

SESSION 5

**Criteria to Assess Cancer Immunotherapy Combinations in Early-Phase Clinical Trials:
Types of Clinical Trial Designs Needed for Regulatory Approval**

MODERATORS

Roy Herbst, Yale Comprehensive Cancer Center (*virtual*)

Hedvig Hricak, Memorial Sloan Kettering Cancer Center

SPEAKERS

Keith Flaherty, Massachusetts General Hospital; Harvard Medical School

Roy Herbst, Yale Comprehensive Cancer Center (*virtual*)

Marc Theoret, Oncology Center of Excellence; Food and Drug Administration

Elad Sharon, Cancer Therapy Evaluation Program, National Cancer Institute

Alexandra Snyder, Generate Biomedicines

Jedd Wolchok, Weill Cornell Medicine (*virtual*)

Novel Immunotherapy Clinical Trial Design

Keith T. Flaherty, M.D.

Massachusetts General Hospital Cancer Center



MASSACHUSETTS
GENERAL HOSPITAL

CANCER CENTER

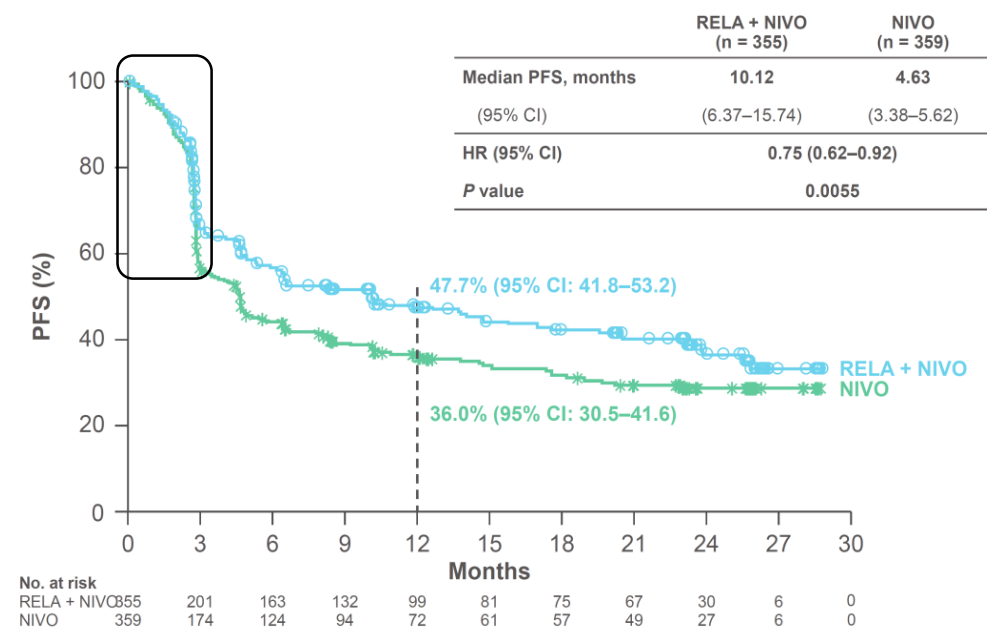
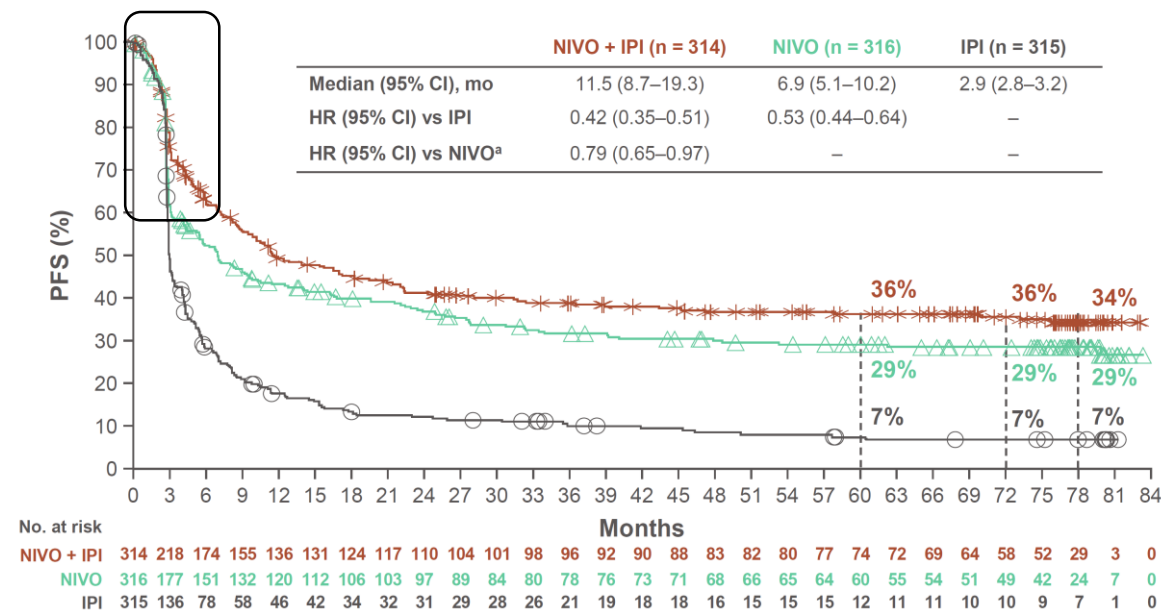
Disclosures

- Board of Directors: Clovis Oncology*, #Strata Oncology*, Kinnate Biopharma*, #Scorpion Therapeutics*
- Scientific Advisory Board: PIC Therapeutics*, #Apricity*, #C-Reveal*, Tvardi*, xCures*, Monopteros*, Vibliome*, ALX Oncology*, Fog Pharma*, Soley Therapeutics*
- Consultant: Nextech, Takeda, Transcode Therapeutics*, Novartis

Founder

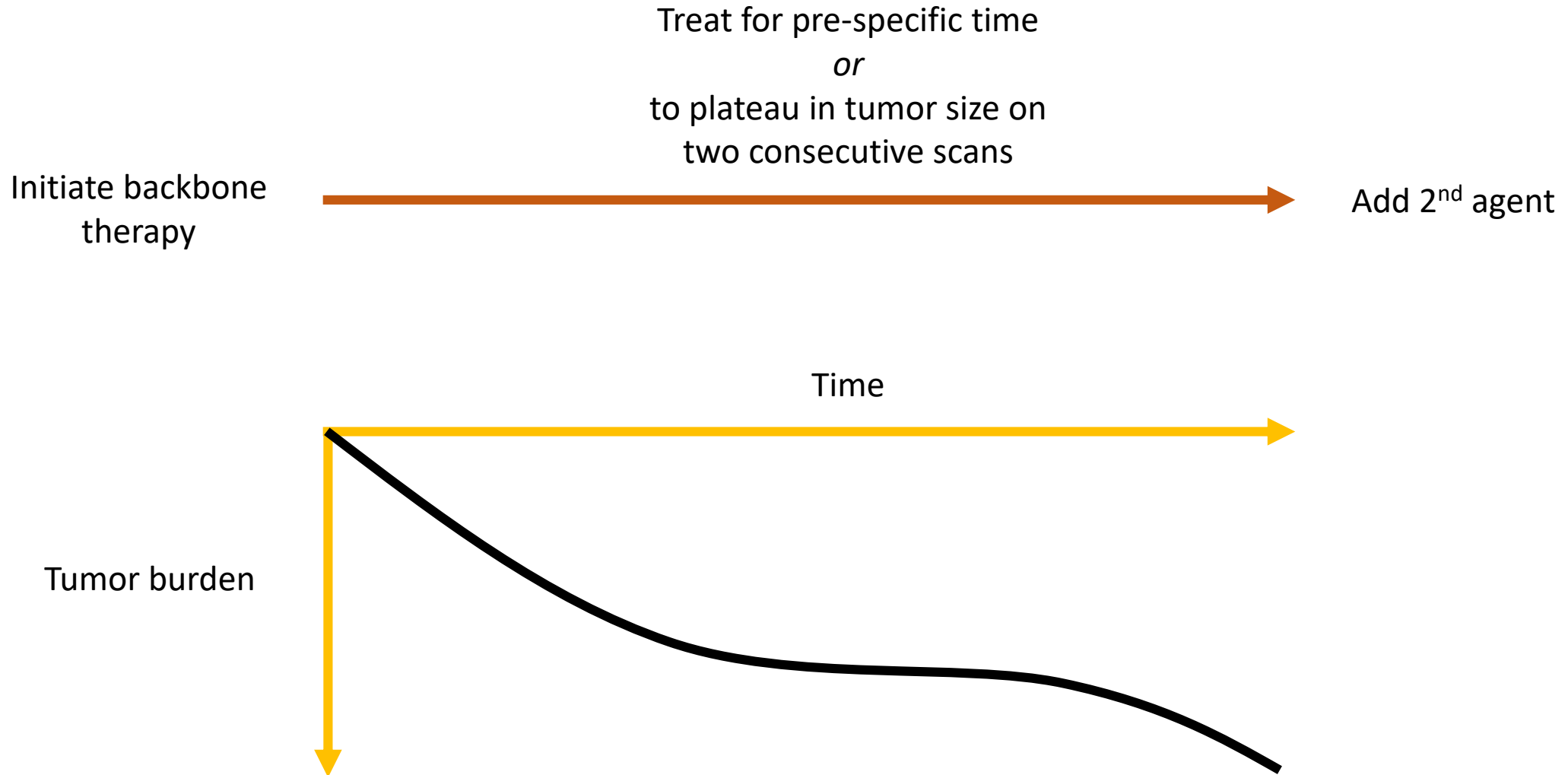
* Stock shareholder

Bypassing standard-of-care

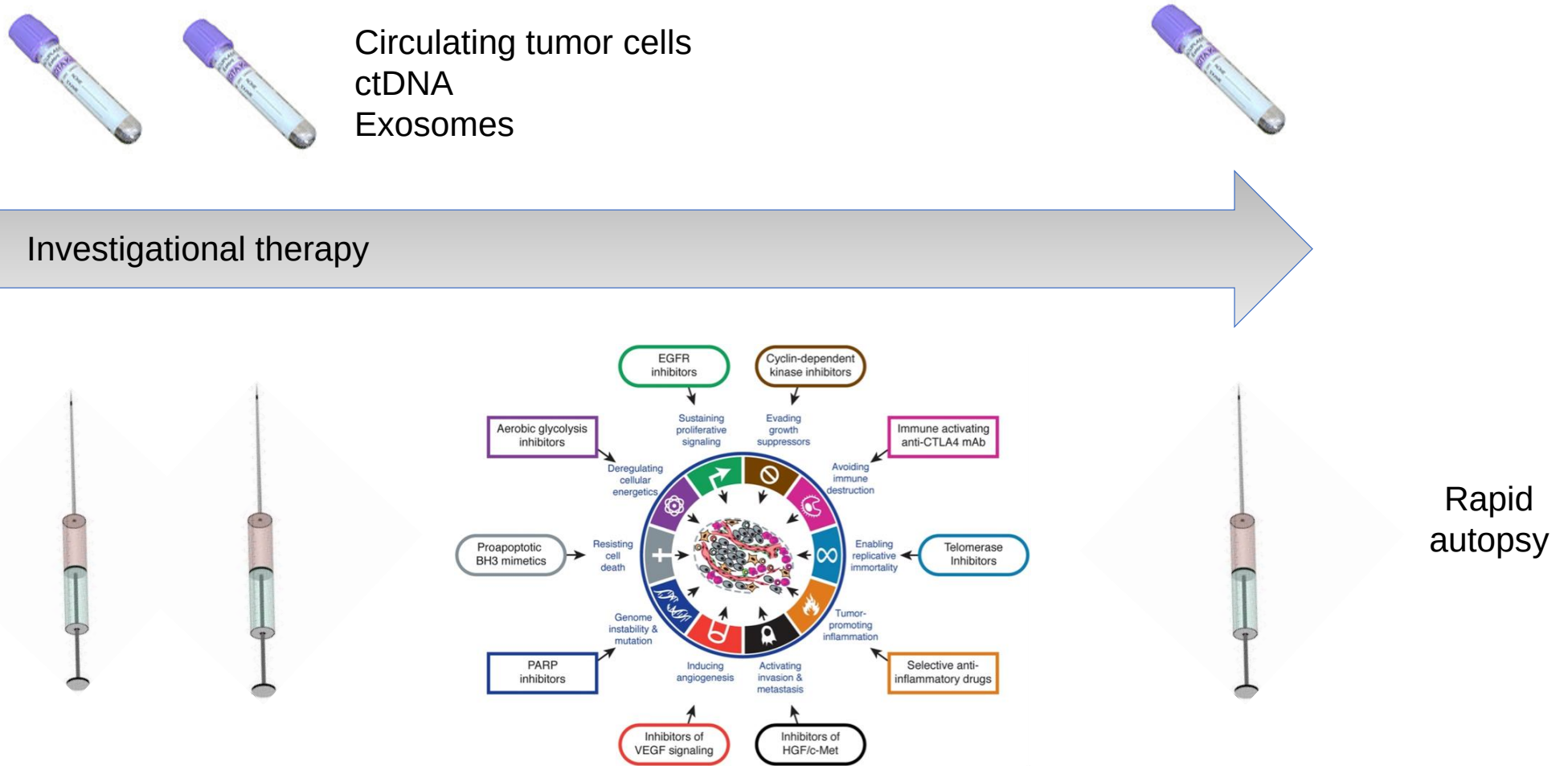


Wolchok et al. ASCO 2021
Lipson et al. ASCO 2021

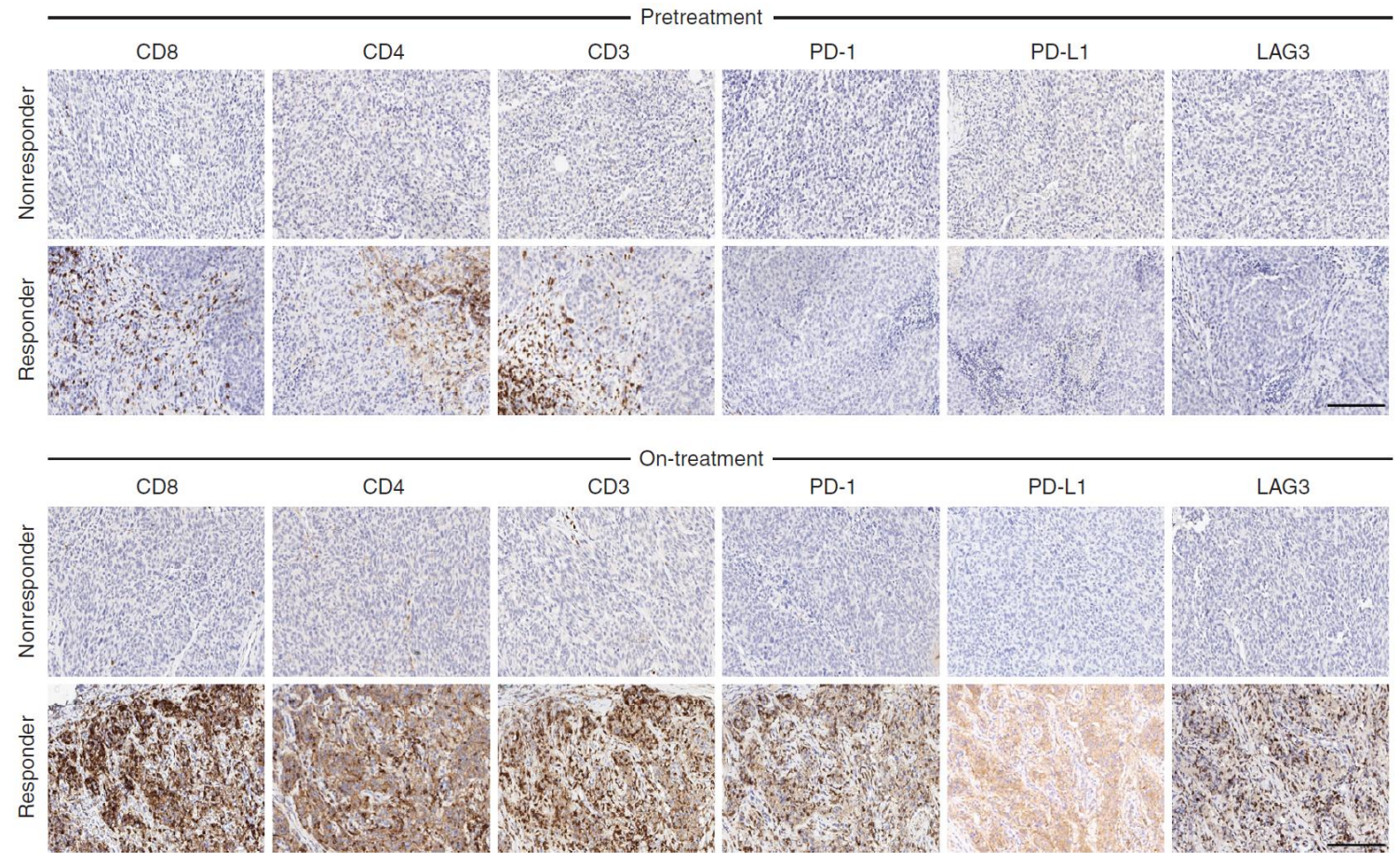
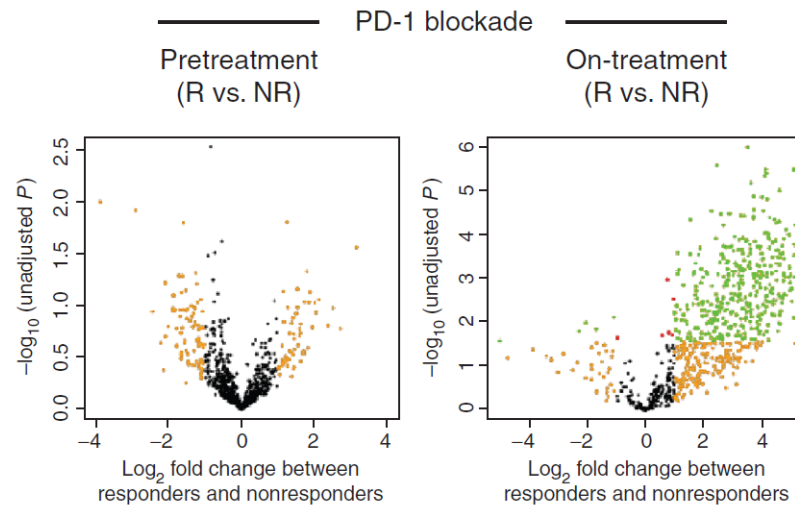
Treating to the point of maximal response



Tumor & blood-based biomarker investigations to understand mechanisms of action & resistance



Early on-therapy biopsy much more predictive of subsequent response with PD-1 monotherapy in melanoma

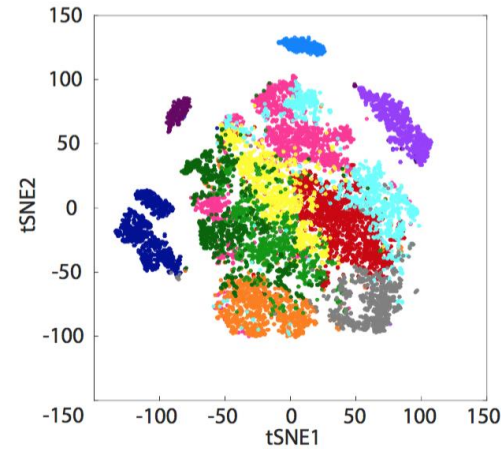


Analysis of single cell transcriptomes of immune cells in melanoma

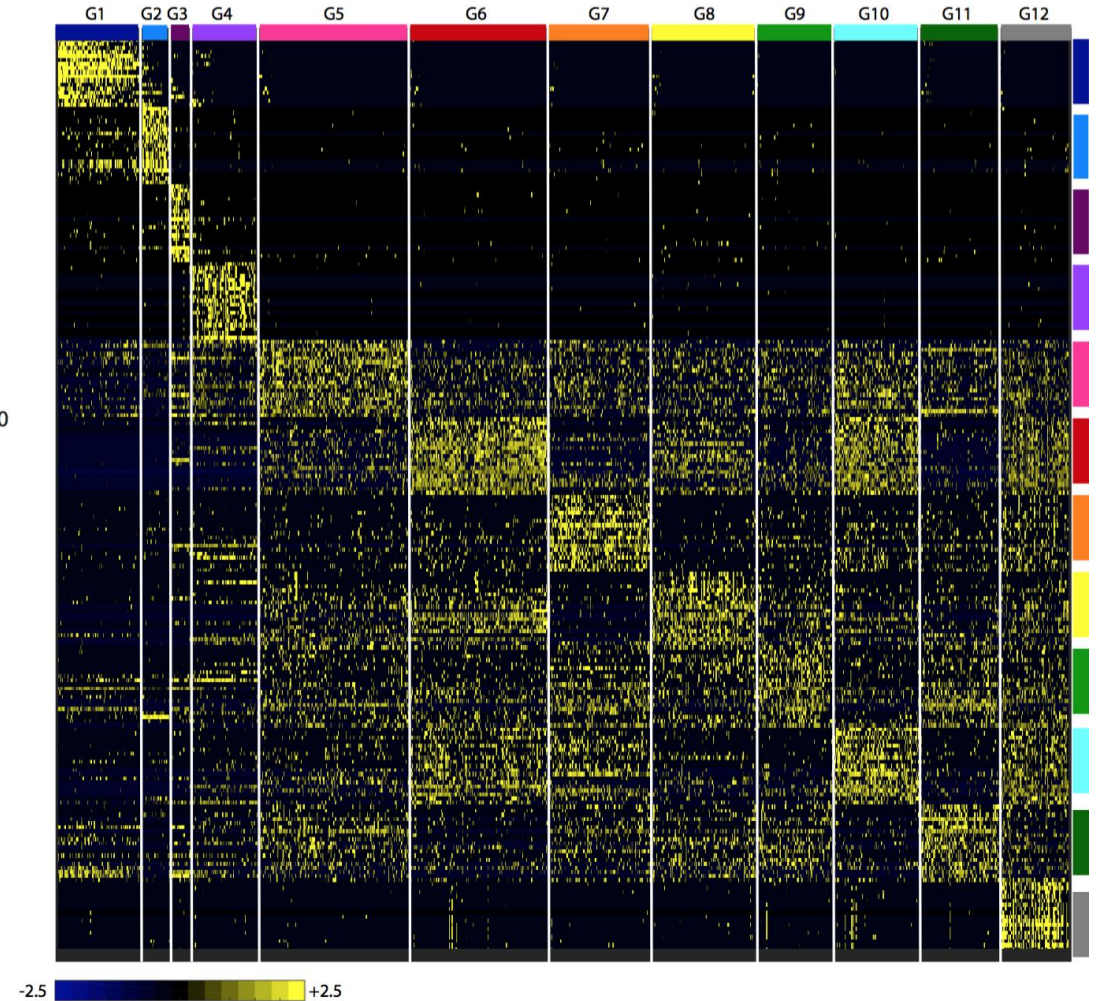
Patients=23

	B	P	Total
NR	7	18	25
R	3	9	12
Total	10	27	37

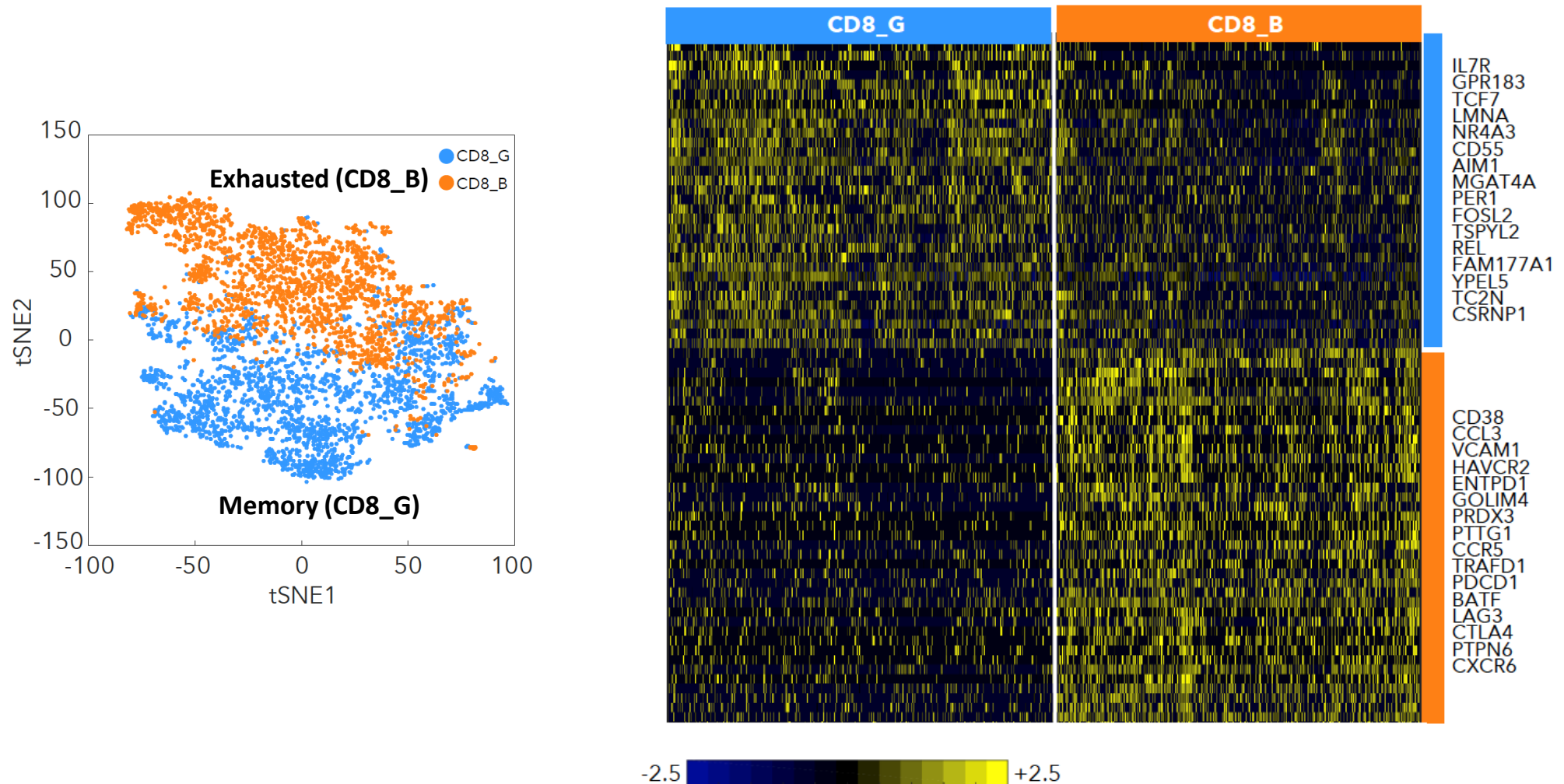
B-baseline; P-post;
R-responder; NR-non-responder



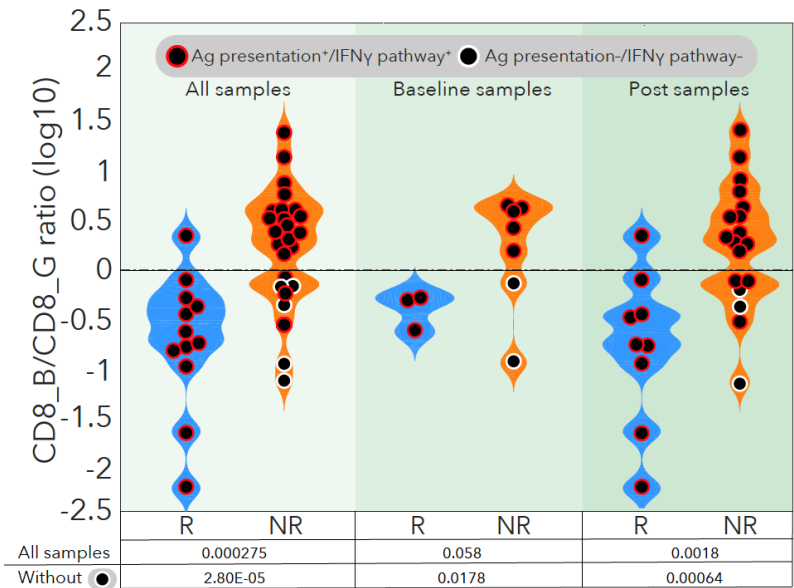
- G1- B-cells
- G2- Plasma cells
- G3- Dendritic cells
- G4- Monocytes
- G5- Lymphocytes
- G6- Exhausted CD8⁺ T cells
- G7- Regulatory T cells
- G8- Cytotoxicity (Lymphocytes)
- G9- Activated CD4⁺ T cells
- G10- Exhausted/HS CD8⁺ T cells
- G11- Memory T cells
- G12- Lymphocytes exhausted/cell-cycle



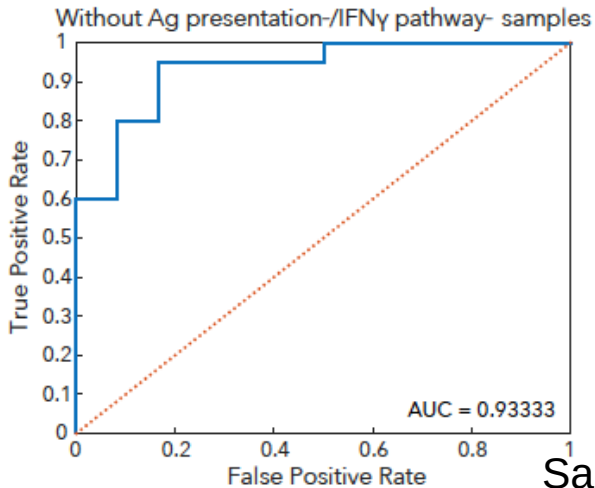
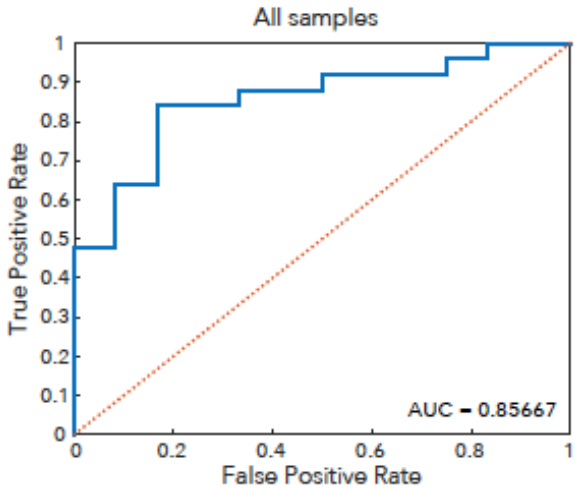
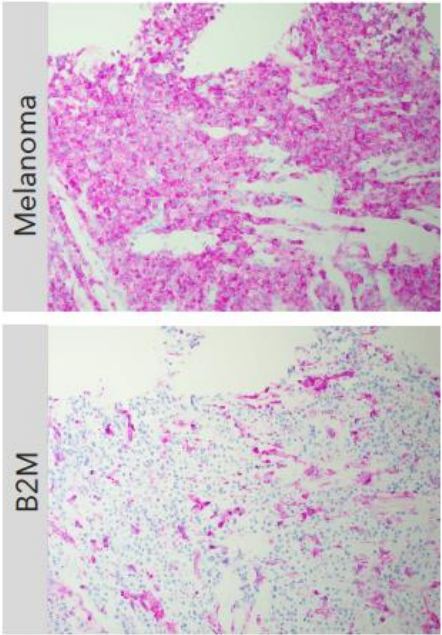
Two CD8⁺ T cell states associate with CPB response



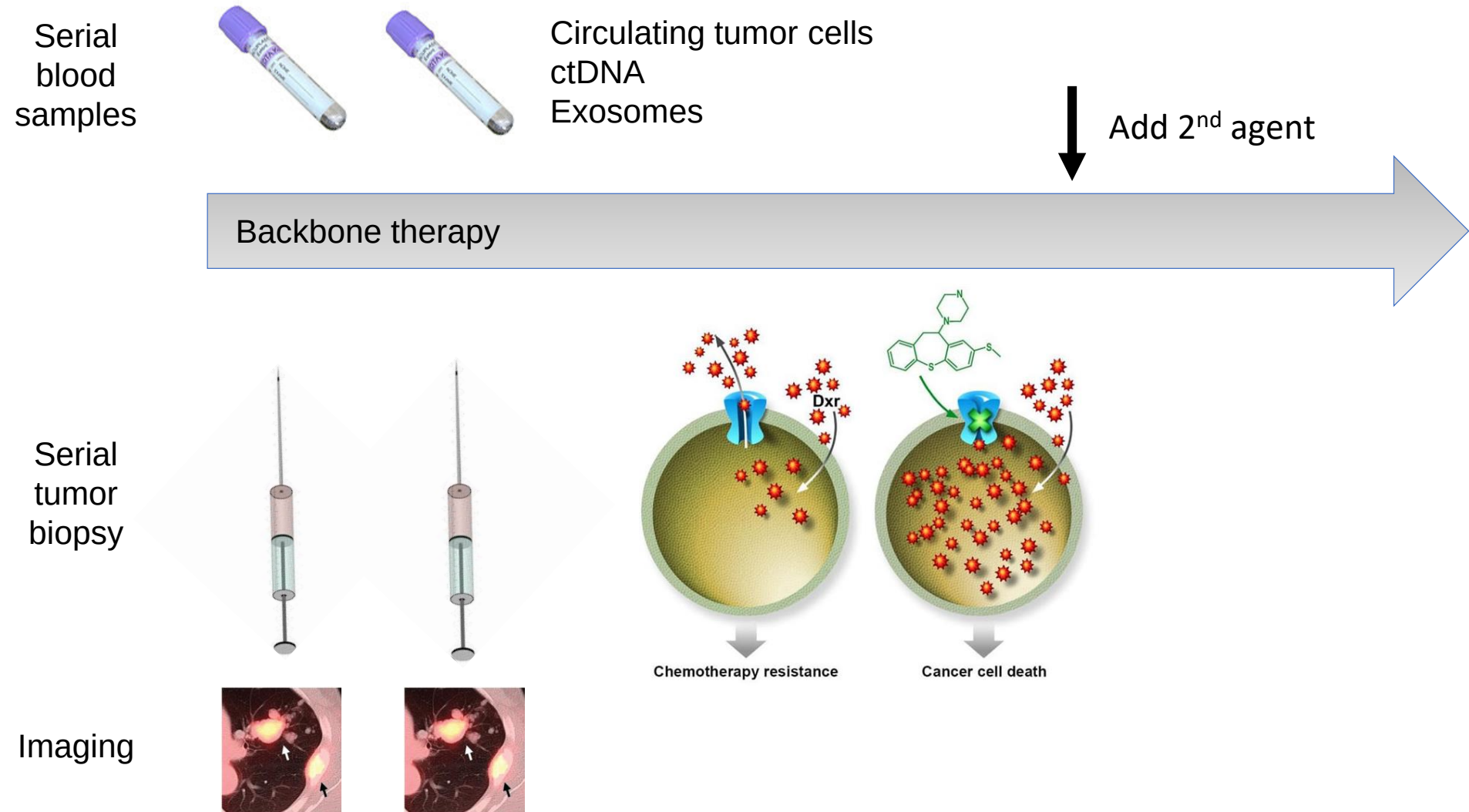
Two CD8⁺ T cell states combined with B2M expression associate with CPB response



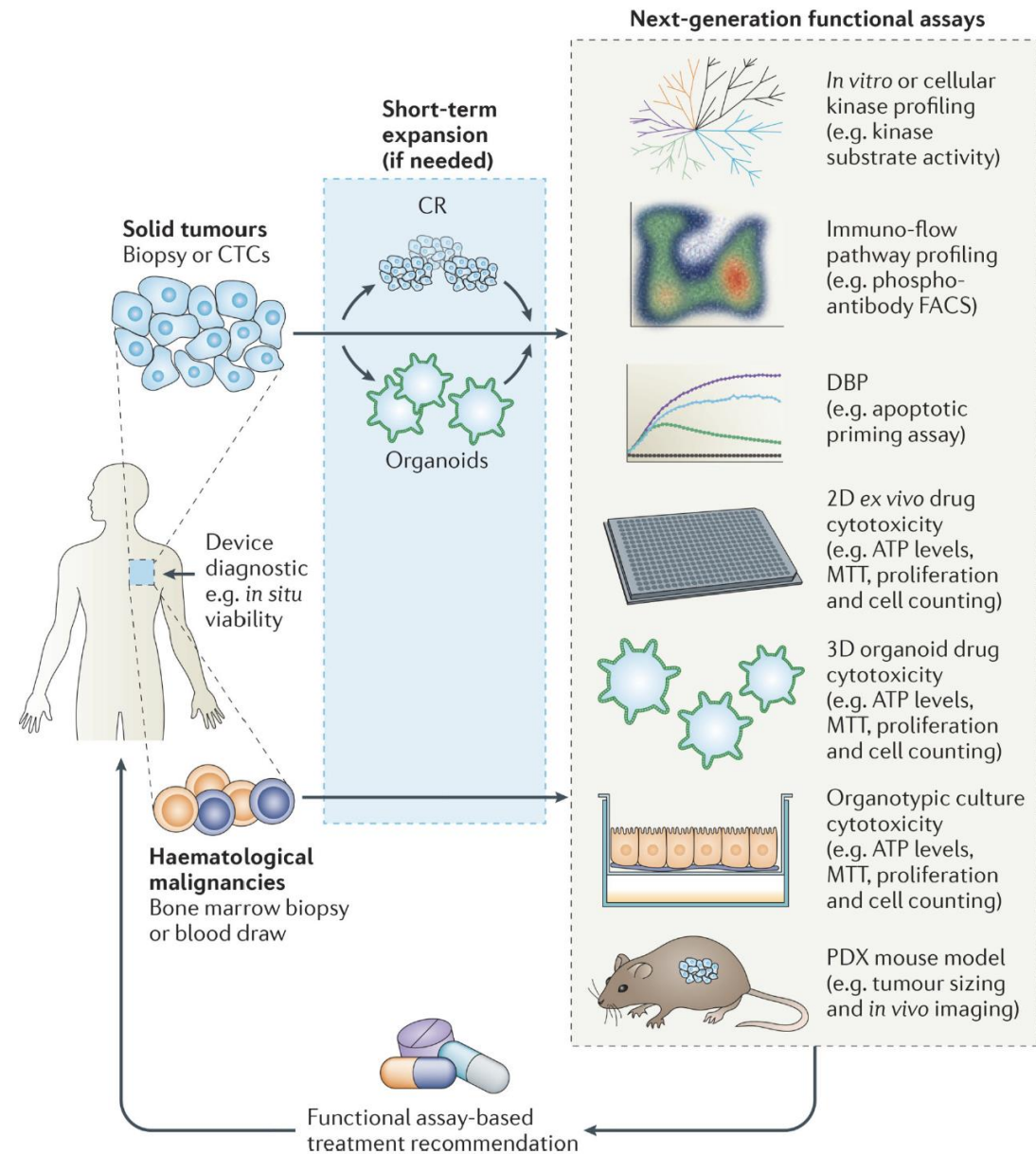
Predictive value



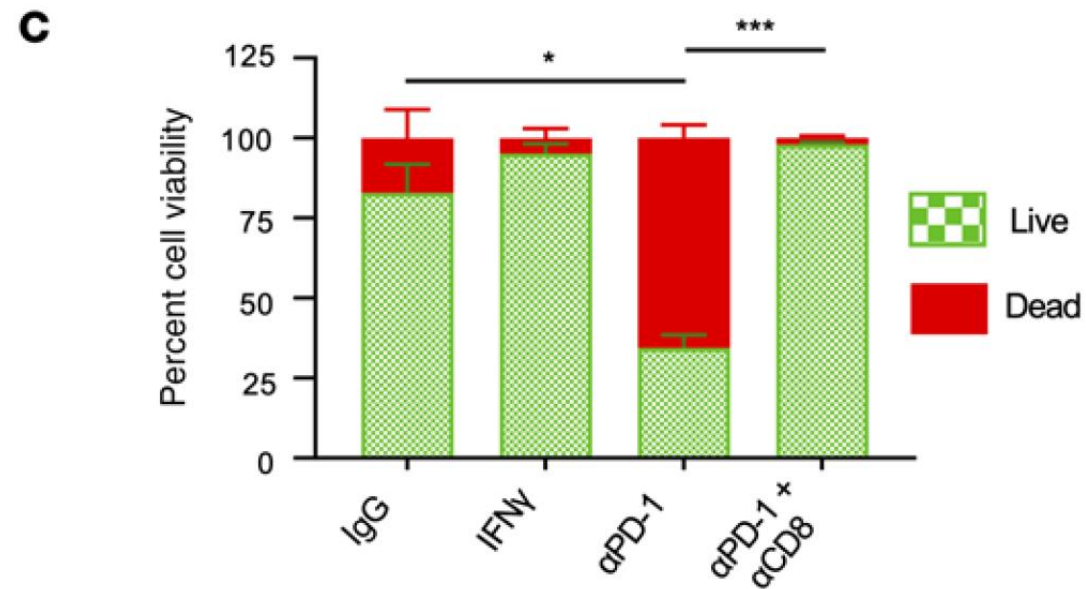
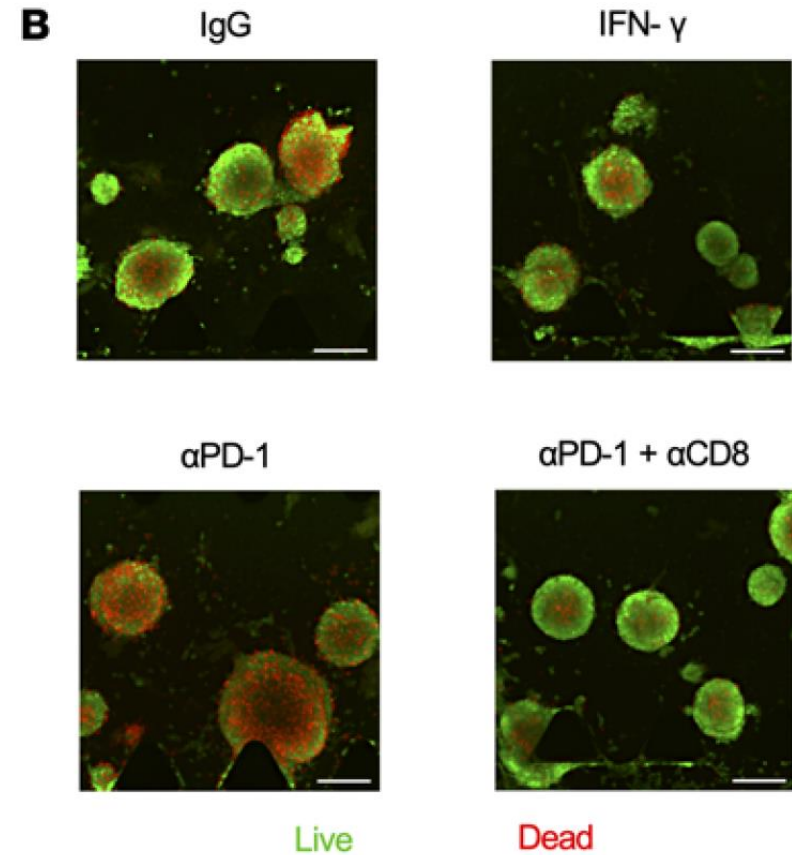
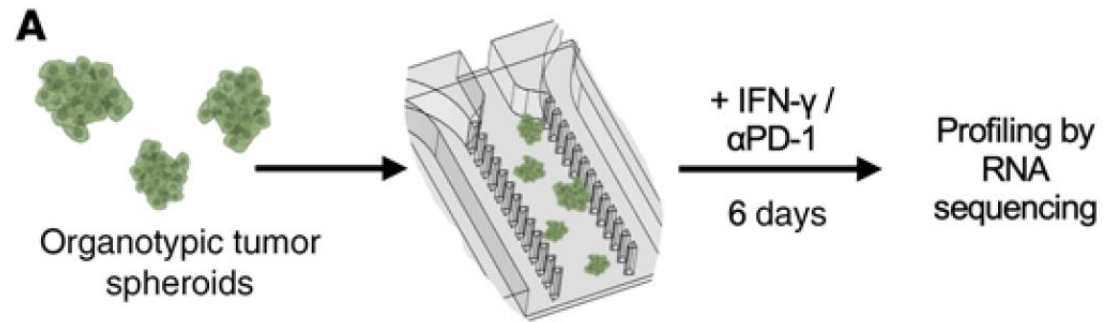
Biomarker-guided addition of 2nd agent



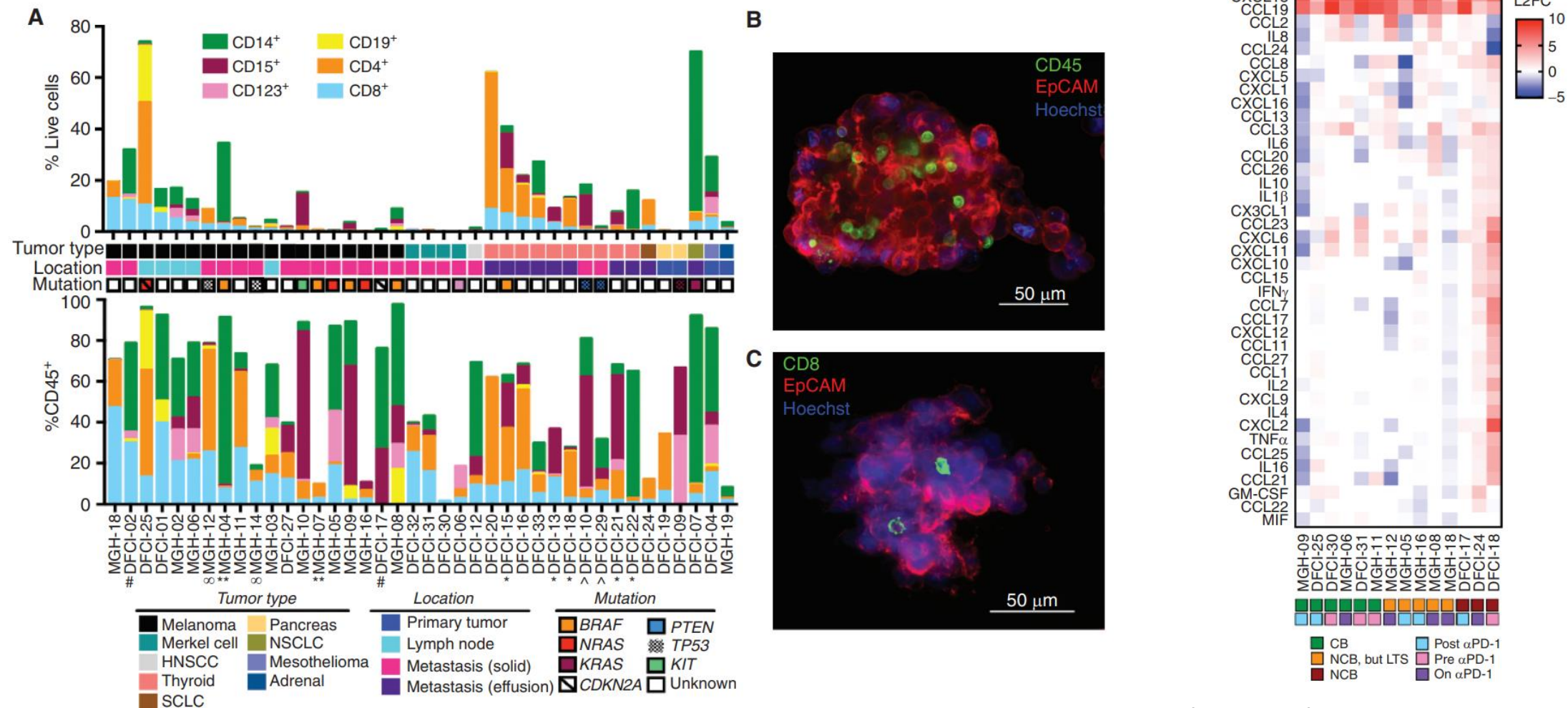
Leveraging *ex vivo* functional diagnostics



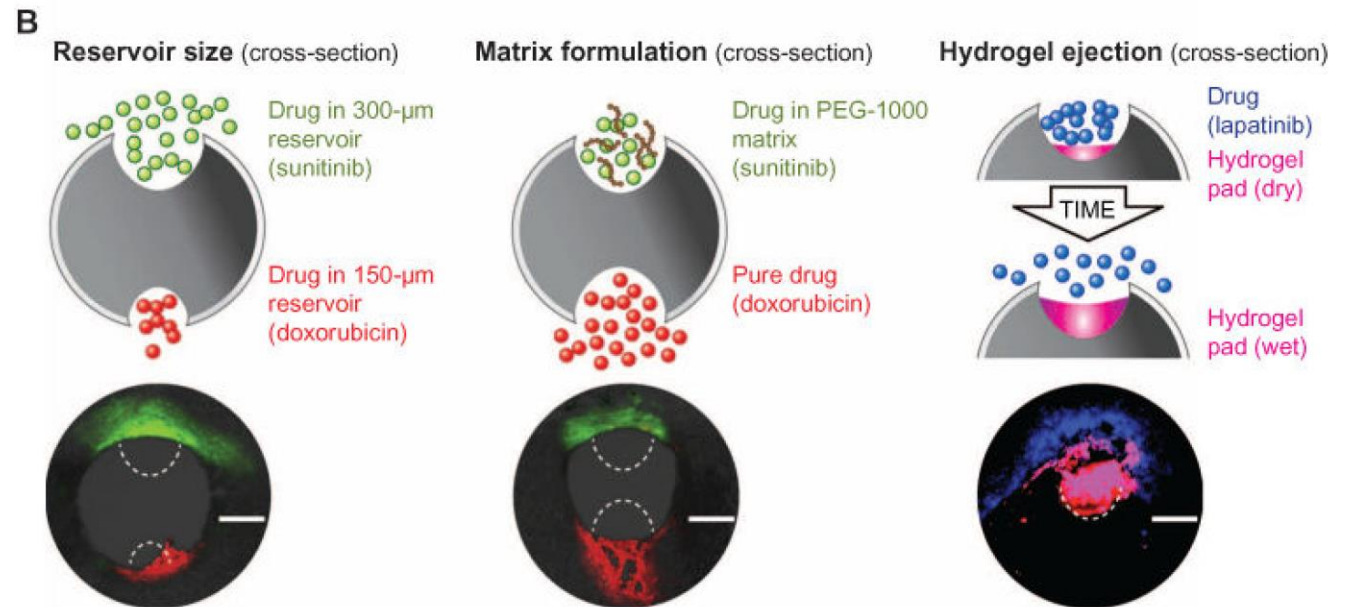
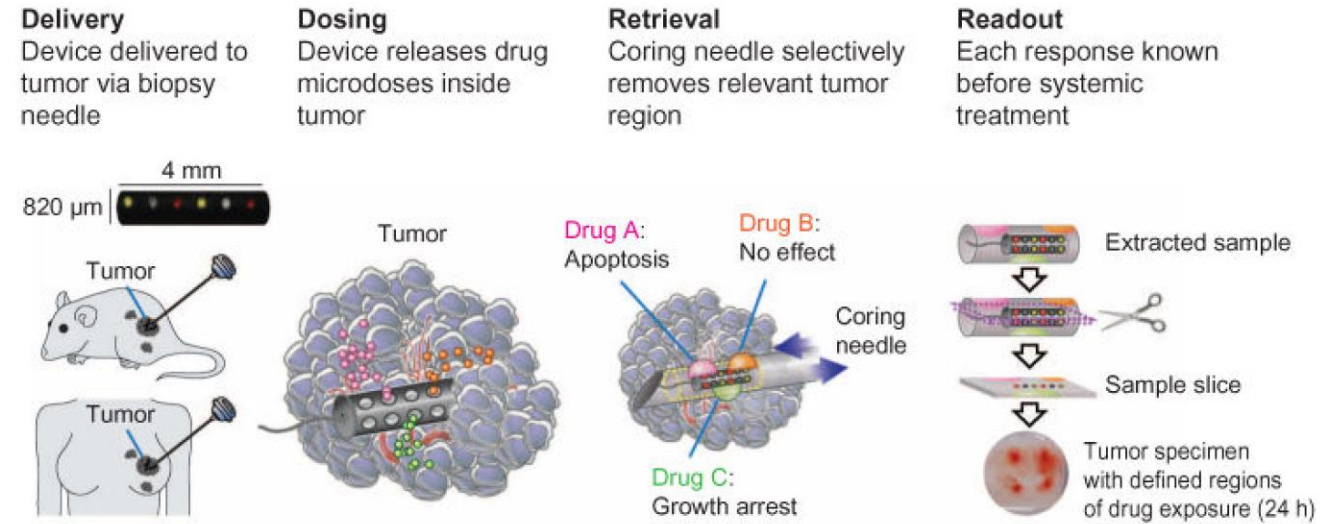
Ex vivo organotypic model for drug screening



Ex Vivo Profiling of PD-1 Blockade Using Organotypic Tumor Spheroids



In vivo testing of novel agents & combinations





MASSACHUSETTS
GENERAL HOSPITAL

CANCER CENTER

Things to do differently

- Identifying subpopulation that derives no apparent benefit from current SoC to triage to first-line investigational therapy
- Adding novel agents to standard-of-care in the setting of suboptimal response
- Using on-therapy immunologic response to guide addition of novel agents
- Jumping to higher order combinations and resolving contribution-of-components later: *ex vivo* & *in vivo* functional diagnostics