CANCER IMMUNOTHERAPY

Data and Specimen sharing- Industry perspective *Genentech*

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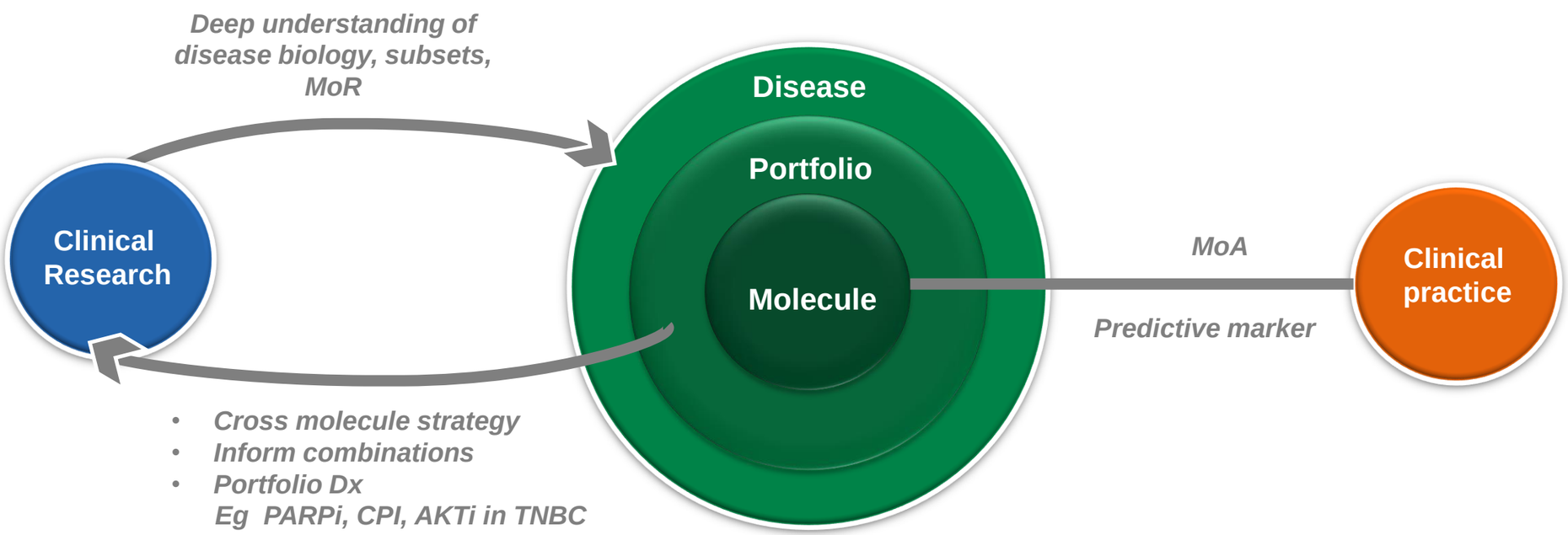
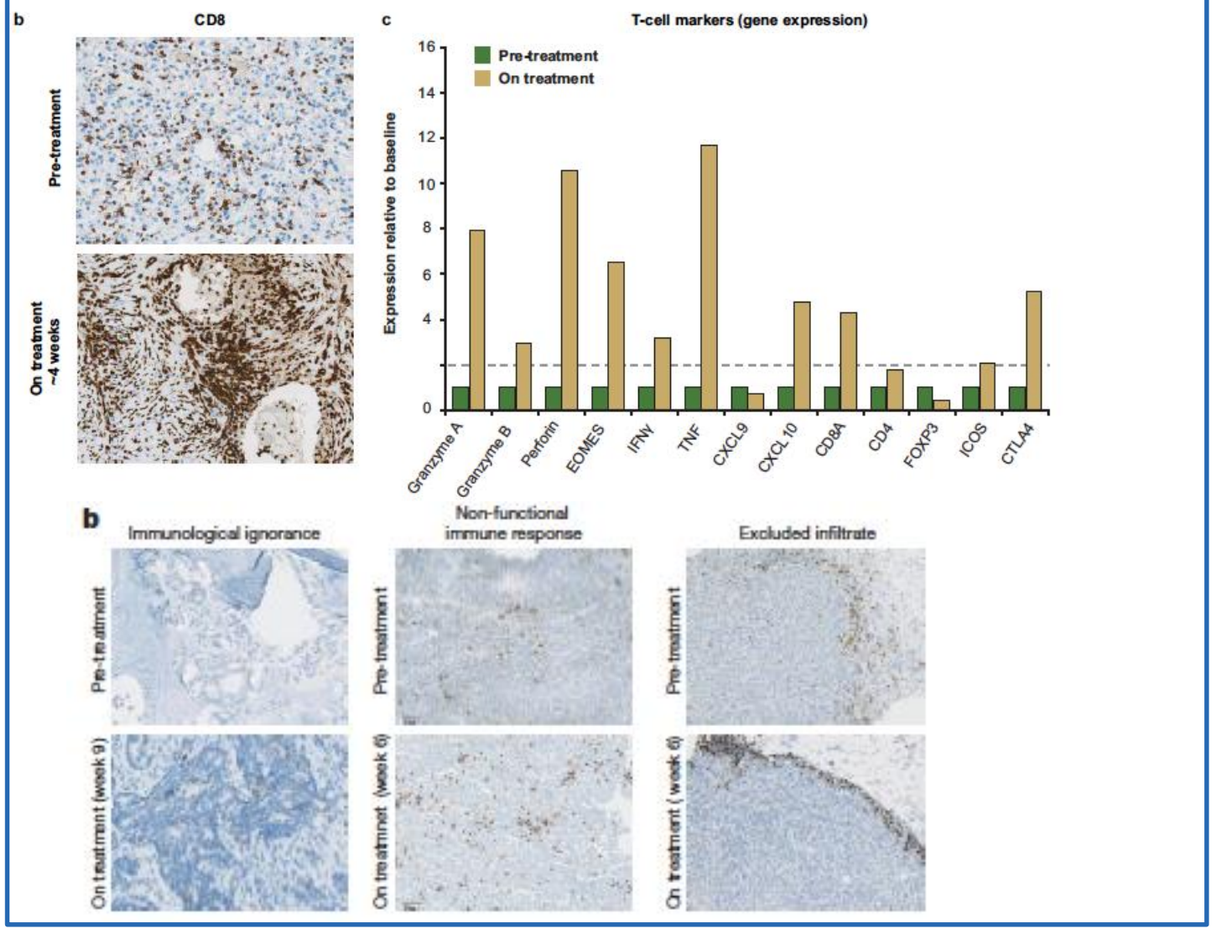
SITC BMW
San Francisco, May 2018

Genentech Biomarker Program



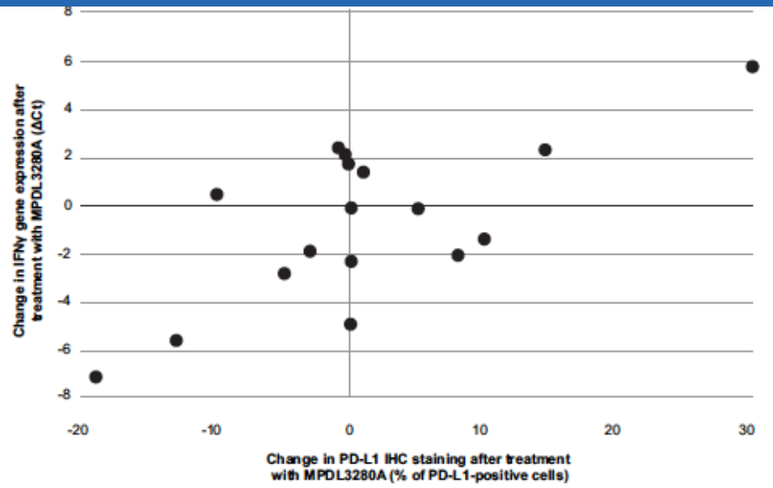
Molecule MoA- the science

Spatial and temporal changes in infiltrating CD8+ T-cells upon atezolizumab tx

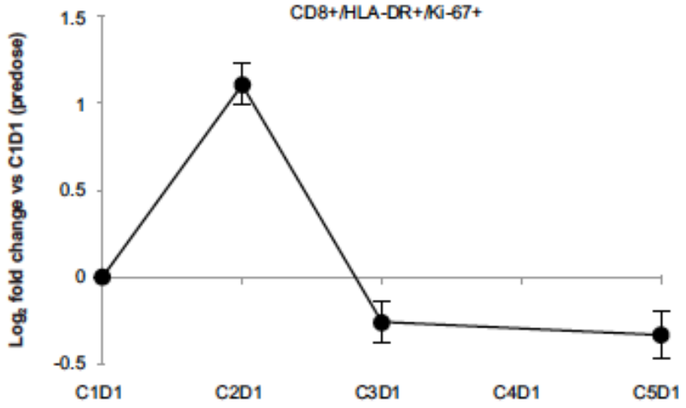


Herbst et al., Nature 2014

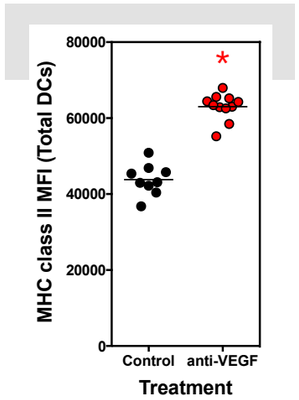
IFNg mediated adaptive regulation of tumor PD-L1 upon atezolizumab tx

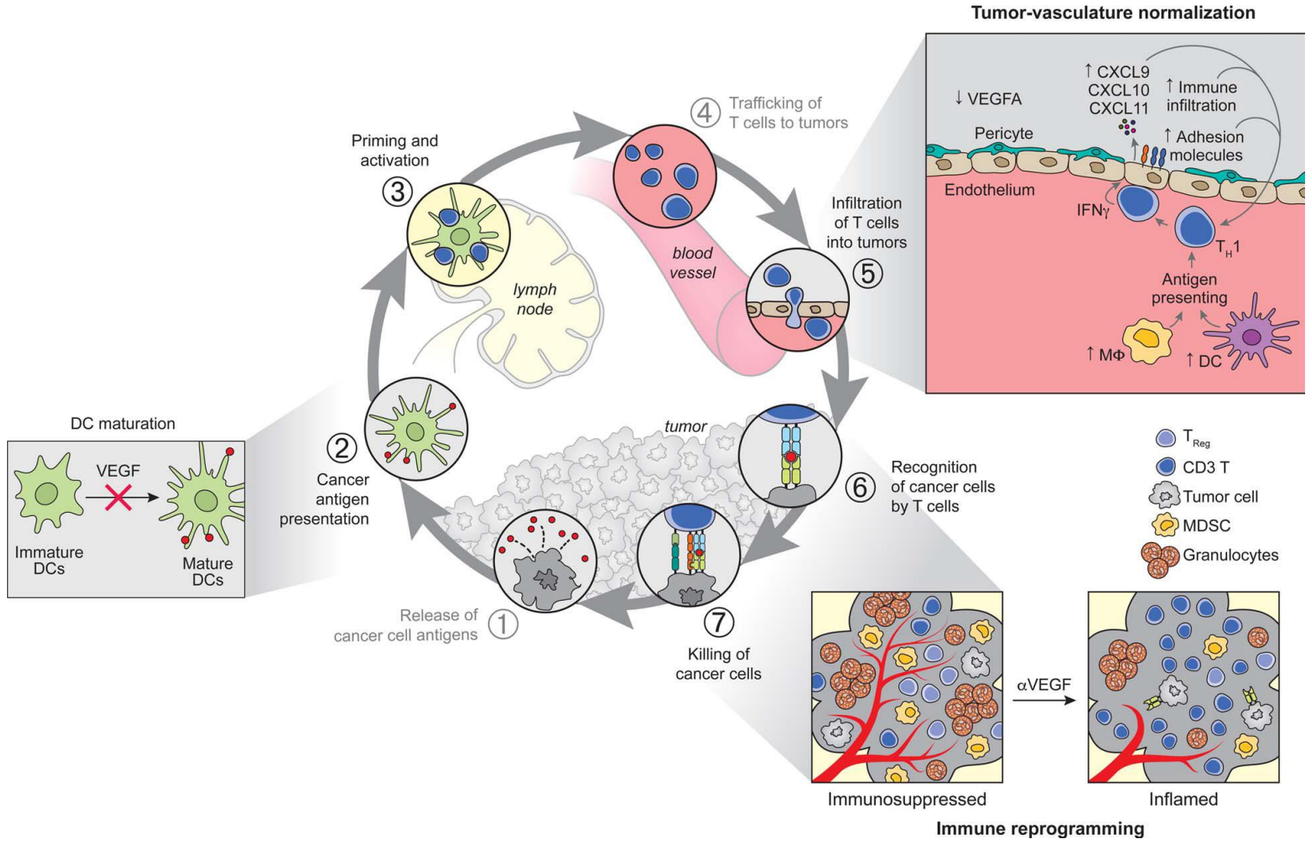


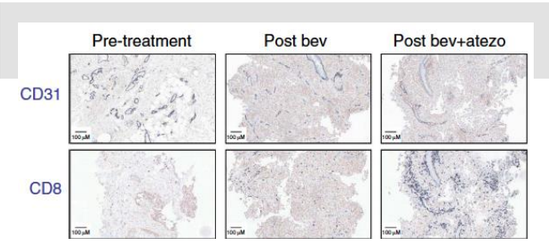
Acute rise in proliferating T-cells and associated cytokines upon atezolizumab tx

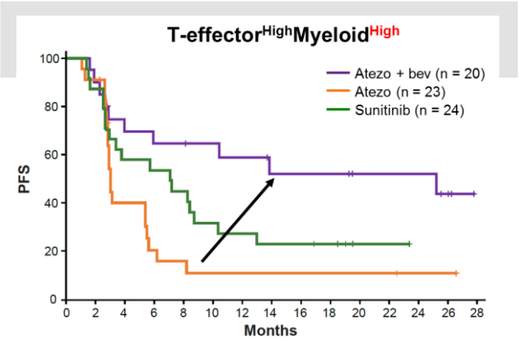


Combinations MoA- Portfolio perspective









Understanding the immune modulatory properties of a-VEGF have guided the regimens for IMpower150, IMmotion151 and IMbrave151

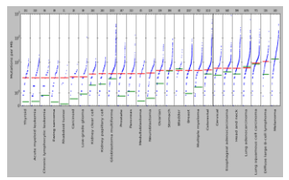
Hegde PS et al., Sem. Canc. Biol 2018; Chen and Mellman, Immunity, 2013; McDermott et al., Nat Med (accepted) 2018; Wallin J et al., Nat Comm 2016

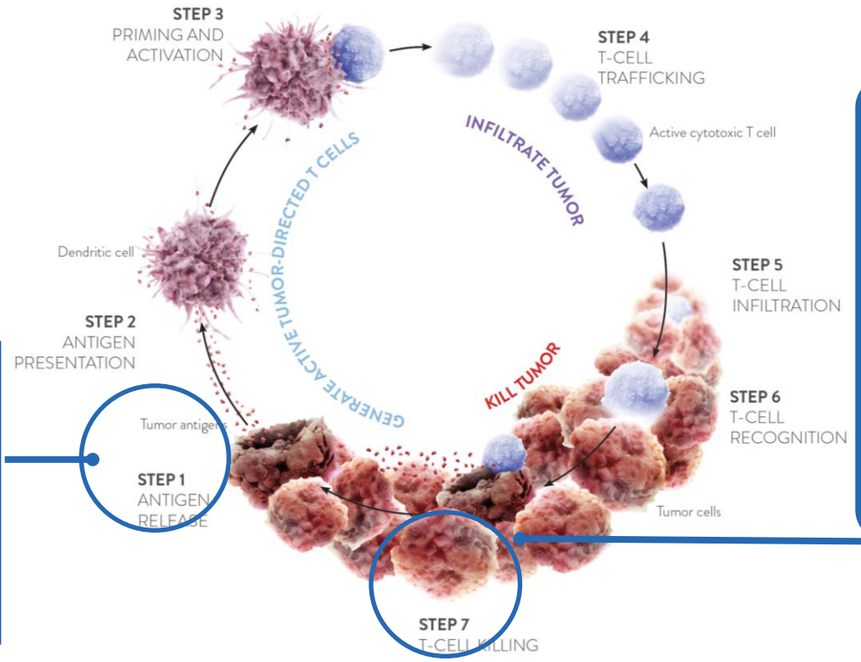
Predictors of response- shape clinical practice

SIGNAL 1

Tumor Mutation Burden

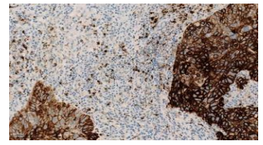
MSI[1], tMB[2]





PD-L1 expression

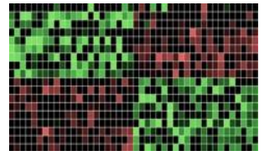
IHC



Tumor Gene Expression

IFNγ signature

NGS



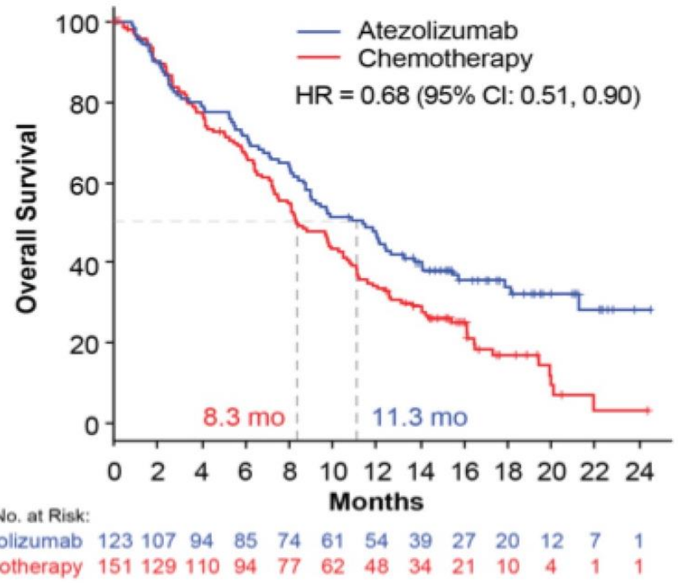
SIGNAL 2

Chen and Mellman, Immunity, 2013
[1]Le et al., NEJM 2015
[2] Powles T et al., Lancet 2017

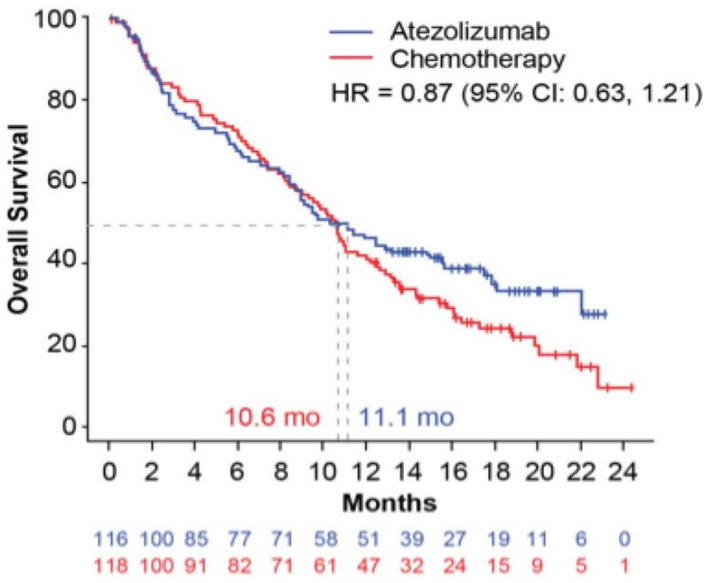
PD-L1 IHC and TMB are predictors of clinical benefit

Example: Ph3 IMvigor211 study in mUC

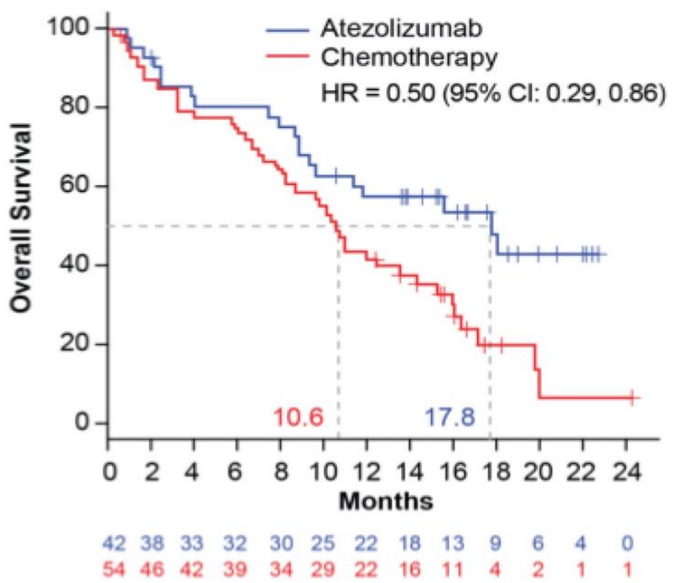
Signal 1
TMB high[a]



Signal 2
PD-L1 IC2/3



Signals 1 + 2
TMB high and PD-L1 IC2/3



Improved OS benefit was observed in patients with high TMB as well as high PD-L1 IC scores

ASCO GU 2018, Powles T
Unstratified HRs are displayed. [a]Median scores were used to define assessment cutoffs: TMB-high (≥ median) or TMB-low (< median). Median TMB in the biomarker-evaluable population was 9.65 mutations/Mb.

Disease tumor immune biology

inflamed **non-inflamed**

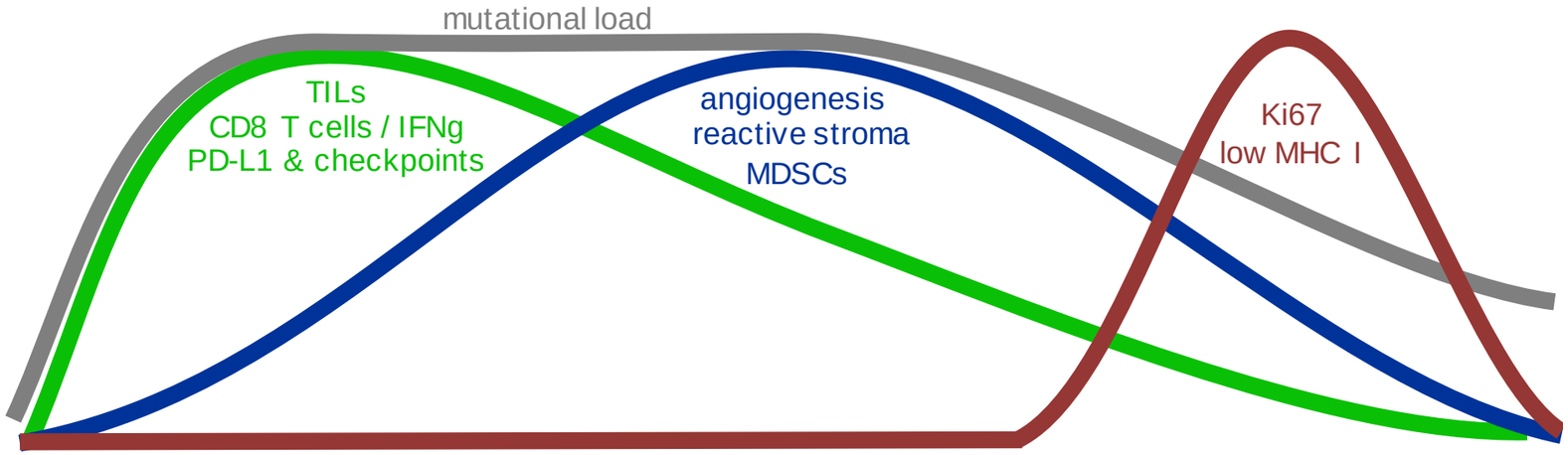
infiltrated

excluded

desert

Leveraged archival tissue RNA and CD8 IHC data from legacy Phase III trials (distinct diseases) and clinical outcomes data to develop a deeper understanding of disease immune biology and prognostic significance

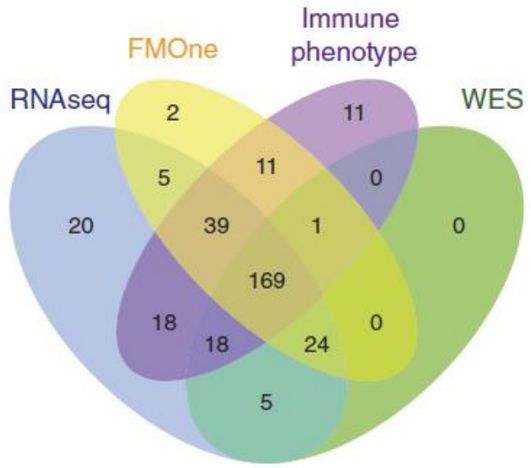
- Disease strategy
- Clinical strategy
- Science

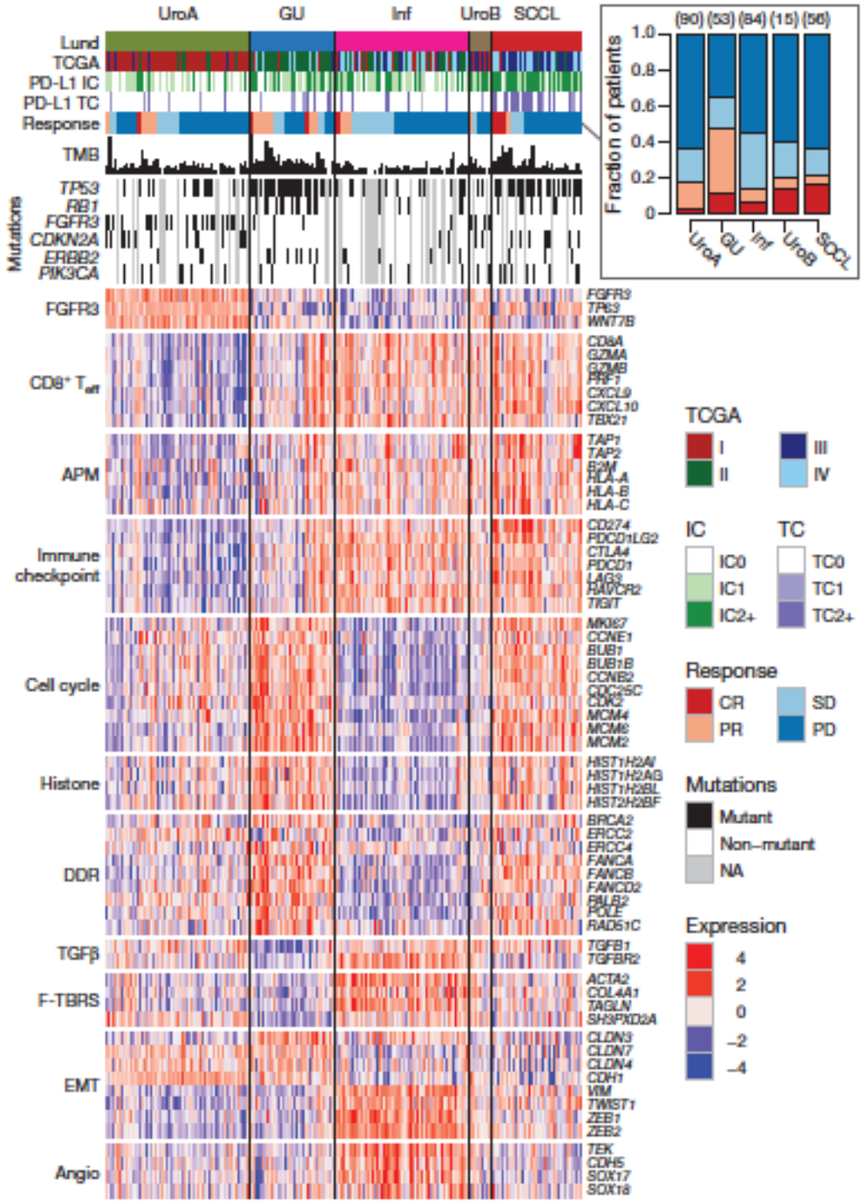


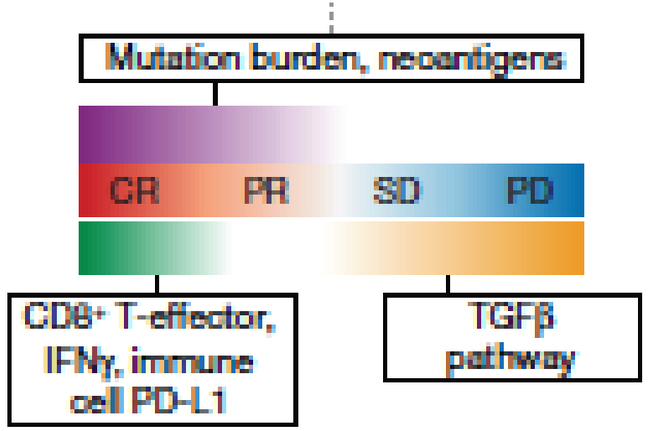
Hegde PS et al., CCR 2016

Impact of molecule on disease understanding

IMvigor210
(Atezo single agent Phase 2 trial): n = 326







Mariathasan S et al., Nature 2018

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Clinical trial biomarker research

- What is the hypothesis being tested?
- Is the study designed to address the question?
- Can the biomarker question be addressed in a multi-institution study?
- eg fresh tissue shipments
- Is the biomarker going to enable a clinical decision?
- Is the assay qualified (non primary ep) or validated (primary/co-pri ep)?
- Preferable to use consistent tools and platforms to address questions within and across trials
- Pre-analytical variables may have a greater impact eg RNA/DNA isolation, PBMC prep
- Preferable to execute a biomarker analysis plan (BAP) signed off by biostats prior to data analysis (adds statistical rigor to hypothesis testing)
    - How is the biomarker defined (eg IFNg signature constitutes x,y,z)
    - What is the cutoff used?
    - What is the expected outcome?
- To enable decisions, independent validation required

Clinical trial specimen collections

Global trials
- Multiple sites (typically 10-100 per trial)
- Real time sample shipment (eg blood FACS)
- Real time data turnaround (eg PD-L1, TMB, MSI)

Centralized testing
- Vendor capability
- Assay performance
- Data quality monitoring

Proper Sample Handling is crucial to executing on biomarker strategy

Collection Type

Archival block or Curls & Slides

And / Or

Screen-fresh biopsy

Blood for PBMC-M*

*Manufacturing

Blood for genotyping

Sample Type

Ship Day Of Retrieval or Sectioning

Fix Within 1 minutes of Procedure

Fill tube Completely

Fill tube completely

Archival Tissue Kit

Slides & Curls

Blocks (empty)

Fresh Tissue Kit

Formalin

10 mL lavender top

5 mL lavender top

Ship To

Curls & Slides: **Refrigerated**

Blocks: **Ambient**

REFRIGERATE
Cannot Freeze!

Ship **Refrigerated** On Day of Collection

Ship **Refrigerated**

Vendor x

USE REFRIGERATED PREMIUM SHIPPERS

Ship **Frozen** On Day of Collection

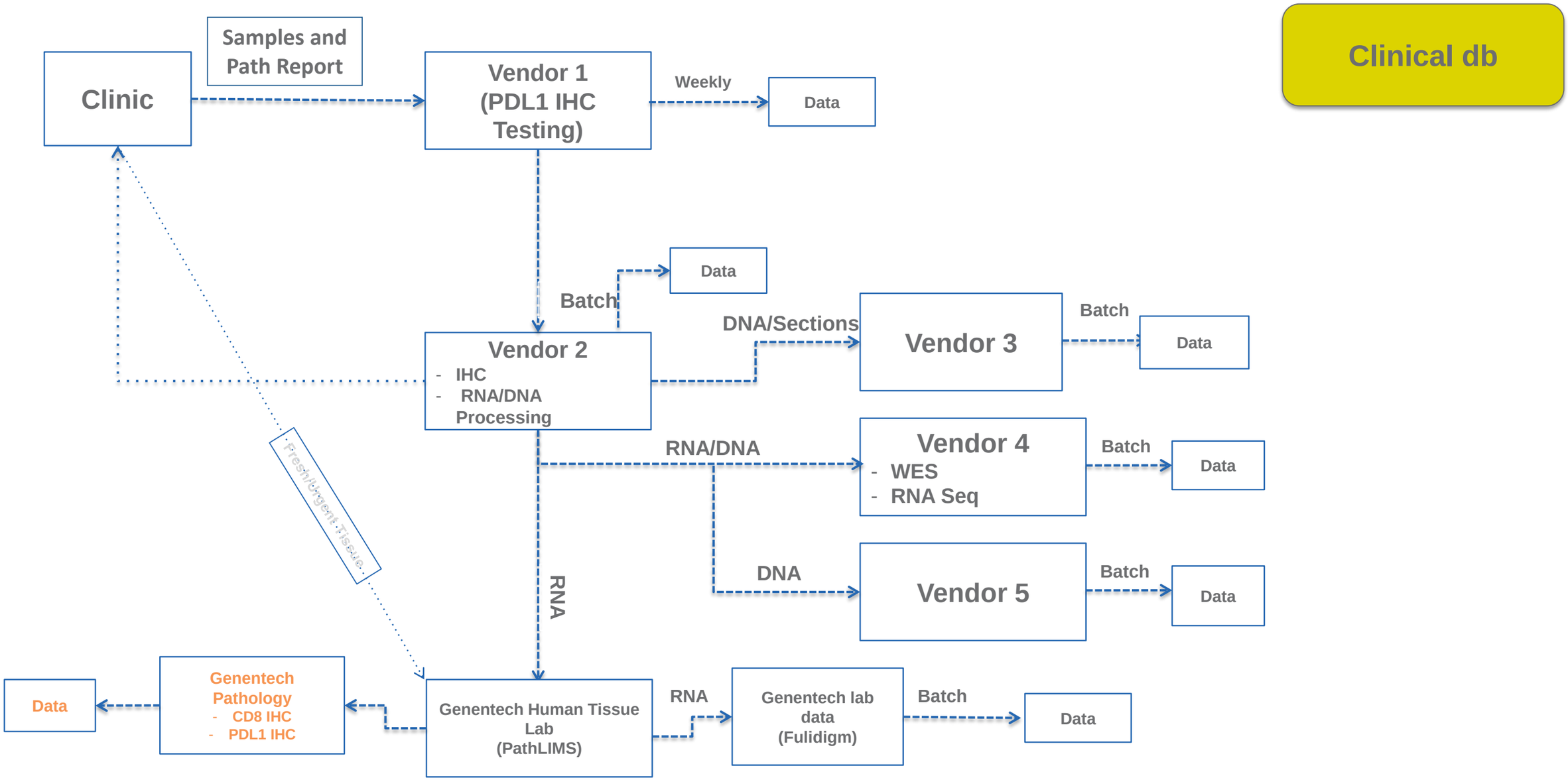
Vendor z

USE REGULAR FROZEN SHIPPERS

Specimens from trials

- Informed consent from the patient to conduct specific research
- Sections usually cut and block sent back to patient within 1 month of receipt
- Managed by trial steering committee
- Not up to sponsor to disseminate to third parties

Example of Single Tissue Flow Lifecycle



Data Management

Tissue tracker

- Mechanism to match IDs (pre-screen, screen, different vendors IDs for data)
- Real-time assessment of tissue quality, how much plasma left, how much tissue

Raw data tracker

- Omics
- Digital path
- FACS
- Plasma cytokines

Analyzed data tracker

- Ppts
- PDFs
- Spotfire files, jmp, codes for analysis etc

Data sharing

Phase I trials

At time of publication, data contributing to publication is shared as per journal requirements

Phase II learning trials

GNE policy is to share data to enable learning on certain trials [IMvigor 210 (mUC), IMmotion 150 (RCC)]

Eg Mariathasan S et al., Nature 2018

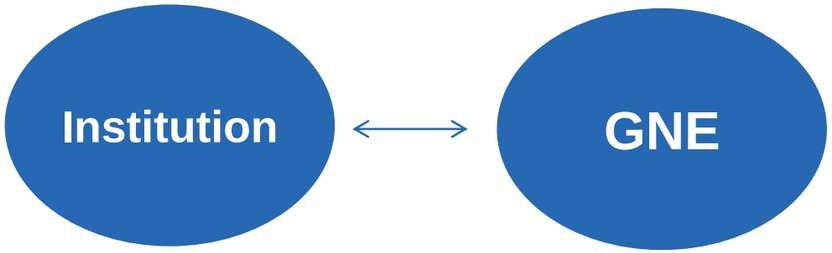
- RNAseq, WES, CD8 IHC, PD-L1 data made publicly available with outcomes data for all 326 patients enrolled in the trial. Easily downloadable.
- Allows TCGA-like learning with clean outcomes data to atezolizumab

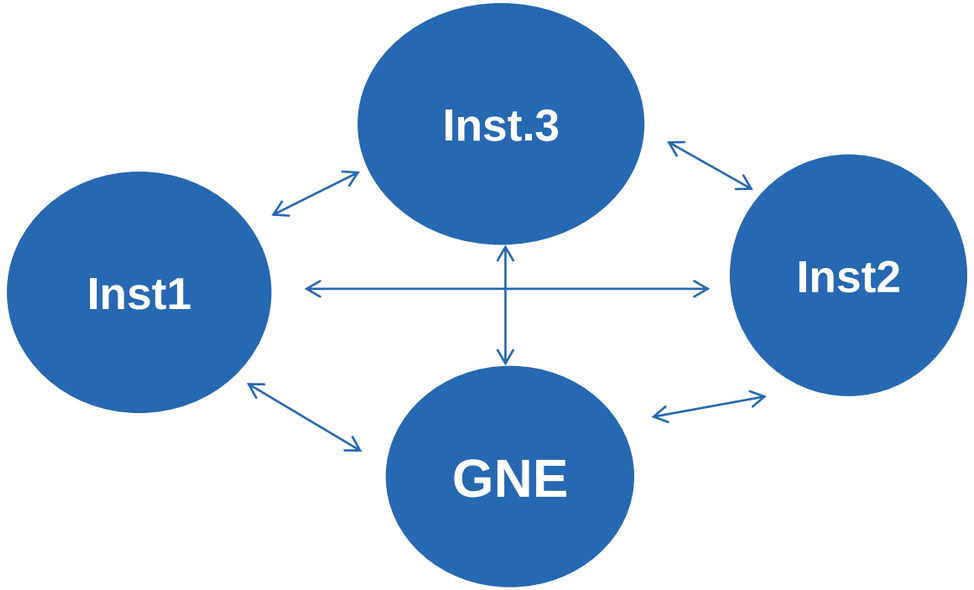
Phase III trials

Typically not data rich

Sharing of data contributing to publication as per journal requirements

Investigator-initiated trials- All about authorship!





- Publication philosophy
- Biomarker statement of work developed and signed between institutions
- Clarity of who does what and timelines for data generation
- Data sharing philosophy within group of investigators
- Generally select CRO for routine data (eg CD8 IHC, PD-L1, RNAseq, DNAseq)
    - Inst. contract with CRO
- Analysis plan depends on expertise within the consortium

Genentech Biomarker Program