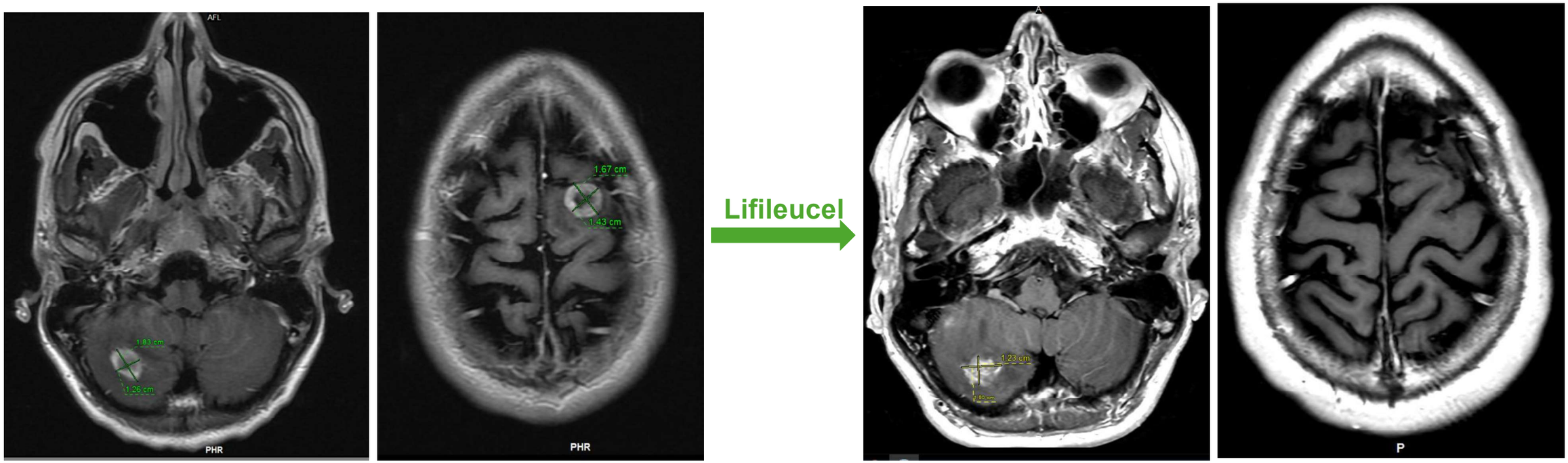


**Baseline** **Month 12**

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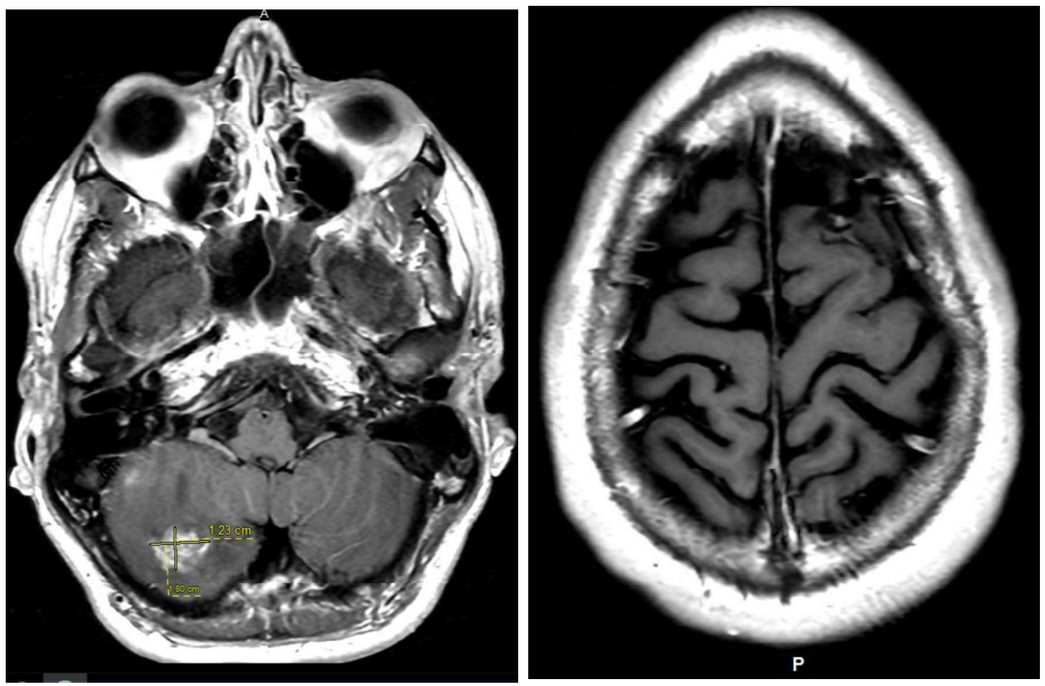
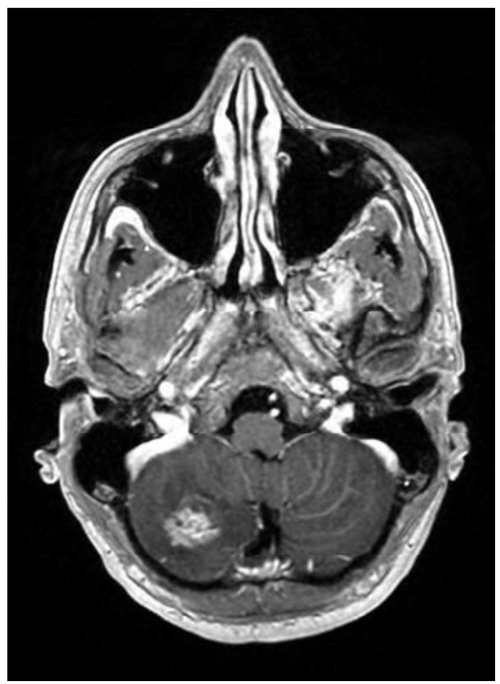



Month 12

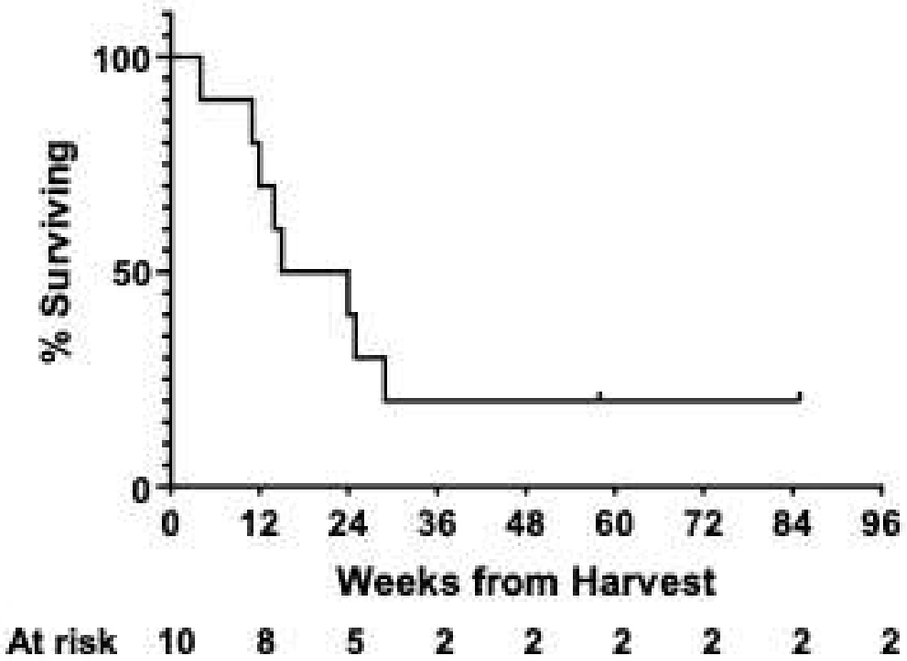


## Month 14

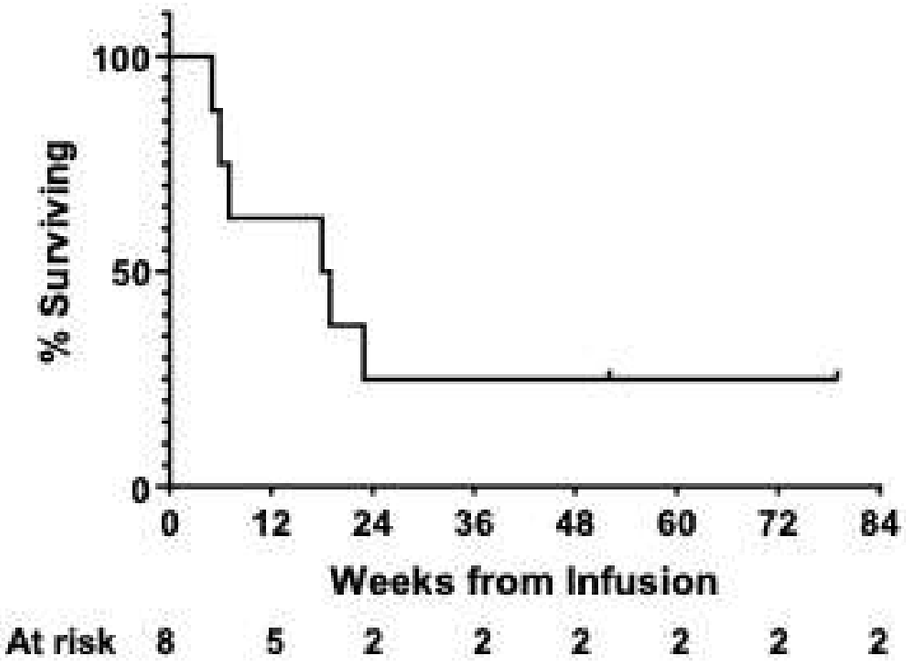
- Growth of previously radiated cerebellar lesion
- Surgical resection with >50% viable tumor then RT
- Now NED for 6 months

# Overall Survival

**Intention to Treat Cohort**




**Patients who Received Lifileucel Infusion**



# Conclusions

- In patients with asymptomatic melanoma brain metastases following progression on an anti-PD-1 containing regimen and (if appropriate) BRAF+MEKi therapy:
  - ✓ Lifileucel administration is feasible
  - ✓ Lifileucel can produce extracranial and intracranial responses, including the potential for durable disease control
  - ✓ With modifications to NMA-LD, elevated platelet transfusion threshold, and seizure prophylaxis, safety of lifileucel was consistent with the known profile for this regimen
- Correlative analyses from tumor, CSF, and blood to be presented at a future meeting
- Planning for an expansion to further evaluate safety and efficacy of this modified lifileucel regimen is underway

# Thank You!

## Thank you to all patients, their families, and their caregivers.

**Alex Shoushtari, MD**
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Andrei Holodny, MD
Stacy Fernstedt, RN

Jannakie Joseph, NP
Alec Lynch
Justina Morgan
Kathy Panageas, DrPH
Mike Postow, MD
June Song, PA
Erin Walicki

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