APPLE Academy 2026

Exploring Cancer Elimination Dynamics in HCC Immunotherapy

Establishing a New Framework for HCC

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Central Doctrines of Cytotoxic Cancer Treatment

Are These Really Applying to Immunotherapy?

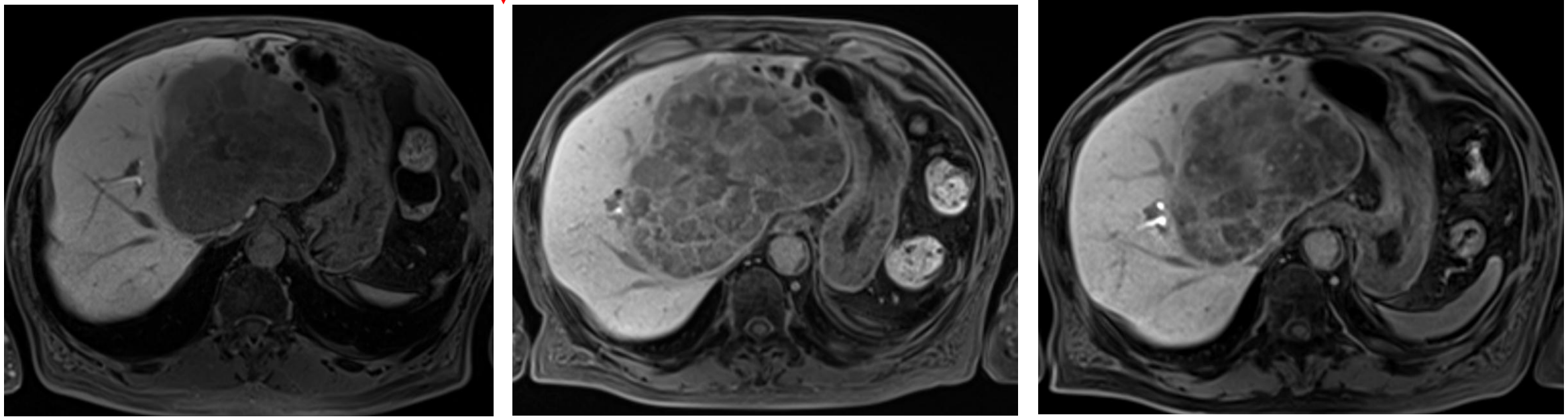
- Radiologically residual tumor = viable tumor
- Cancer is killed fractionally over time
- Residual tumors are more aggressive

Atezo-Bev

Baseline

4m

7m



AFP (ng/mL): **35931**

14579

PD

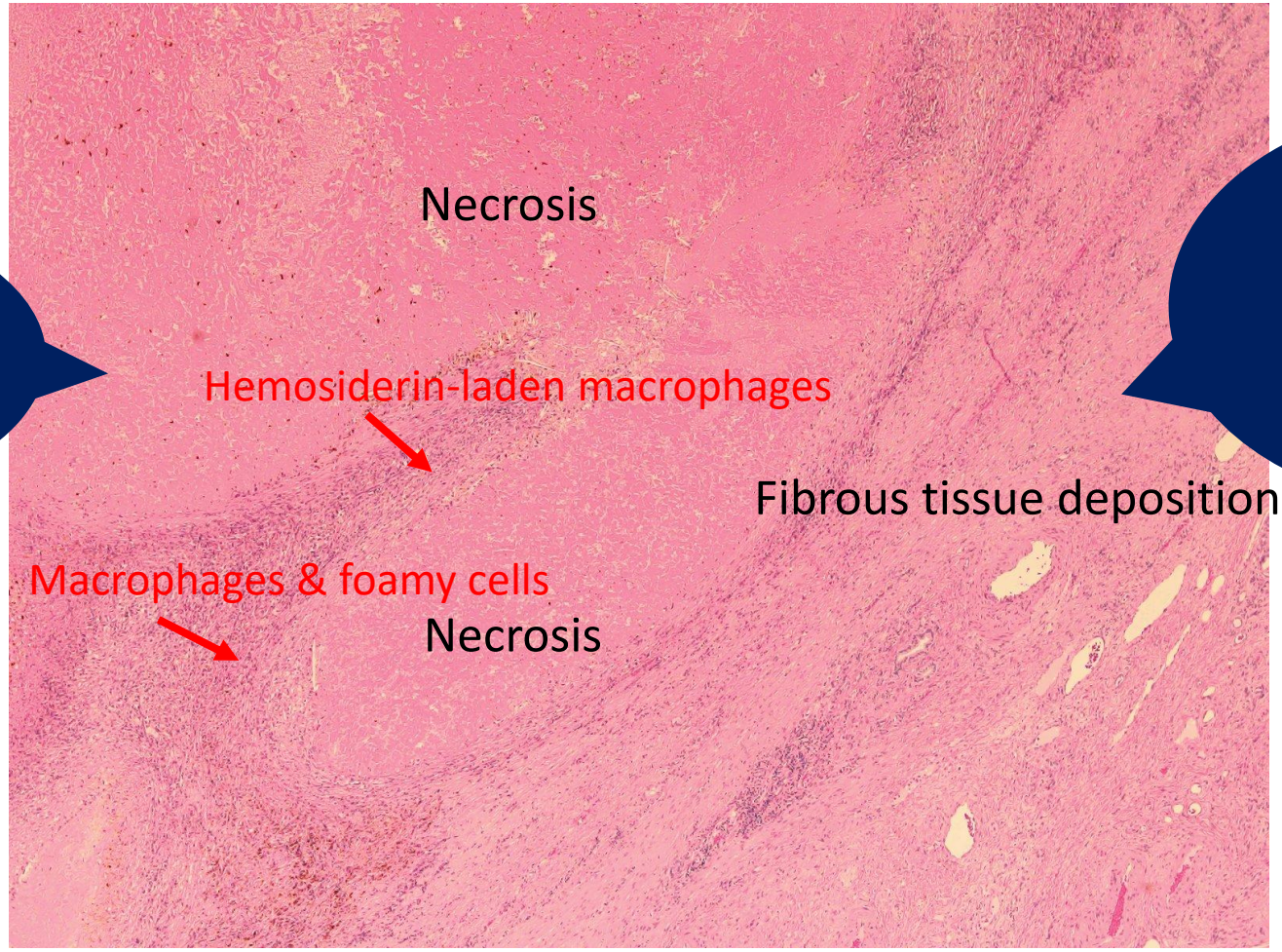
3.8

SD

Courtesy of Dr. Akihiko Soyama, Nagasaki University, Japan.

Shen YC, et al. J Clin Oncol 2024;42:4060-70

No viable tumor cells

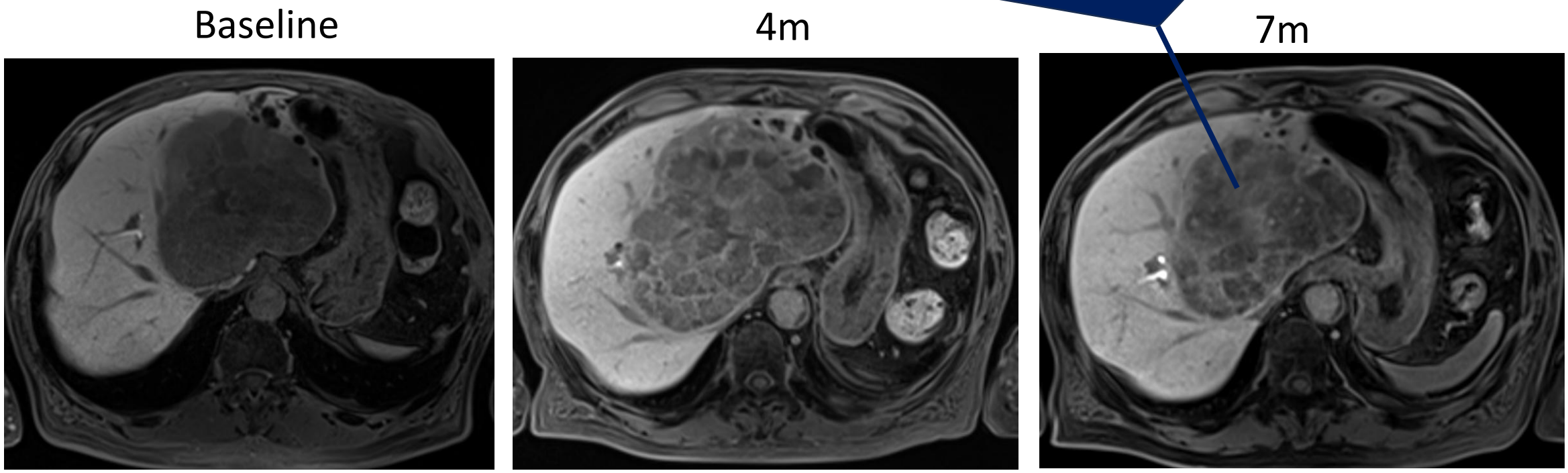


No T cells

Courtesy of Dr. Akihiko Soyama, Nagasaki University, Japan.

Shen YC, et al. J Clin Oncol 2024;42:4060-70

Ghost Tumor
(Radiologically residual tumor without viable tumor cells)



AFP (ng/mL): **35931** **14579** **3.8**

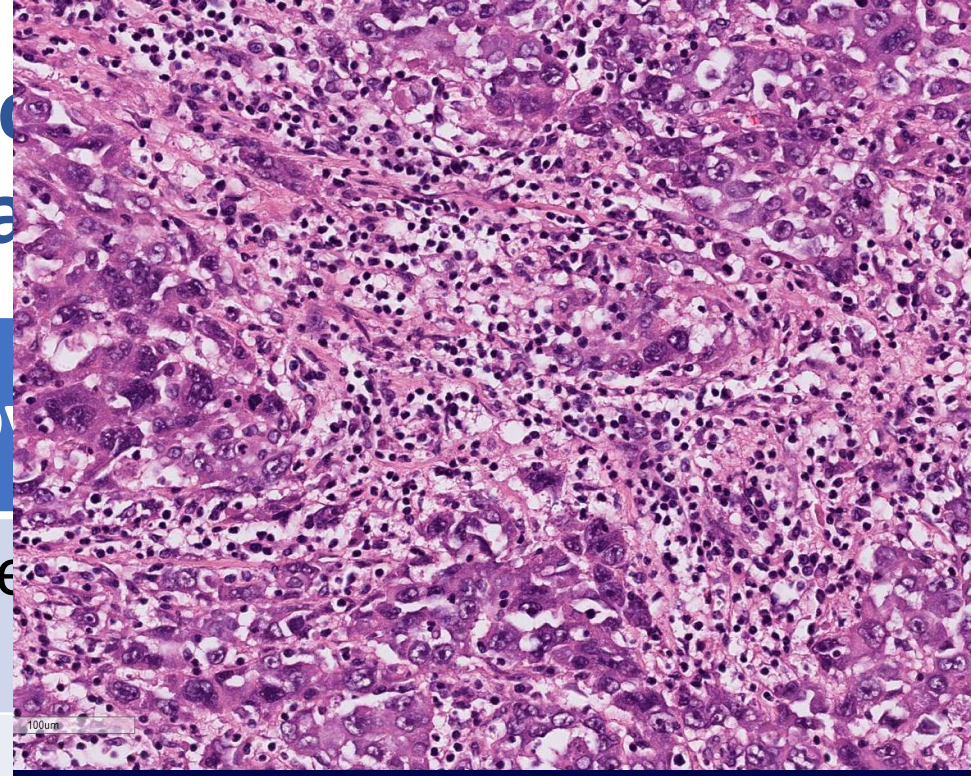
PD **SD**

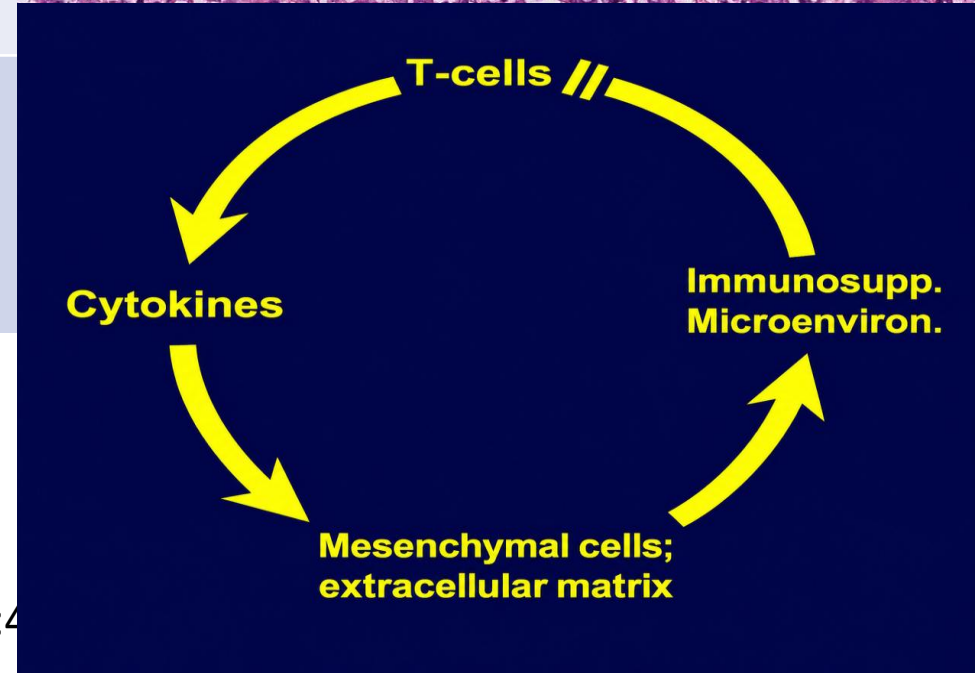
Courtesy of Dr. Akihiko Soyama, Nagasaki University, Japan.

Shen YC, et al. J Clin Oncol 2024;42:4060-70

Why Ghost Tumors Comm
After Immunothera

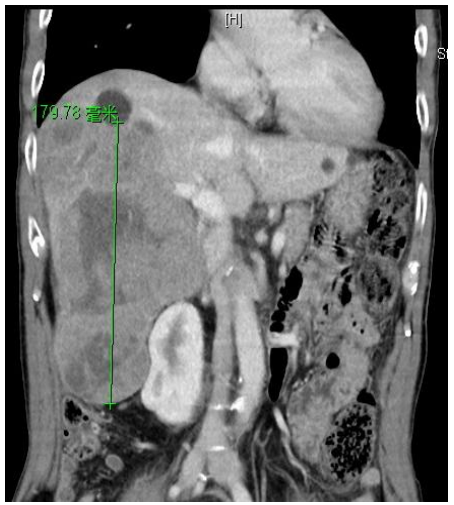
	Immunotherap
• Mechanism of cancer killing	Immune-mediate necrosis
• Immune cell infiltration	Strong
• Mesenchymal cell activation and stromal remodeling	Prominent

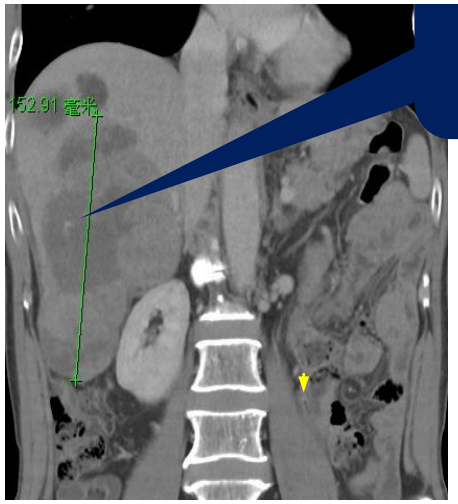


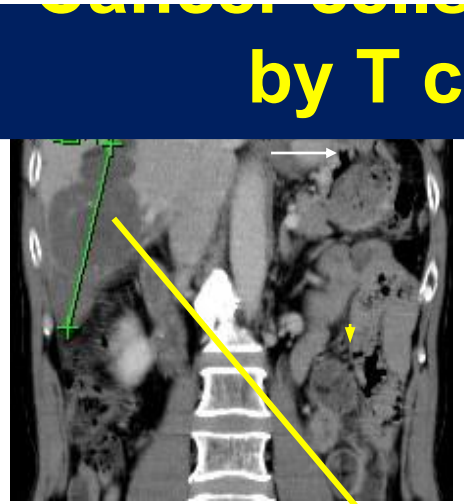


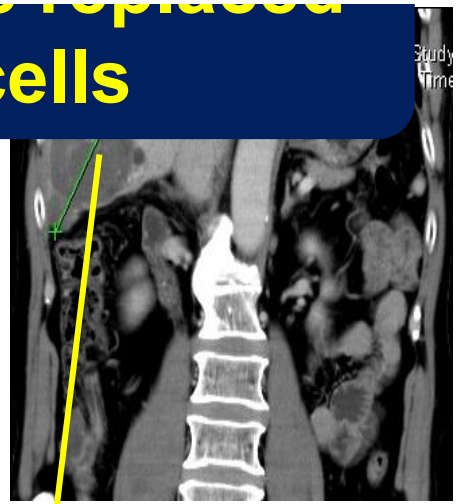
Kroemer G, et al. Nat Immunol 2022;23:4

Complete Cancer Elimination -- A Very Early Event

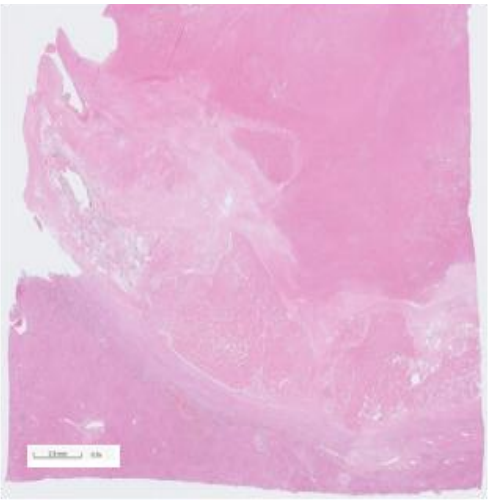


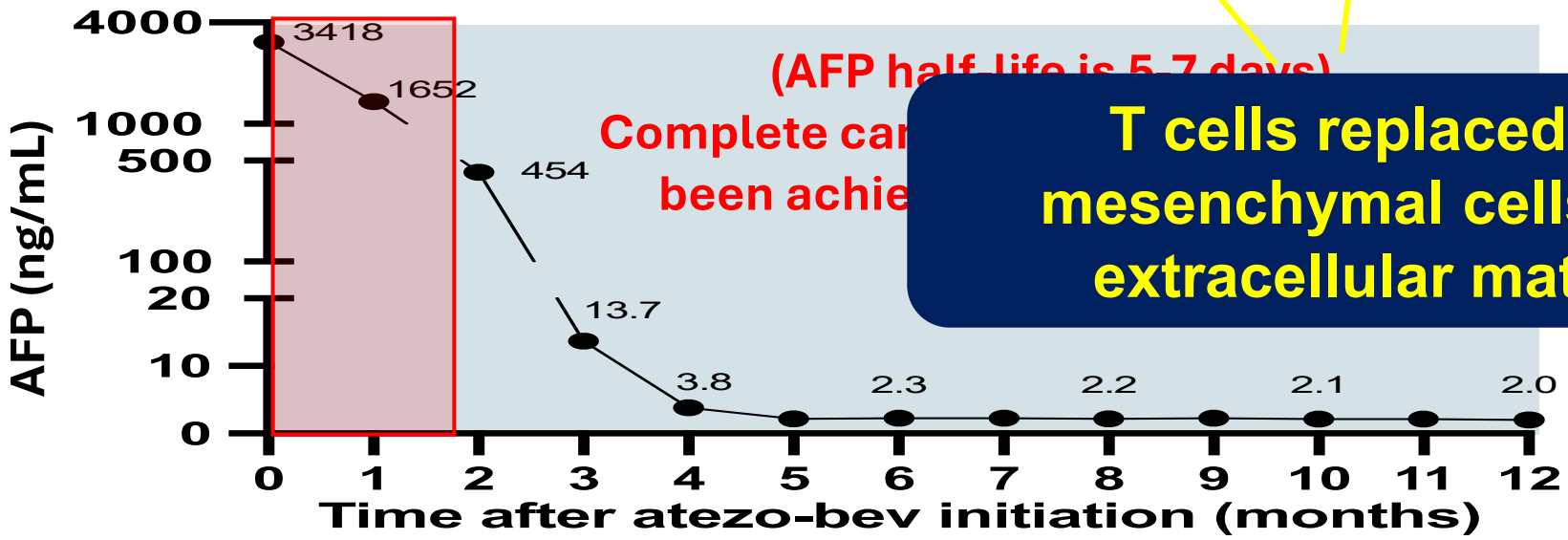






Cancer cells replaced by T cells

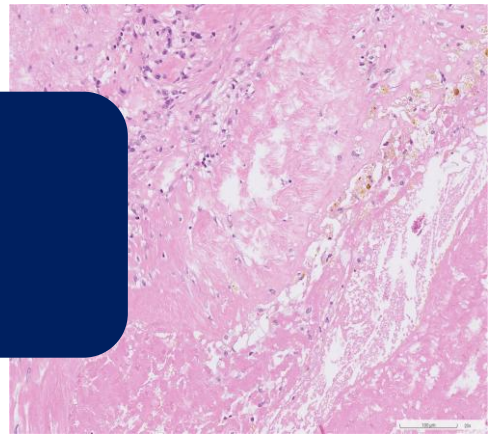




(AFP half-life is 5.7 days)

Complete cancer elimination has been achieved

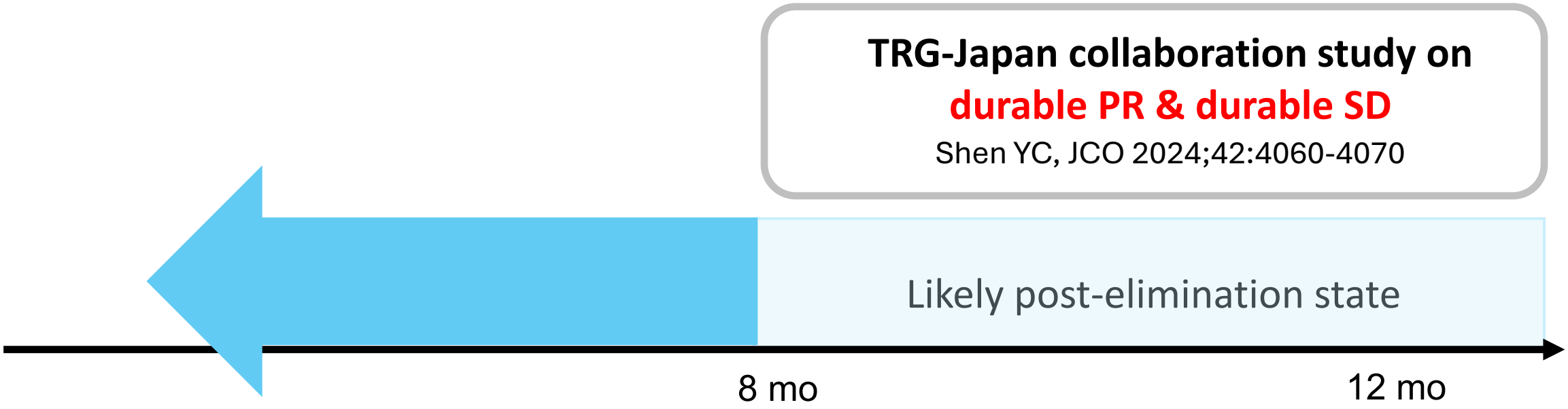
T cells replaced by mesenchymal cells and extracellular matrix.



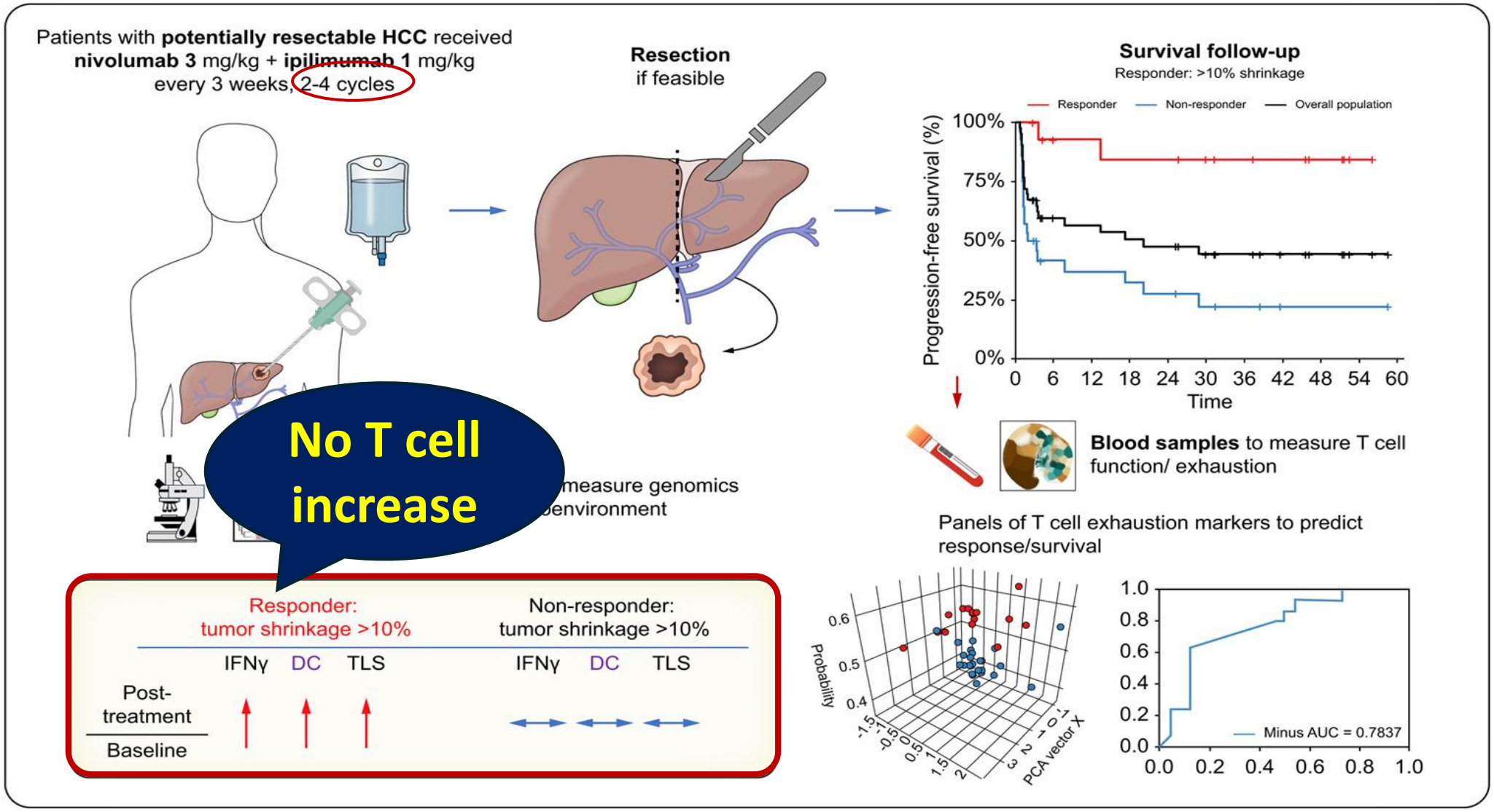
Courtesy of Dr. Chih-Hsien Cheng, CGMH, Taiwan

The Active Immune Elimination Window

Late surgical specimens may already miss the active immune elimination phase

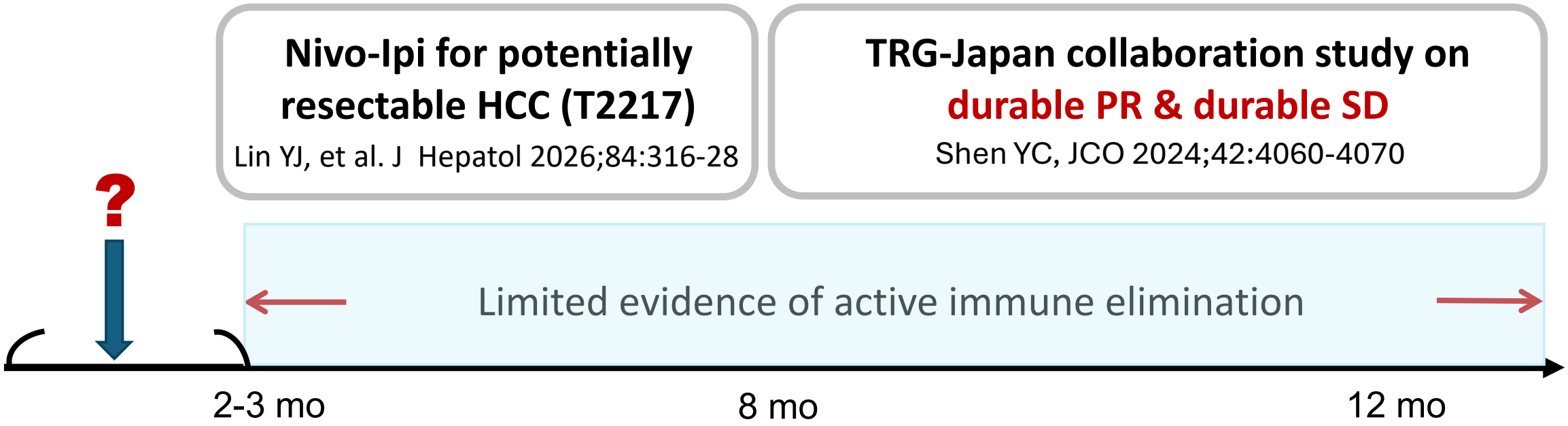


Nivolumab Plus Ipilimumab For Potentially Resectable HCC: Long-term Efficacy And Biomarker Exploration

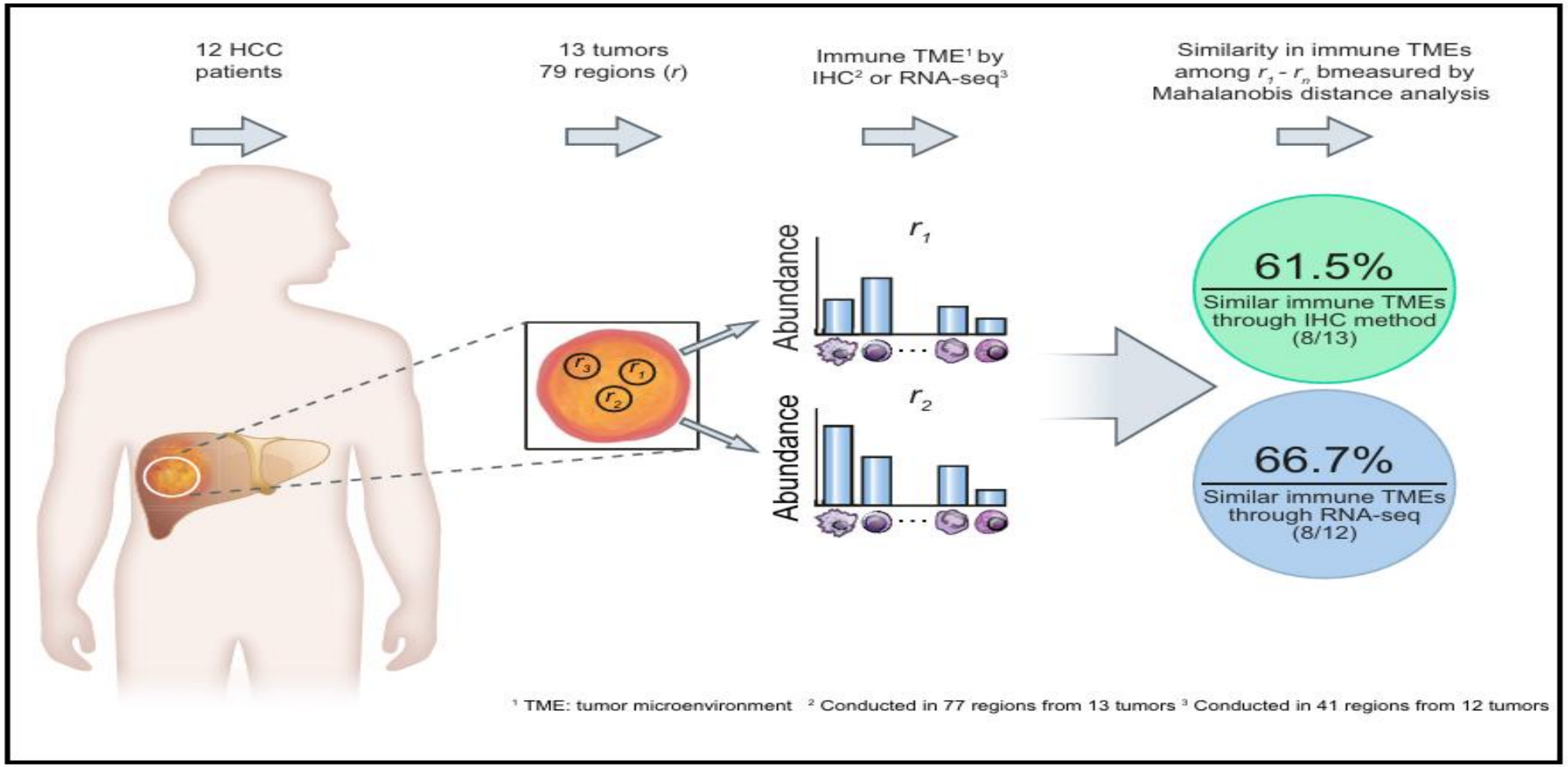


Lin YJ, et al. J Hepatol 2026;84:316–328

The Active Immune Elimination Window



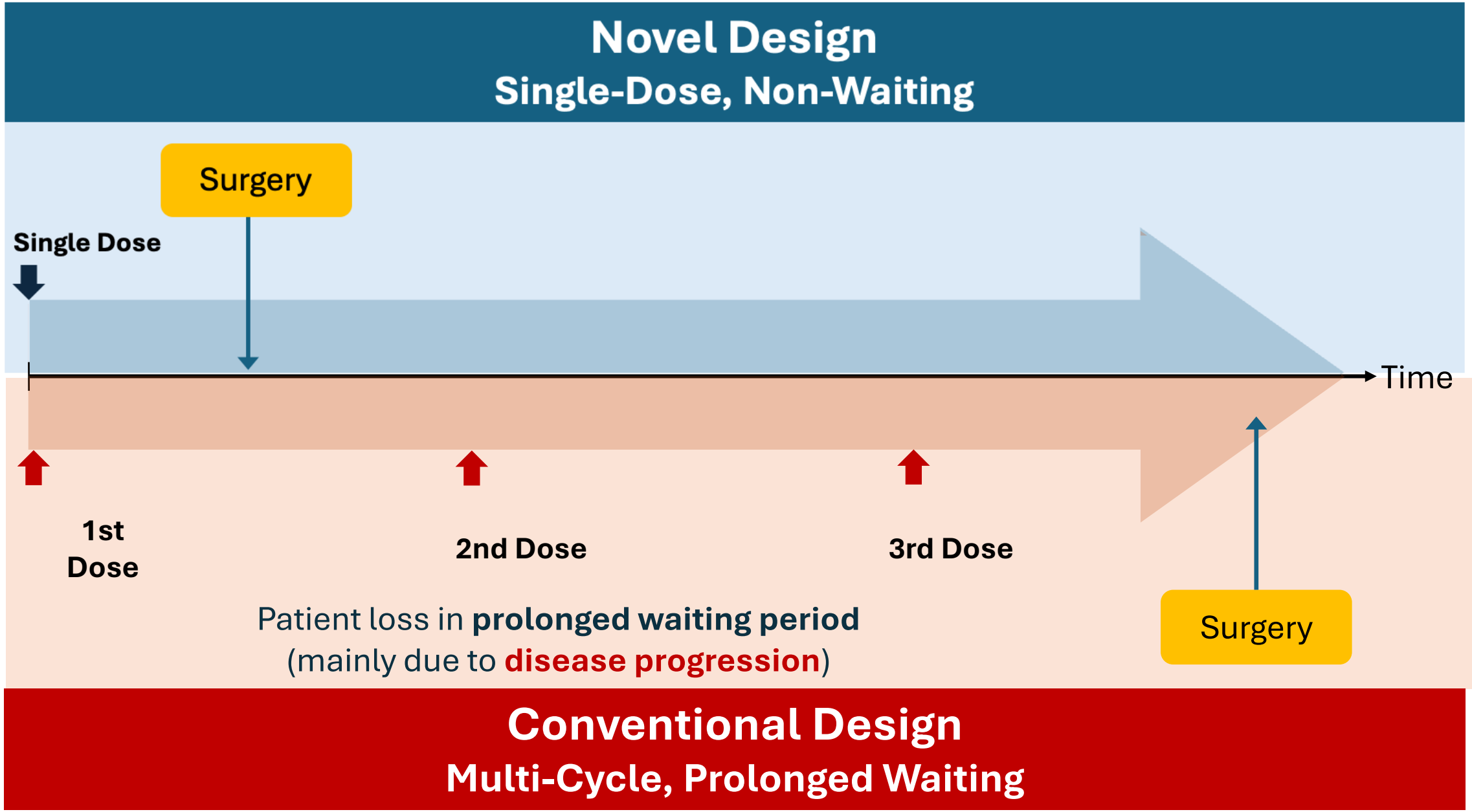
Why Early On-Treatment Biopsies May Still Miss Active Elimination



Shen YC et al. J. Hepatol. 2020;72:489–497

An Abbreviated Neoadjuvant Strategy

A potential solution for both biological interrogation and neoadjuvant feasibility

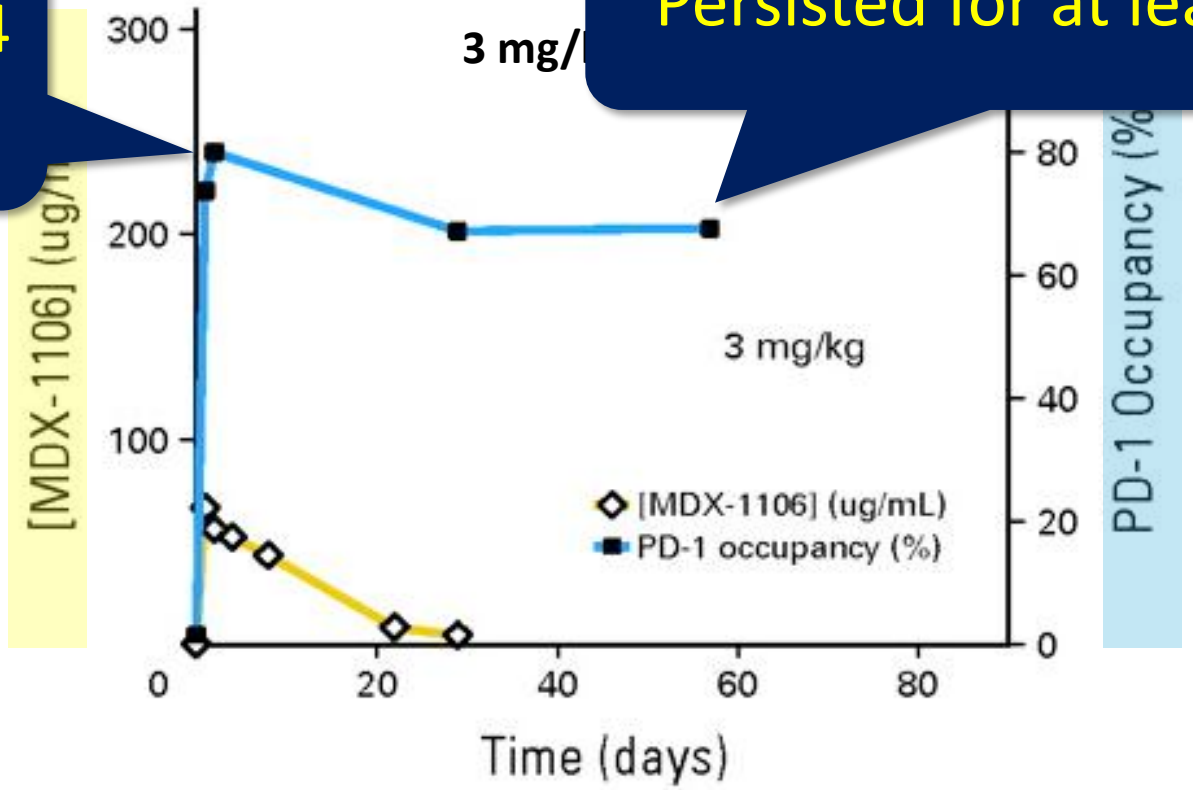


Chen KK, et al. Biomed J. 2026 May 19:100994

A Single-Dose Nivolumab Provides Sustained PD-1 Blockade

Plateaued at 4-24 hours

Persisted for at least 60 day

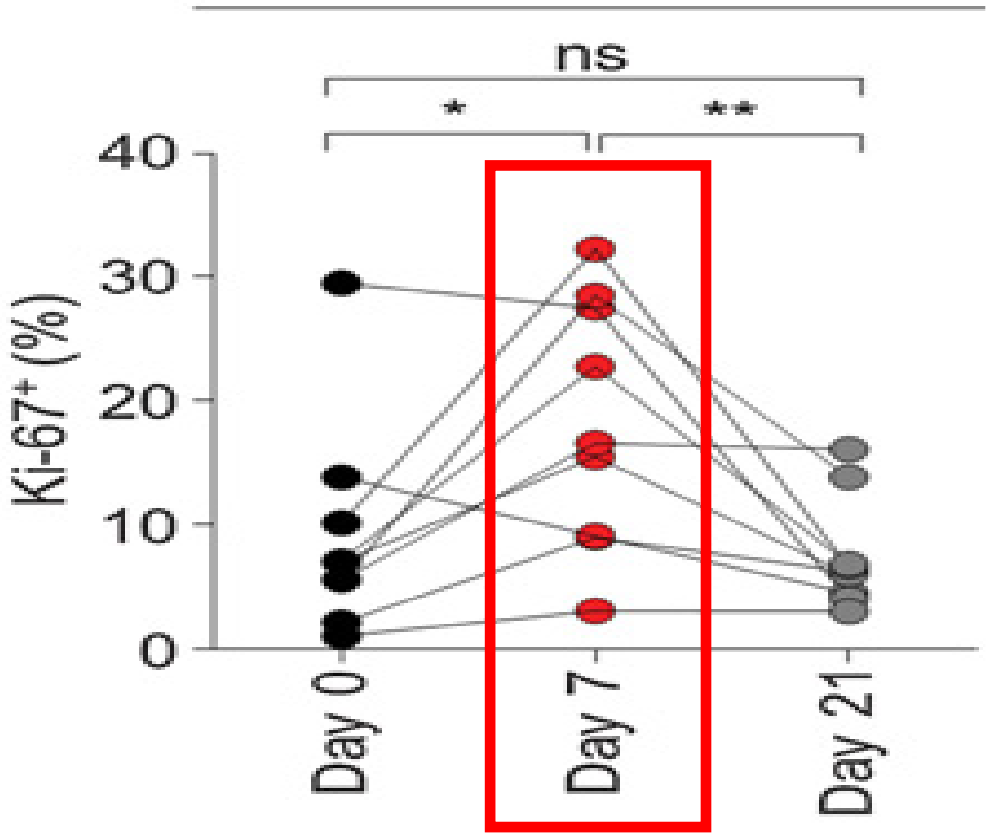


Brahmer JR, et al. J Clin Oncol 2010; 28:3167-3175.

Peripheral Immune Activation Detectable Within Days

NSCLC patients receiving anti–PD-1

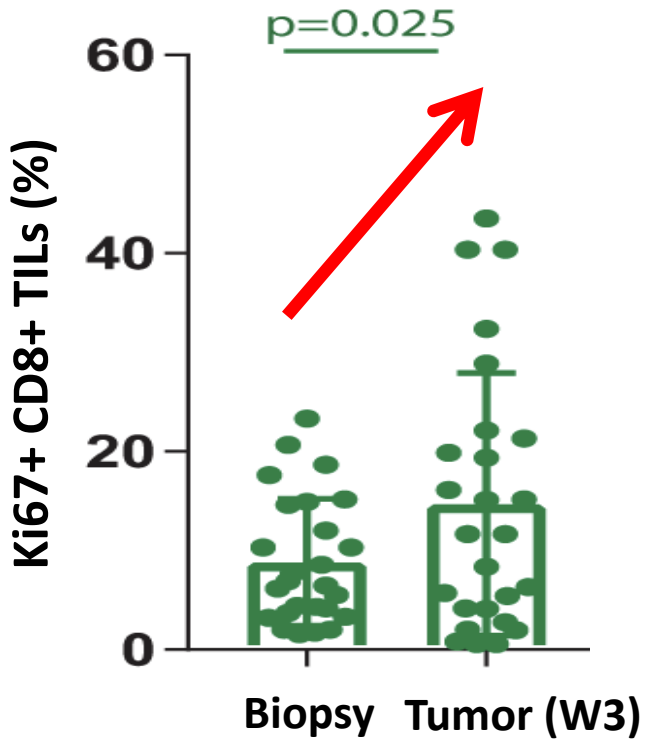
PD-1+ CD8+ T cells in PB



Kim KH, et al. Clin Cancer Res 2019;25:2144-2154

Meaningful Pathological Response after A Single-Dose Anti–PD-1 (Melanoma)

Biopsy → **Anti–PD-1 × 1** —(3 wks)→ **OP**



MPR: 30%

pCR: 18.5%

Huang AC, et al. Nat Med. 2019; 25: 454–61.

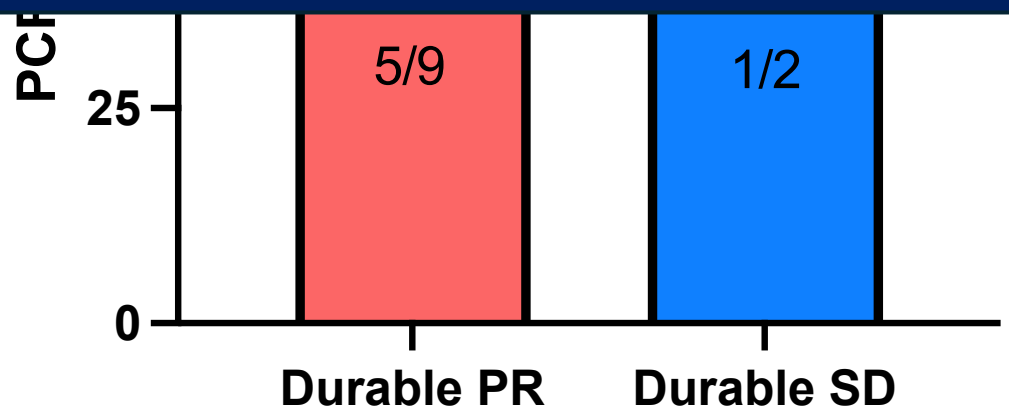
An Upcoming Exploratory Study for Single-Dose Neoadjvuant Nivolumab in Resectable HCC

Recruitment starting September 2026

- Preserve surgical feasibility through an abbreviated design
- Capture the earliest phase of immune-mediated cancer elimination
- Establish a translational platform for post-immunotherapy tumor dynamics

Nearly Half of the Residual Tumors from Durable Responders Are Still Viable

ICI preferentially eradicates highly immunogenic tumor populations, while less immunogenic tumors persist.

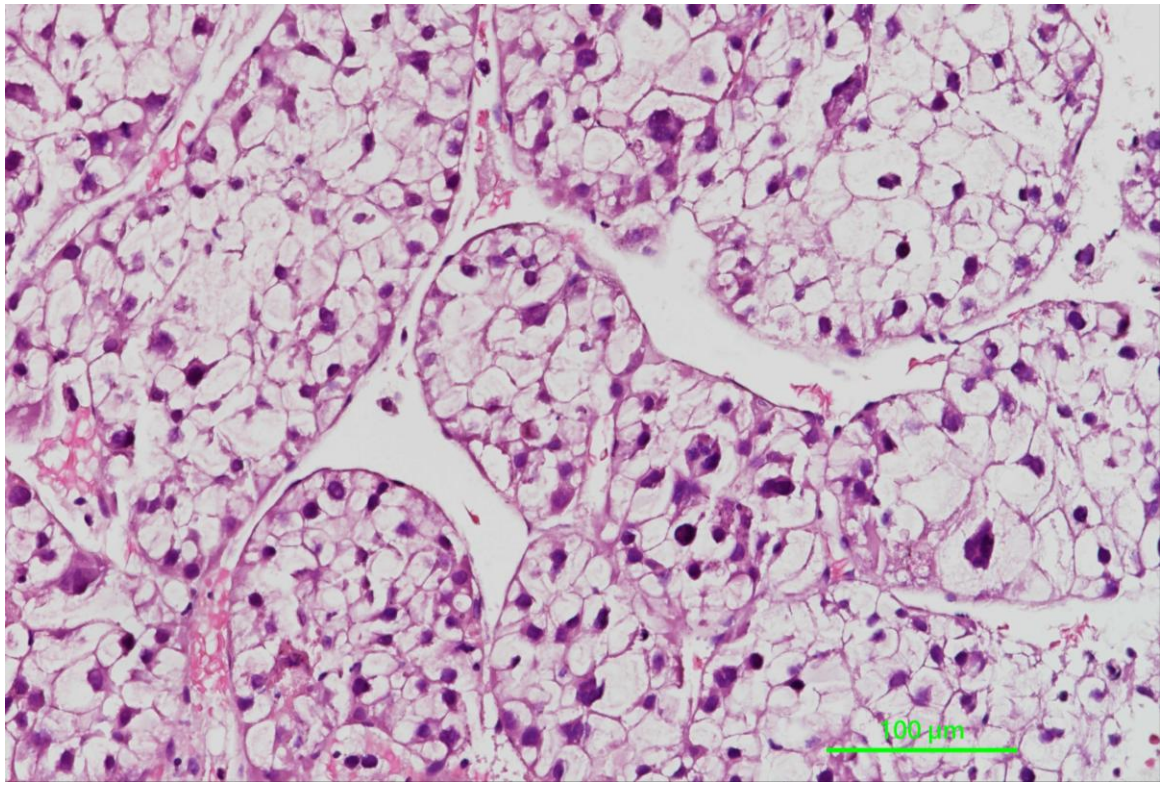


Shen YC, et al. J Clin Oncol 2024;42:4060-70

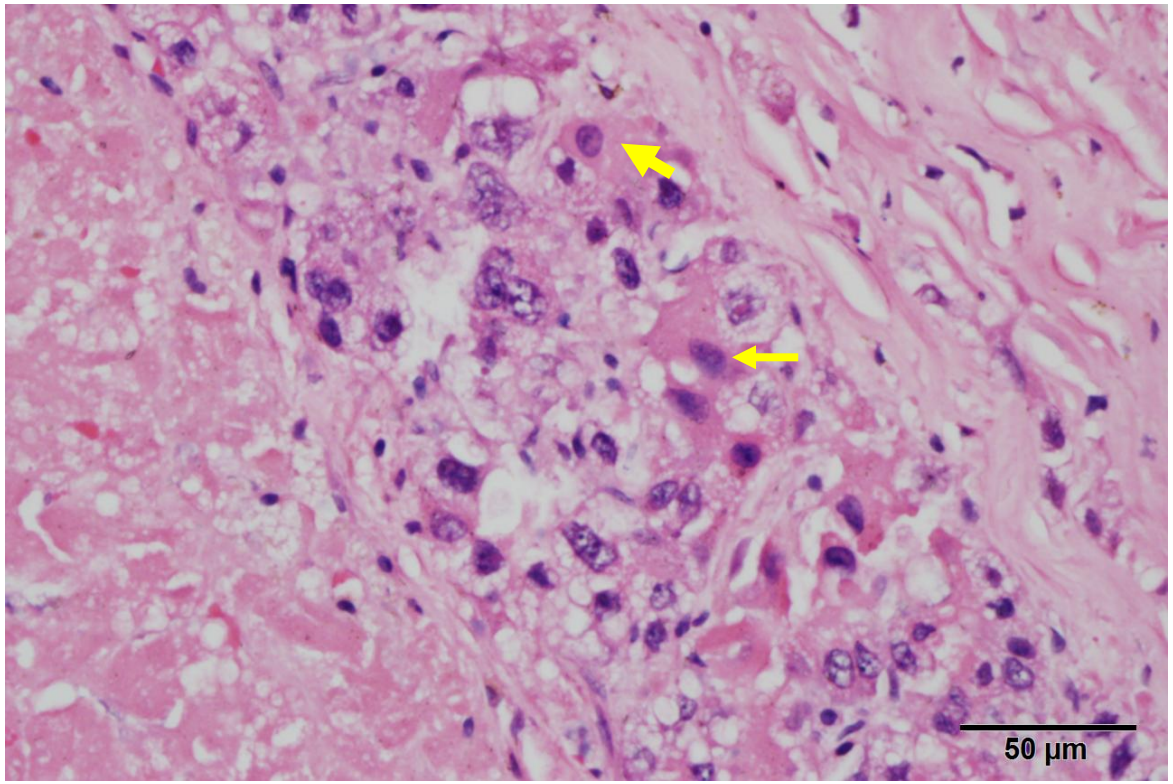
“Asthenia” Pattern

A biologically weakened residual tumor state with minimal immune activity

Baseline

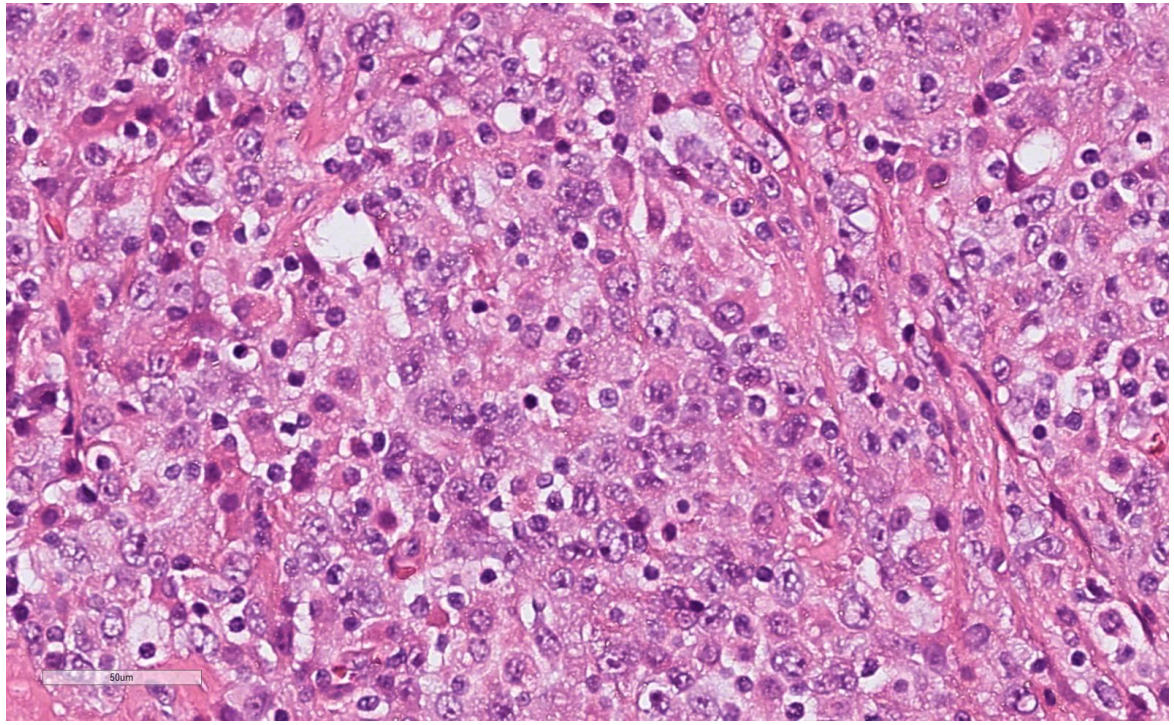


12 months after ICI (Autopsy)

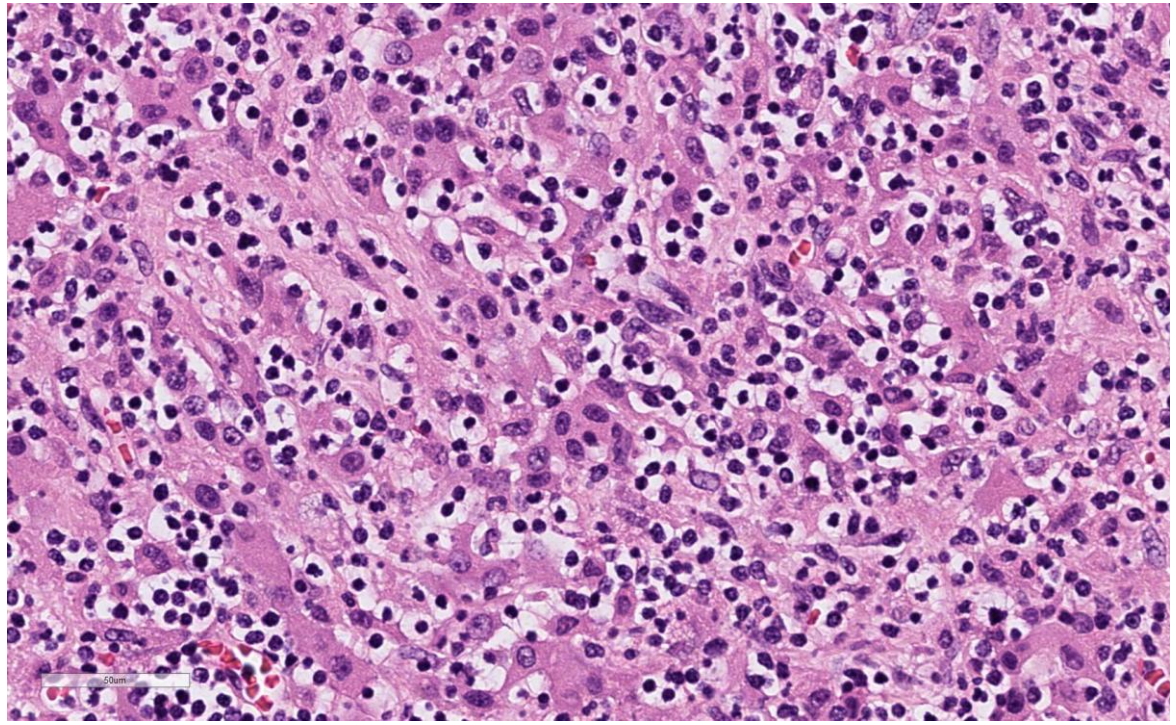


“Immune Equilibrium-Like” Pattern

Baseline

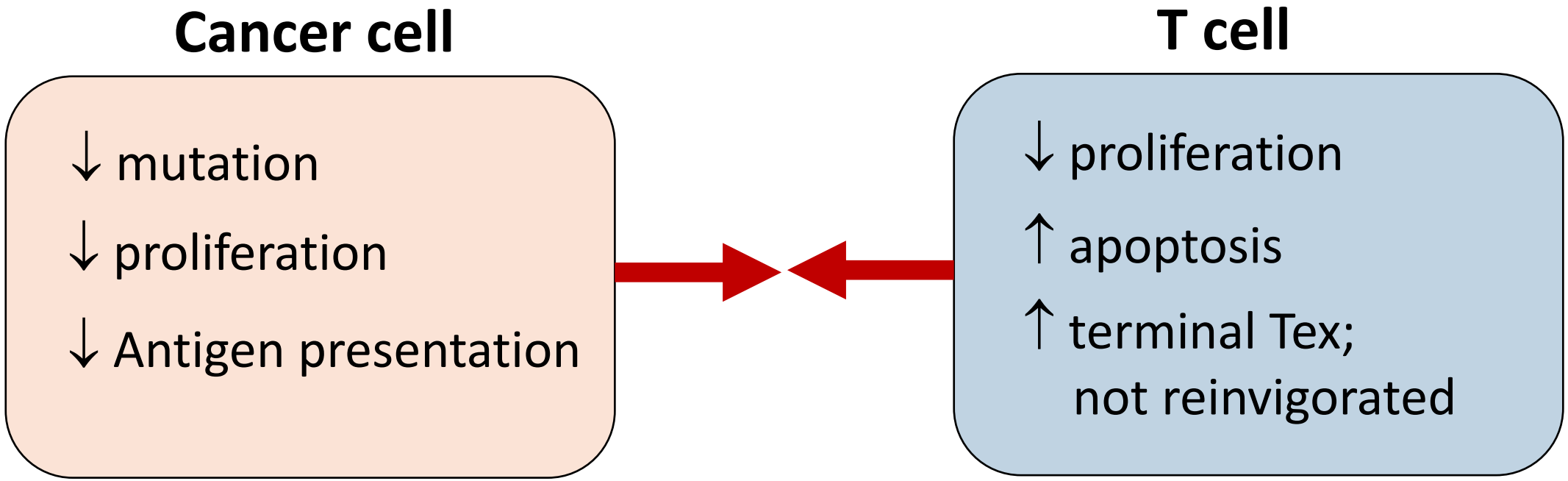


19 months after ICI



“Immune Equilibrium-Like” State

Both cancer cells and T cells are functionally weak



A Multinational Platform for Post-ICI Tumor Biology

- Taiwan, Japan & South Korea
- 50 post-ICI tumors collected, target ≥ 200 tumors
- Spanning early to late post-ICI time points
- Spanning response, persistence, and escape states

Establishing a New Framework for Immunotherapy

Conventional Chemotherapy Paradigm	Proposed Immunotherapy Paradigm
Radiologically residual tumors = viable tumors	Radiologically residual tumors → heterogeneous states
Fractional cancer killing → requires repeated tx	Early cancer elimination → prolonged tx unnecessary
Residual tumors = aggressive tumors	Residual tumors may not be aggressive tumors

We need a different framework for immunotherapy to better interpret tumor response, residual disease biology, and treatment duration.