



# Advancing IO Treatments for Cancer Patients: Opportunities and Challenges

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VP Translational Medicine & Regulatory Affairs*

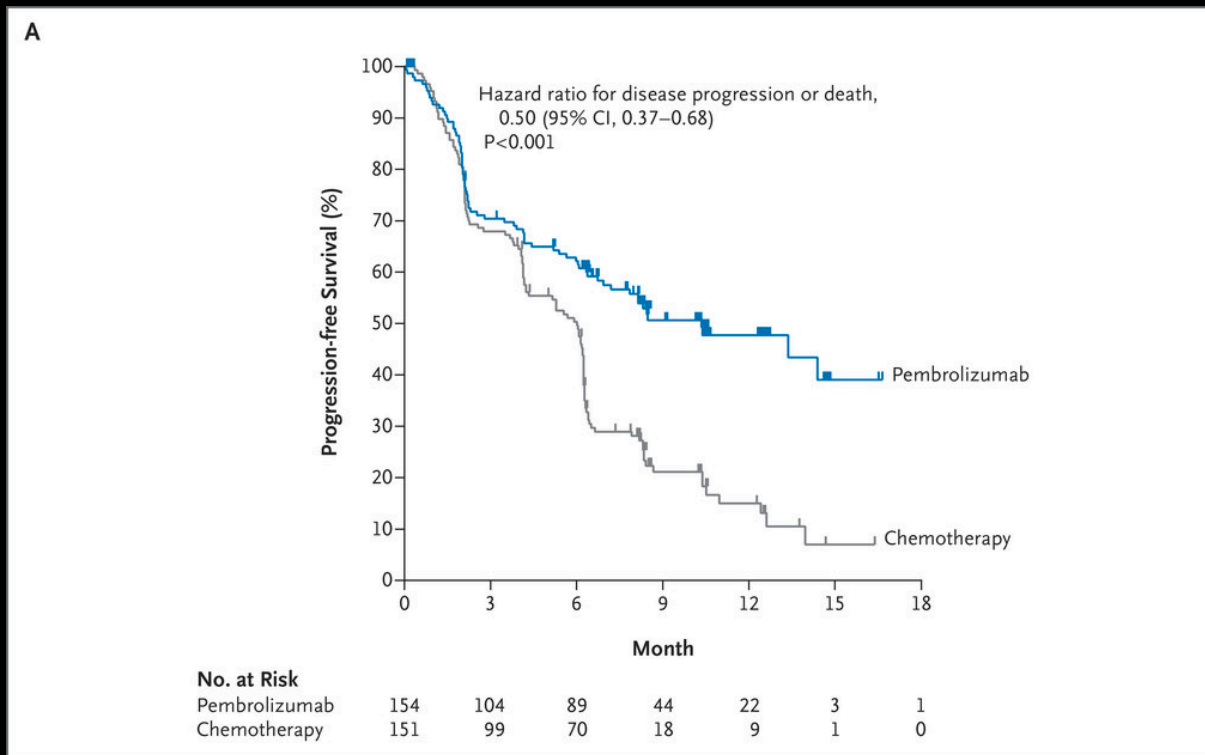




# LOOKING BACK

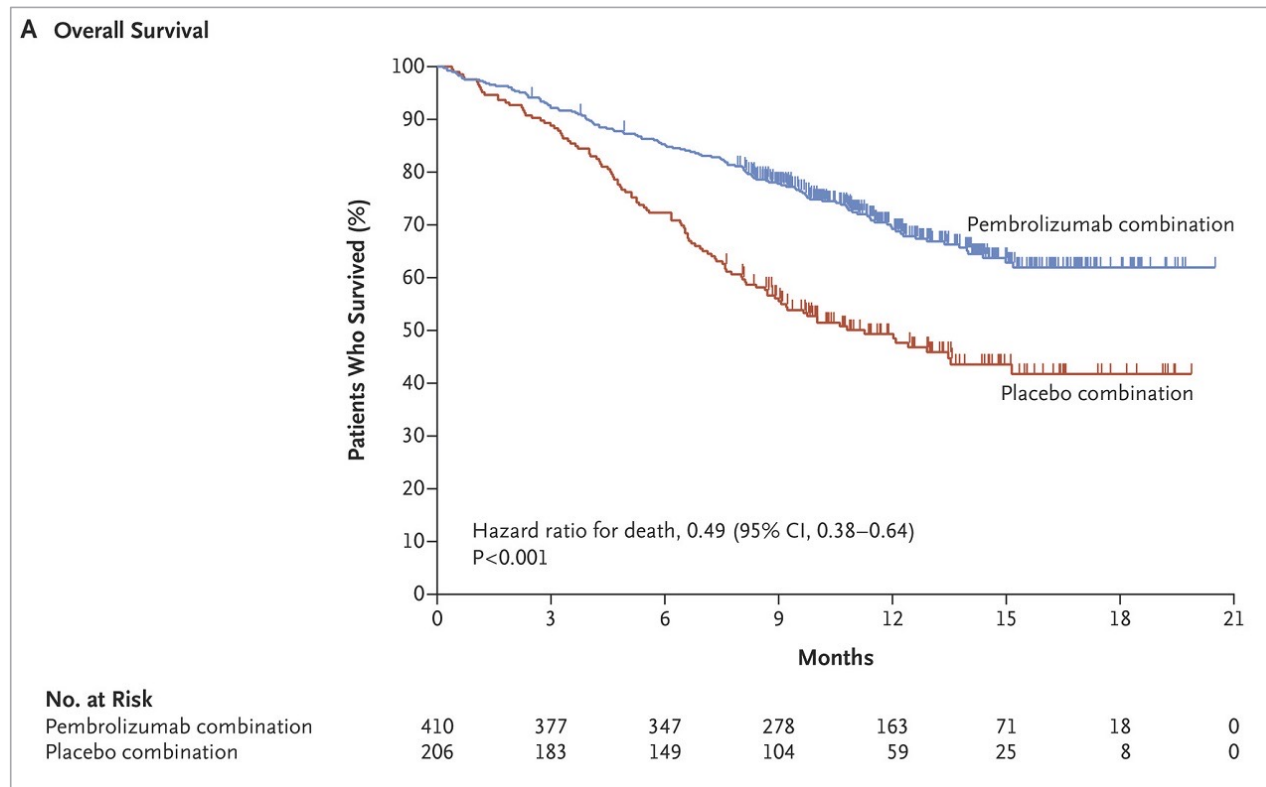
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# Monotherapy Immunotherapy Patients Live Longer



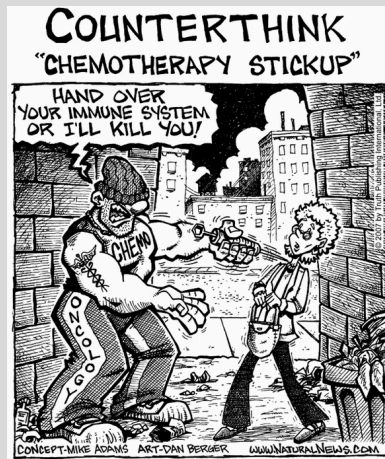
Reck M et al. N Engl J Med 2016;375:1823-1833.

# Combination Immunotherapy Patients Live Longer



# Changing the Paradigm for Oncology Treatment

## CHEMO / RADIATION / SURGERY



- Cut it out (if possible)
- Poison the tumor
- Wait for escape
- Poison again

## IMMUNOTHERAPY



**Mr T cell.**  
*pities the fool who expresses  
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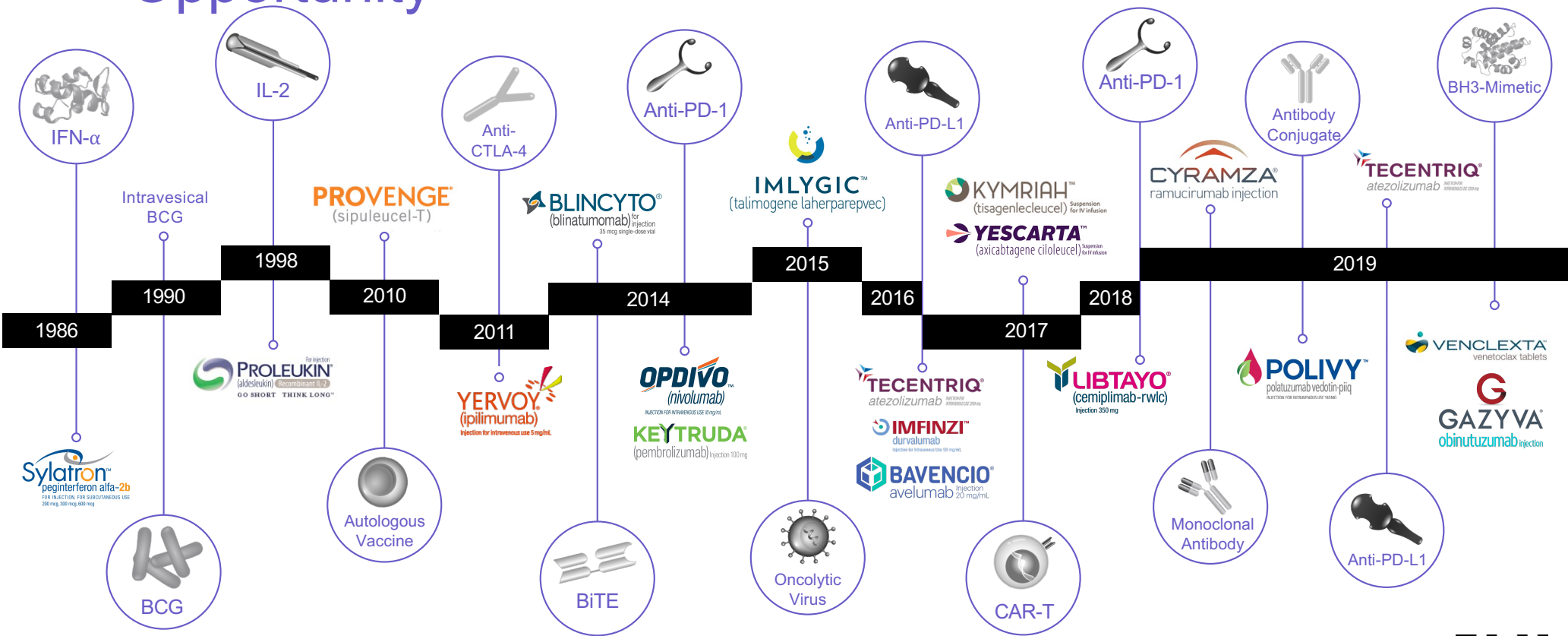
- Re-educate the immune response to treat tumors as **non-self**
- Unleash the immune system brakes and turn on the gas
- Specificity, memory, durability and infectious anti-tumor activity



# Challenges that Remain with Immune Checkpoint Therapies

<b>Patient Selection</b>	Not all patients respond to checkpoint inhibitors
<b>Unique Toxicities</b>	Some patients treated go on to develop autoimmune disorders (rashes, diarrhea, insulin-dependent diabetes, among others)
<b>Science-driven Novel Combos</b>	We need to better understand what combinations work, why some are successful and why others are not
<b>Difficult Tumors</b>	How can we understand more about hot vs. cold tumors so we can clearly define the differences and determine how to best treat them?
<b>Beyond PD1s</b>	There are two distinct patient populations that are PD-1 resistant
<b>Predictive Factors</b>	Many unknown factors could influence treatment, specifically a patient's gut bacteria

# Immunotherapy FDA Approvals – Realized Opportunity





# Opportunities for Improving Patient Survival

## **T cells activation works**

CAR-T, T cell engagers, microbiome, others

## **Patient selection works**

MSI, TMB, PD-L1

## **Paradigm shift**

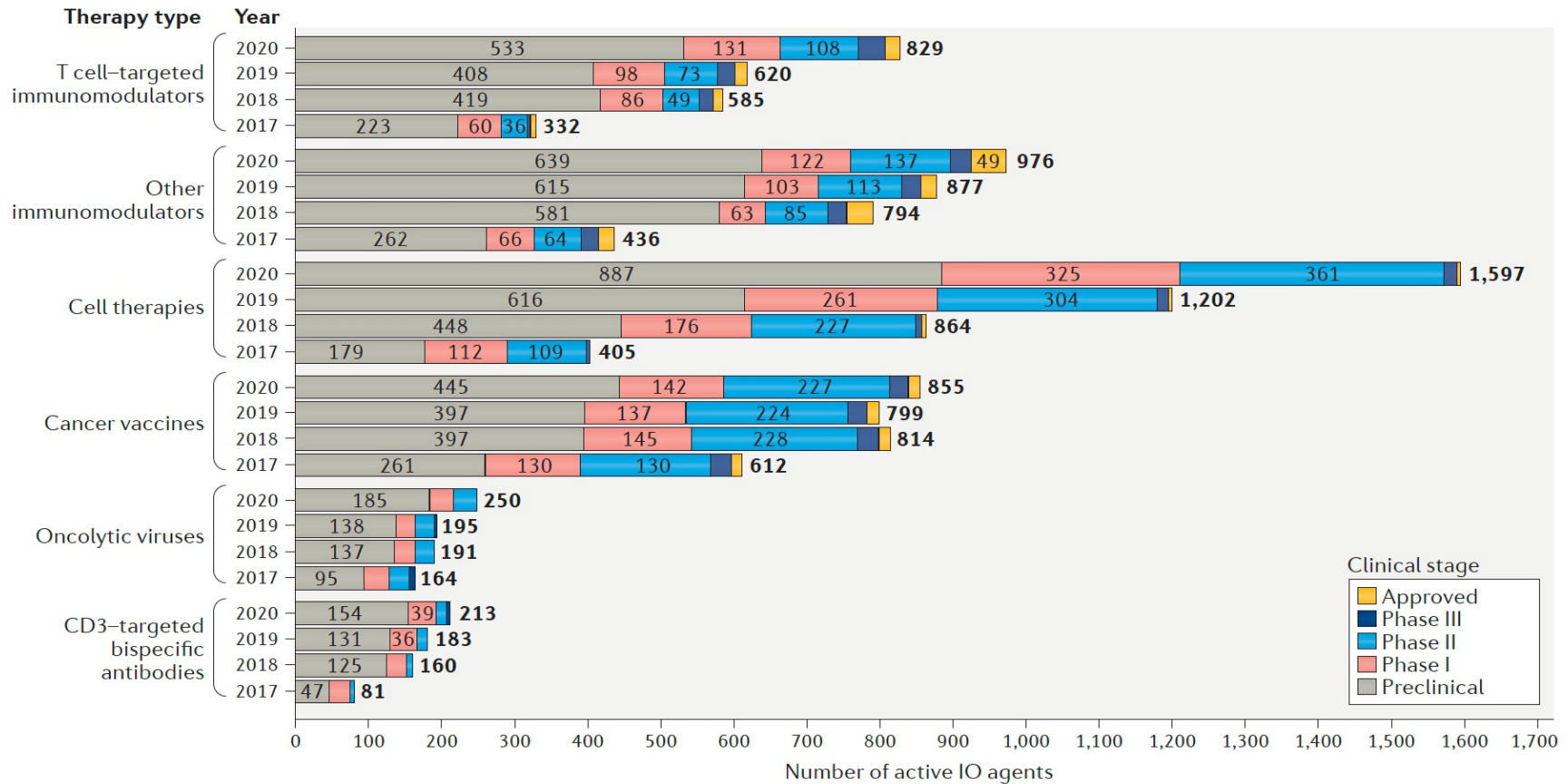
Tumor agonistic, pan or multi-tumor approaches based on immune state, blood-based approaches (liquid biopsy)

## **Enable biomarker technologies**

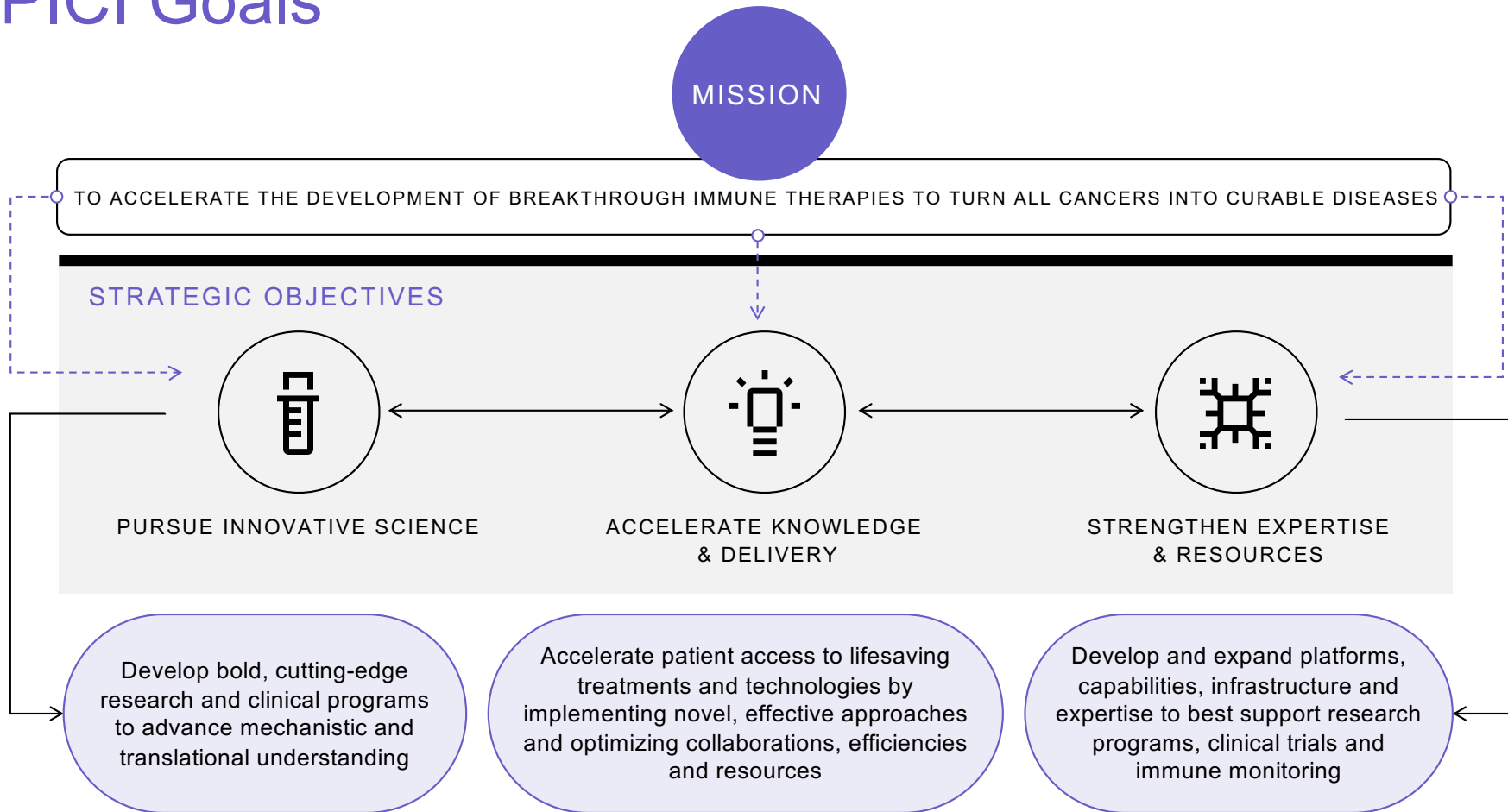
Multomic analysis keeps expanding; tumor biopsies more common



# Immunotherapy Approaches Under Development



# PICI Goals





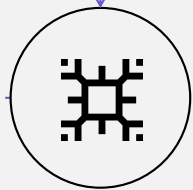
LOOKING FORWARD

# Leverage Collaboration and Robust Capabilities



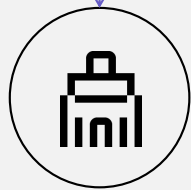
LEAD INVESTIGATOR  
Robert Vonderheide, MD, DPhil

PRINCE



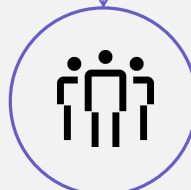
TRANSLATIONAL SUITE

Validate panels across multiple assays



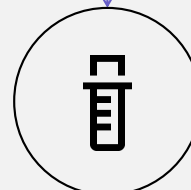
CLINICAL

Deliver high quality clinical data in record time



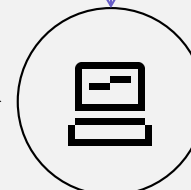
COLLABORATION

PICI, 7 research institutions, CRI, biotech & pharma partners



BIOTRUST

Centralize and standardize sample collection, processing and archiving



INFORMATICS

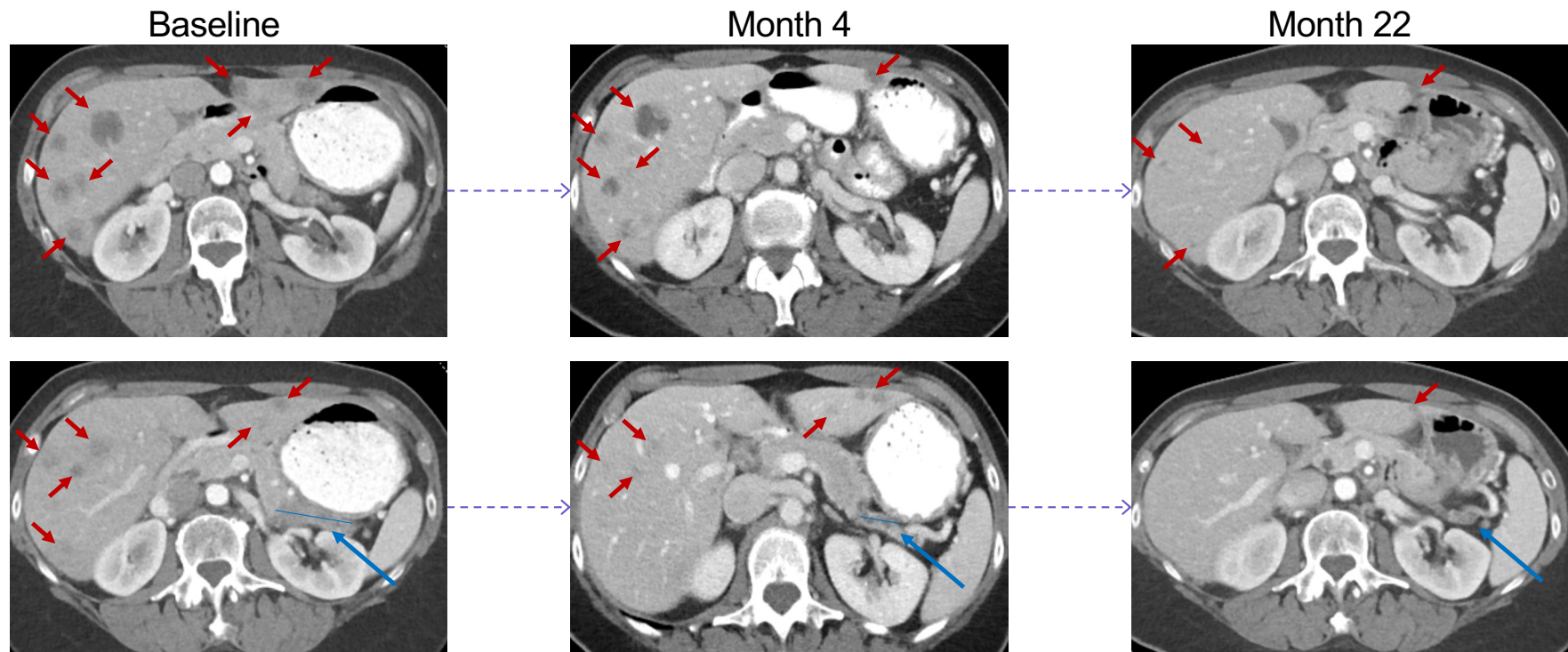
Deep data analysis and data integration

Combining immunotherapy with chemotherapy shows promise for treating advanced pancreatic cancer, shrinking tumors in a majority of evaluable patients – **20 out of 24**

RESULTS



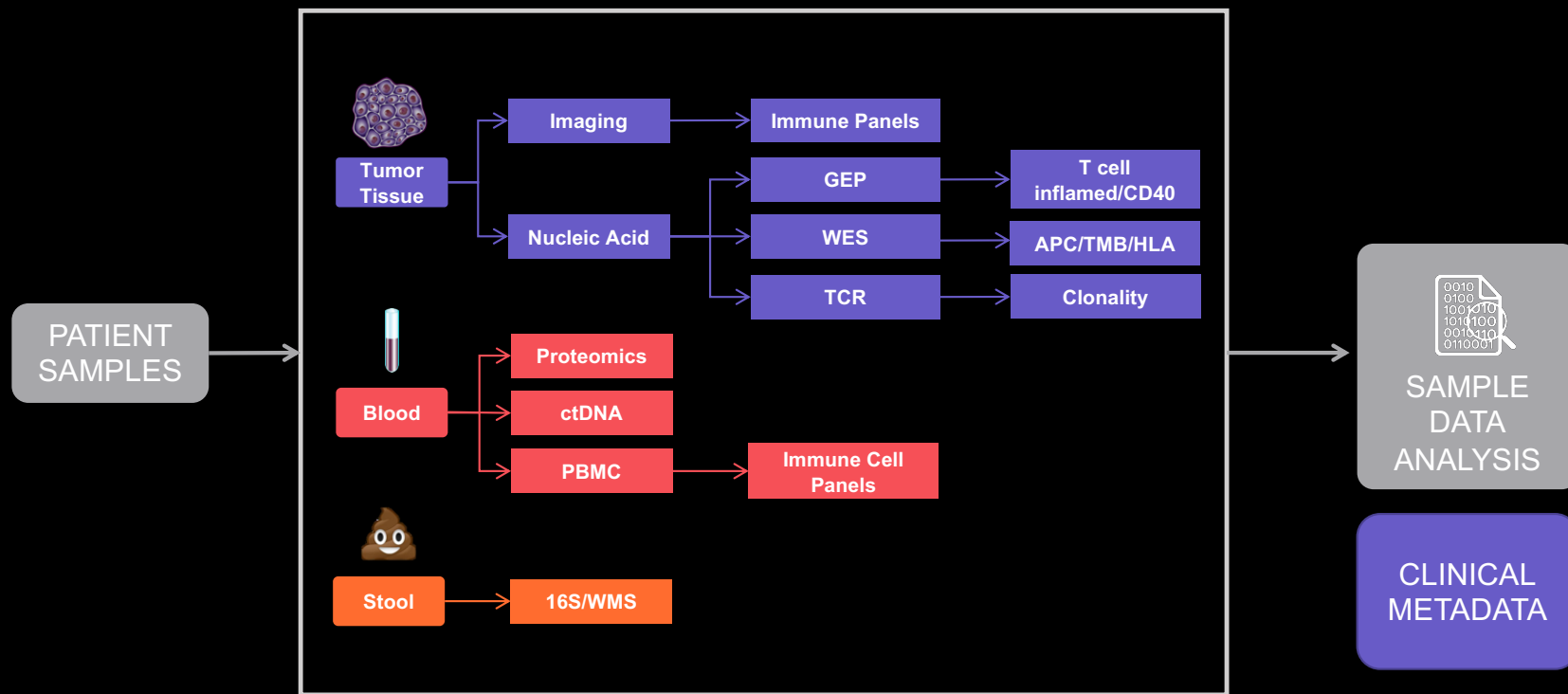
# Before and After: Patient Scans Demonstrate Significant Tumor Shrinkage



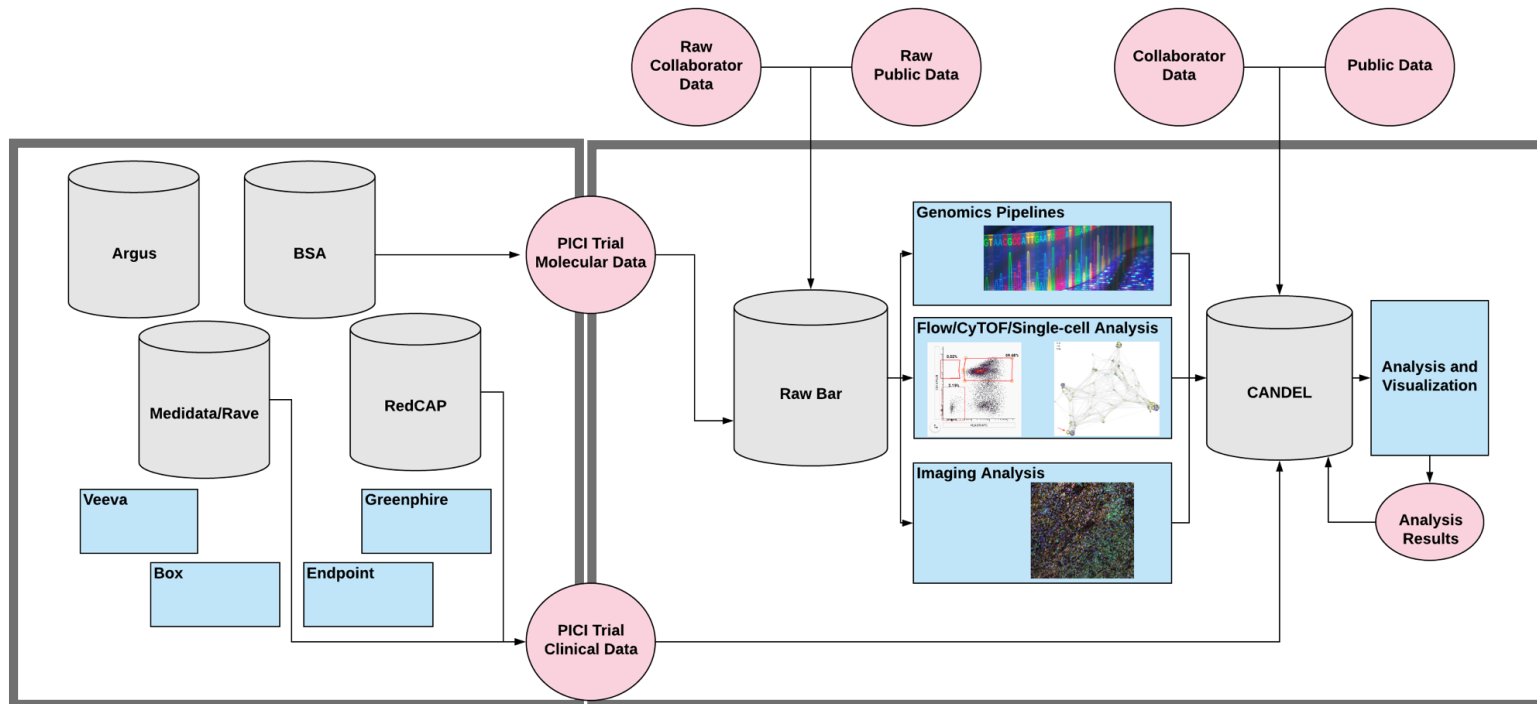
- ↓ Liver metastases
- ↓ Primary pancreatic cancer

66 year old female with metastatic pancreatic adenocarcinoma who initially had more than 50 liver metastases enrolled on the clinical trial and being treated with gemcitabine, nab-paclitaxel and APX005M, currently still undergoing active treatment for nearly 2 years

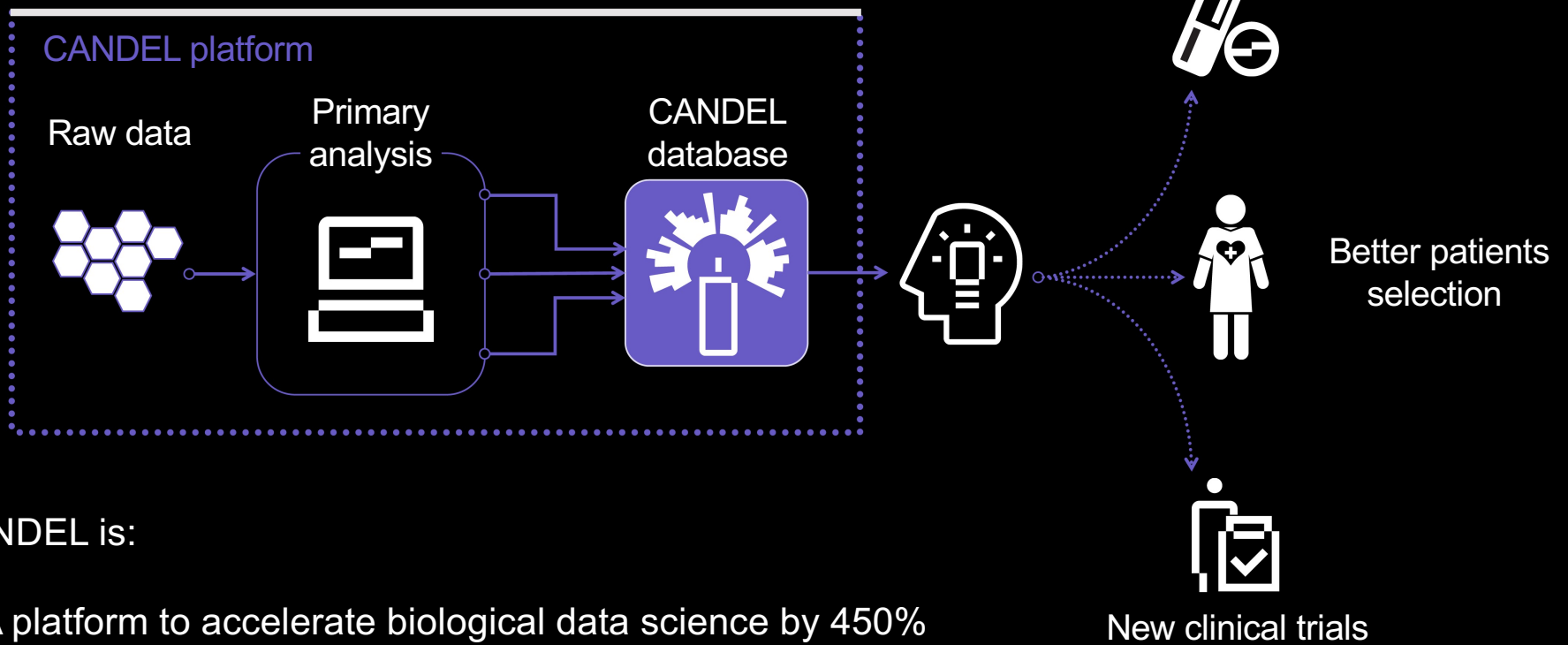
# PICI Translational Suite: Multi-omic Longitudinal Analysis



# Systems and Infrastructure to Enable Integrated Reporting - Clinical and Biomarker



# The CANDEL Platform for Biological Data Science

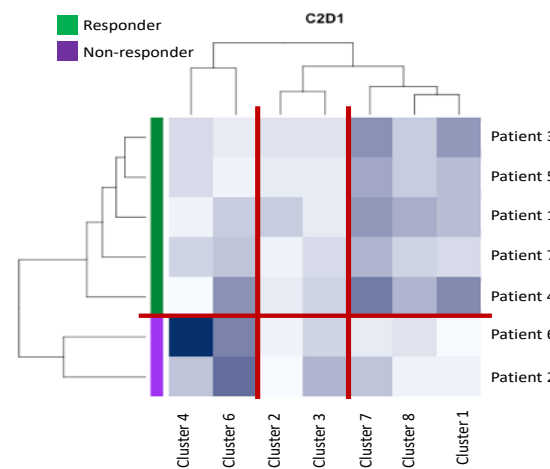
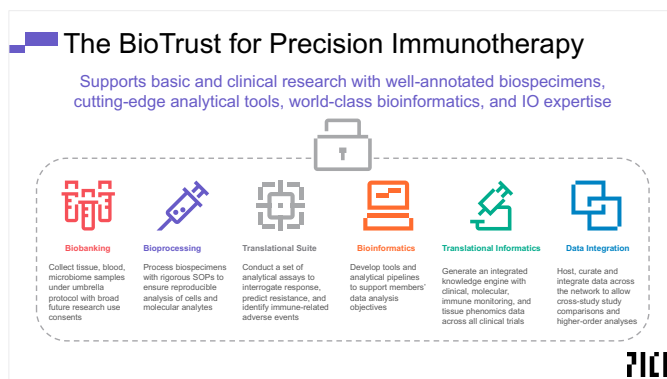
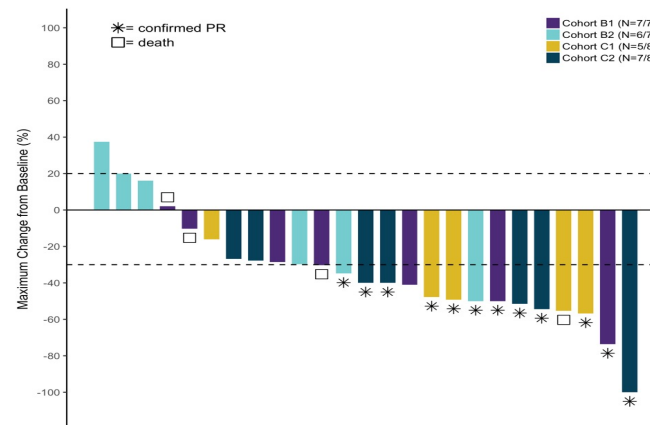
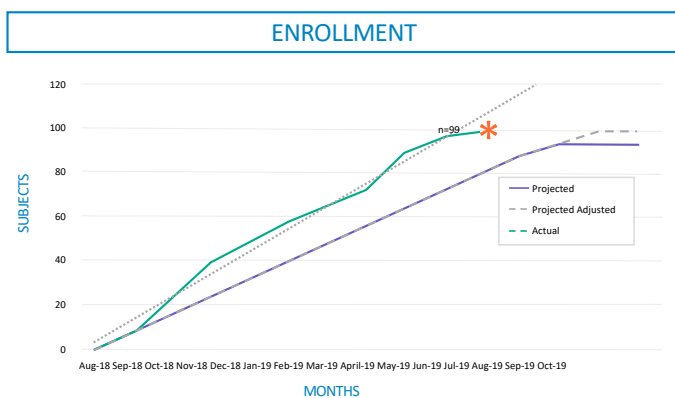


CANDEL is:

- A platform to accelerate biological data science by 450%
- A curated data collection comprising almost 40000 samples



# Delivering on the Promise: Innovative, Fast, Nimble, Highest Quality



# Immunotherapy for Pancreatic Cancer

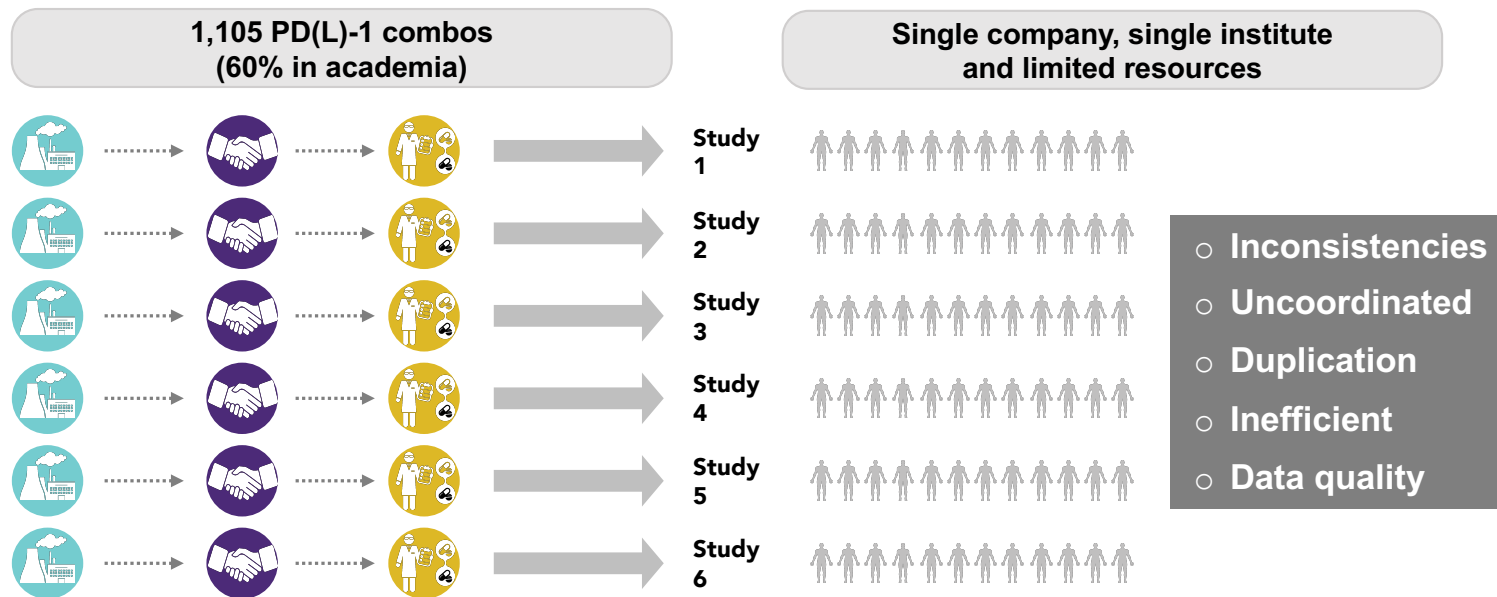
**What we have learned** Activating an antitumor immune response is possible. Not all patients.

**PDAC challenges** Low T cell infiltrate, stroma and immune suppression, low neoantigen burden

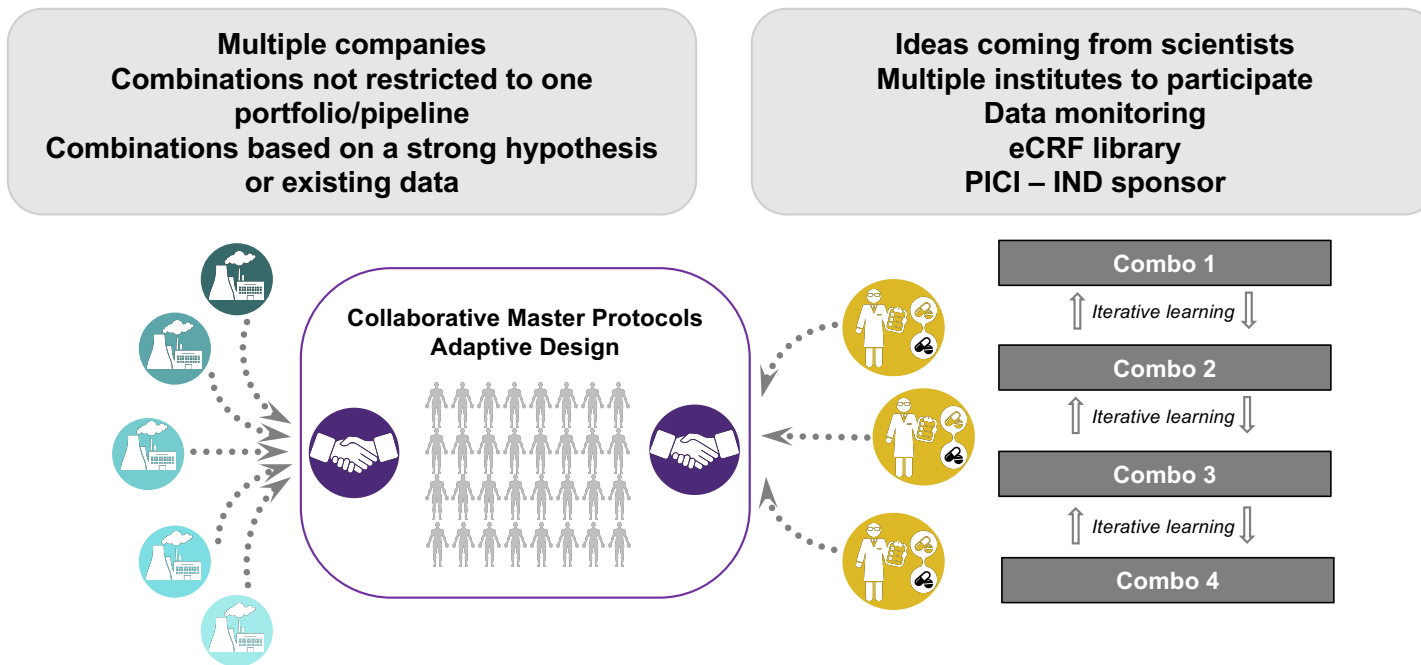
**Science-driven novel combos** Can we leverage the findings to advance PRINCE findings and other clinical hypotheses

**Difficult Tumors** How can we understand more about hot vs. cold tumors so we can clearly define the differences and determine how to best treat them?

# Single Exploratory Studies with Predefined Drugs and Arms



# Adaptive, Biomarker Rich Studies PICI Clinical Trial Platform



# Transform Data into Knowledge to Drive Results



## BIOMARKER PANELS IN PICI TRANSLATIONAL SUITE

- Use this rich clinical and translational data to inform clinical trial testing
- Track many markers (TCF7, TOX, CD38 and CD39, etc.) based on your research interests
- Rely on all of you to contribute and provide input; then integrate everything together in one place



## ADVANCE NOVEL APPROACHES IN HARD TO TREAT TUMORS

- More than PD-(L)1
- Novel dosing schedules
- Cell therapy focus



## INVESTIGATORS PROPOSING BYOC FOR PLATFORM STUDIES

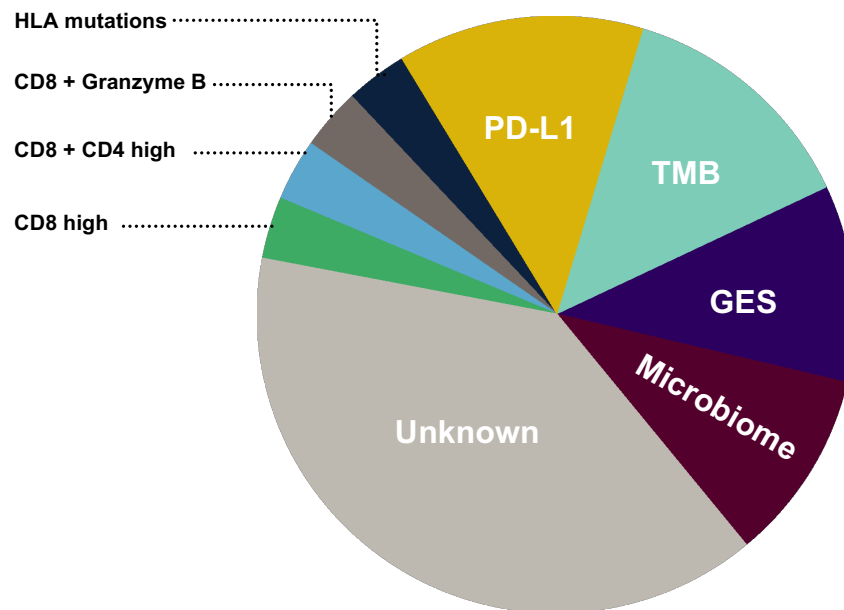
- Tested Bob Vonderheide's combination first through the PRINCE trial
- Looking at previous learnings from your research and adding new combinations



## DATA INTEGRATION AND ANALYSIS

- Working with all of your institutions to integrate data from multiple sources, creating a richer data set
- Provide access to larger data sets that aren't accessible outside of our network

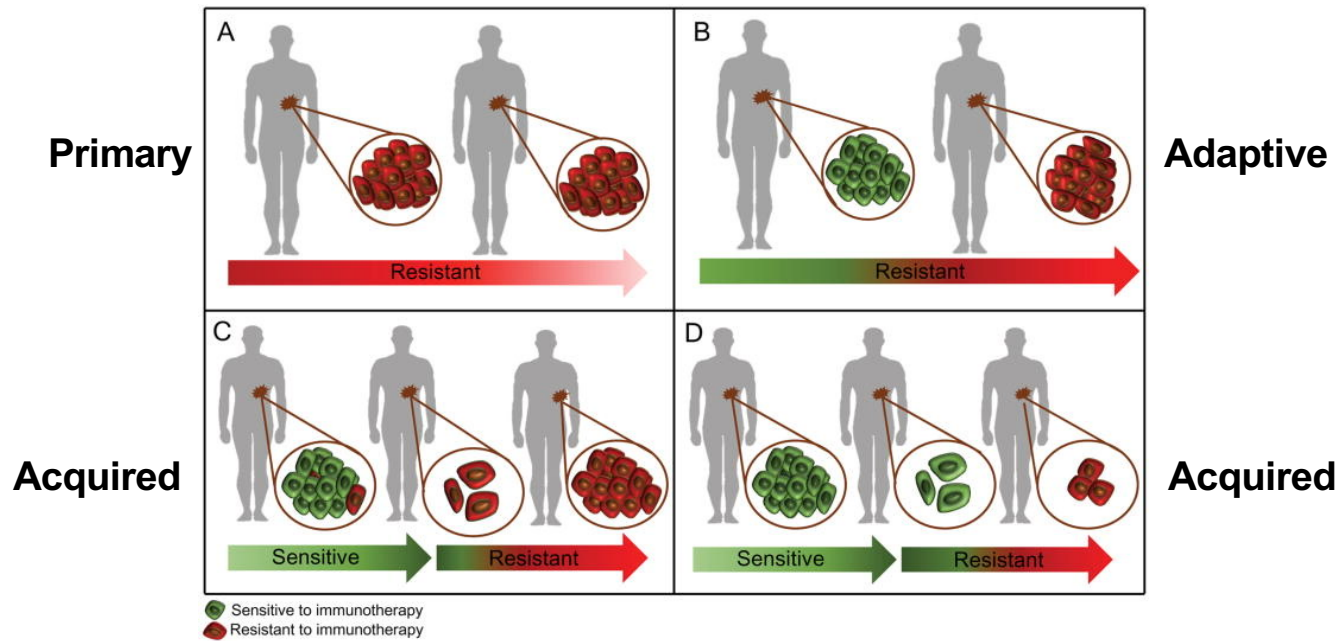
# Defining the Immunogram to Determine Who to Treat and What Combinations



## *Multi-Parameter Predictive Biomarkers for IO?*

- Change of mindset
  - Not a single predictive biomarker
  - Not a single technology
  - May not be stable
- How to integrate different technologies
- Algorithm to inform who to treat and/or exclude from treatment?

# Defining PD-1 Resistance



**(Several) intrinsic and extrinsic tumor factors lead to PD-1 resistance.**

## PD1 Resistance

### Definition

- How to have uniform classification?

### Numbers

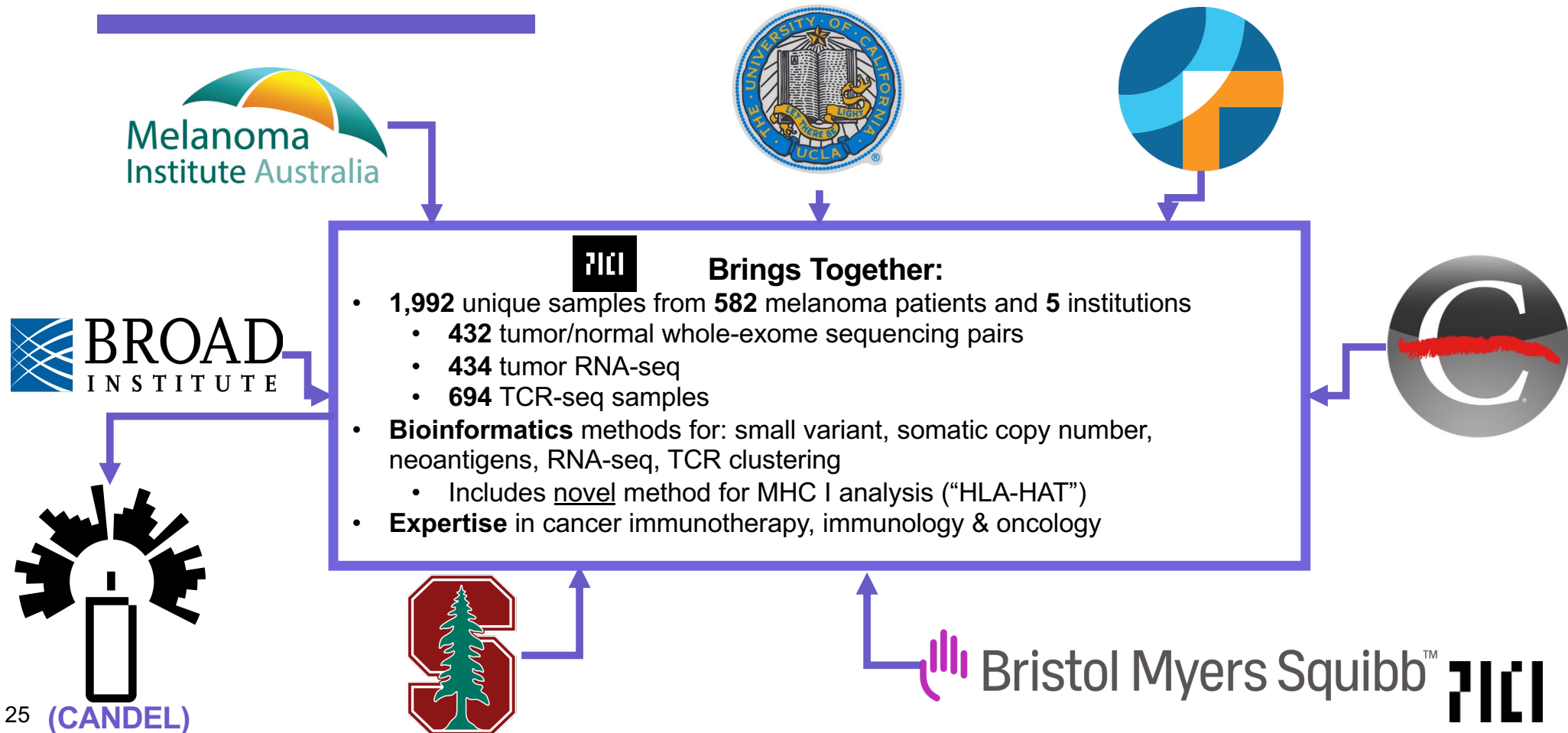
- Multiparameter analysis hard to define in small trials

### Data Sharing

- A major hurdle



# MORRISON: Unite Scientists (and Data) to Understand Immunotherapy Resistance



## Project Example: MORRISON

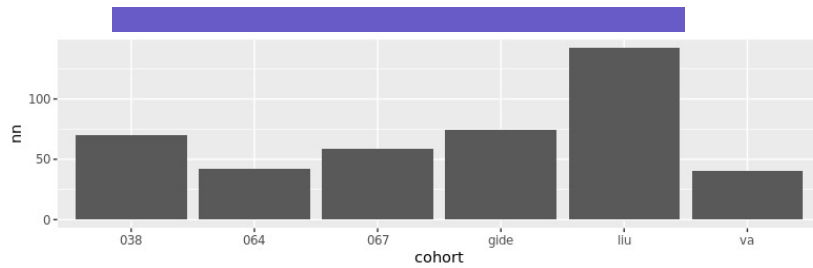
- **Goal:**
  - Integrate and harmonize existing and new molecular + clinical data from melanoma patients treated with immune checkpoint blockade.
  - Develop and apply best-in-class bioinformatic methods for whole-exome seq, RNA-seq and TCR-seq.
  - **Core question: what are the molecular subtype of resistance to ICI in melanoma?**
- Partnership with Ribas lab at UCLA has accelerated efforts.
- Shared effort (funding and data) PICI, BMS and CRI



Bristol Myers Squibb™



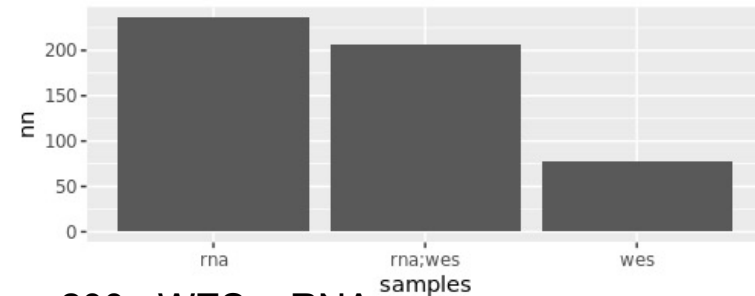
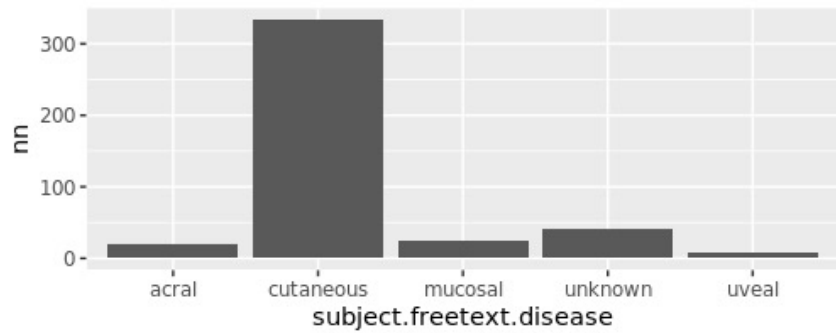
# MORRISON Cohort Overview



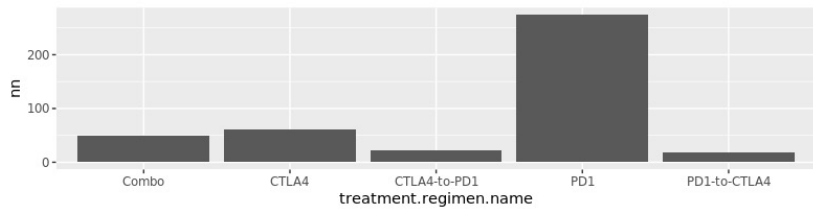
N = 427  
(post filtering)

All subjects have these fields annotated:

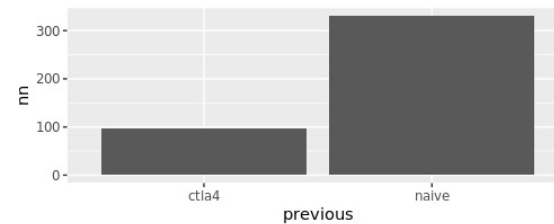
- Melanoma subtype
- Previous CTLA-4
- RECIST response to treatment
- Gender
- Age



200+ WES + RNA  
250 RNA only ; ~80 WES only  
80% are from pre-treatment



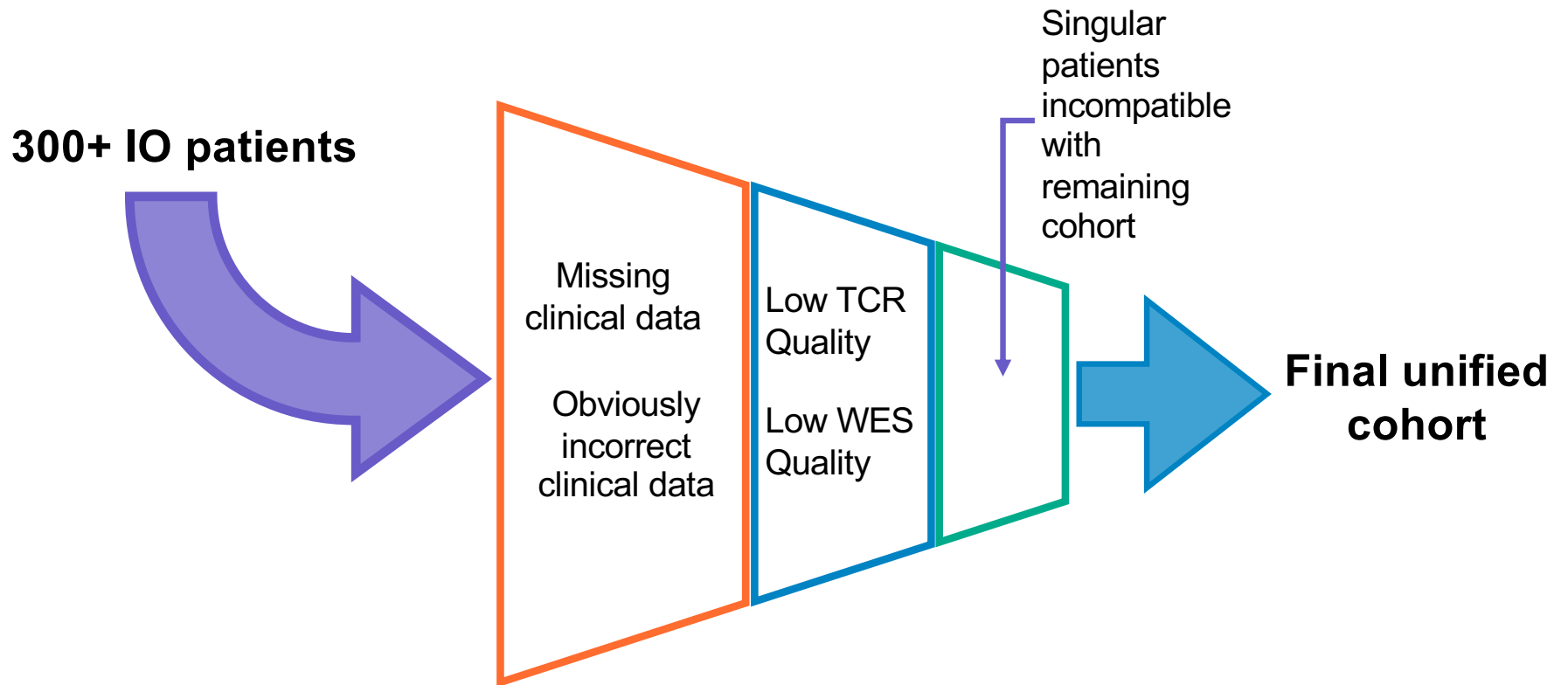
Most patients are treated with PD1



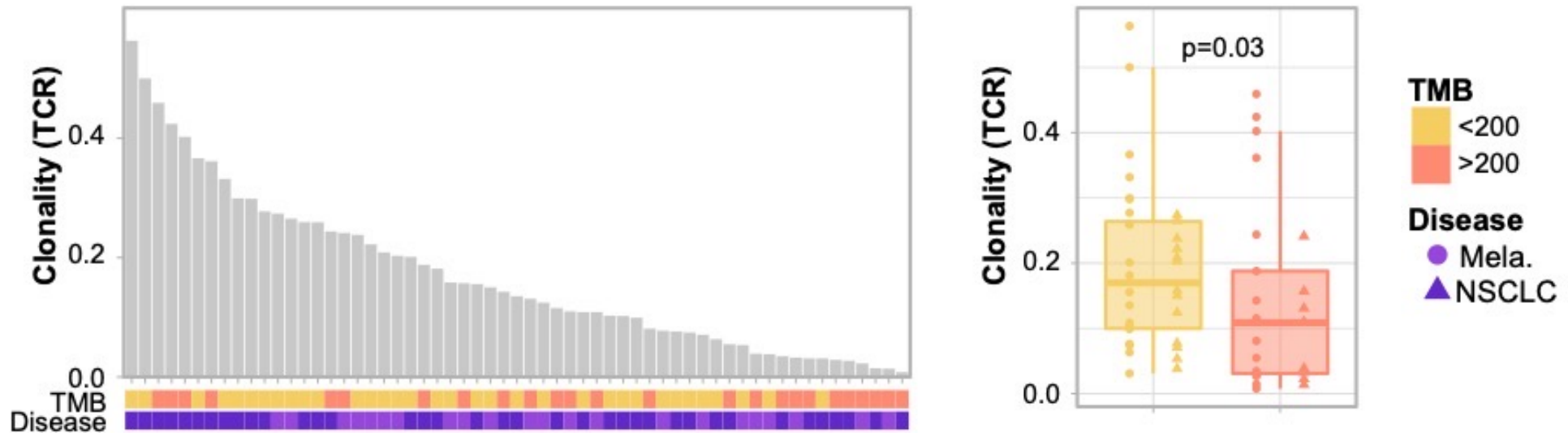
~75% of ipi-naïve at time of treatment.



# Traverse The Data Funnel For Question Of Interest



# TMB Status is Associated with TCR Clonality



**“The total number of mutations in a tumor affect how the immune system responds to it”**

# MORRISON Results: The Power of Integrated Data

## Background:

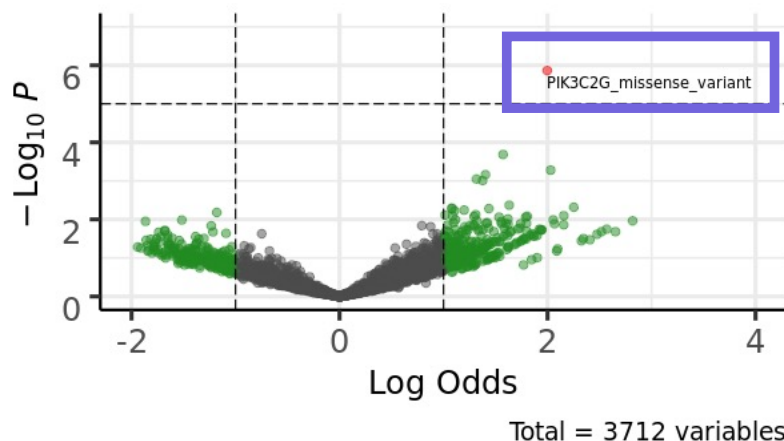
- To date, no single cancer mutation has ever been found to associate with immunotherapy response.

## Approach:

- Develop **novel machine learning method** to sensitively detect point mutations associated with response, controlling for other factors.
- Apply method to **largest cohesive immunogenomic database** of melanoma ICI patients.

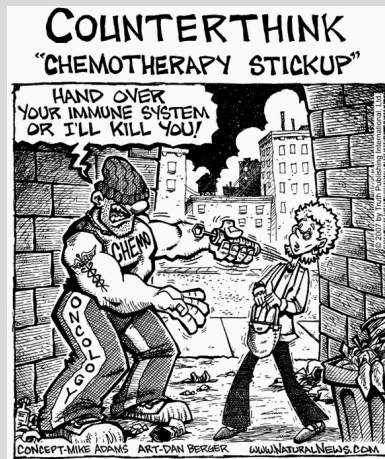
## Results:

- Identified a single mutation associated with response to ICI.
- Signal validates in 4 independent cohorts.
- Independent of TMB, treatment status.



# Changing the Paradigm for Oncology Treatment

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## IMMUNOTHERAPY



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- Re-educate the immune response to treat tumors as **non-self**
- Unleash the immune system brakes and turn on the gas
- Specificity, memory, durability and infectious anti-tumor activity

# Addressing the Unwanted Side Effects of Immune Therapy

## IMMUNE THERAPY AND SIDE EFFECTS:

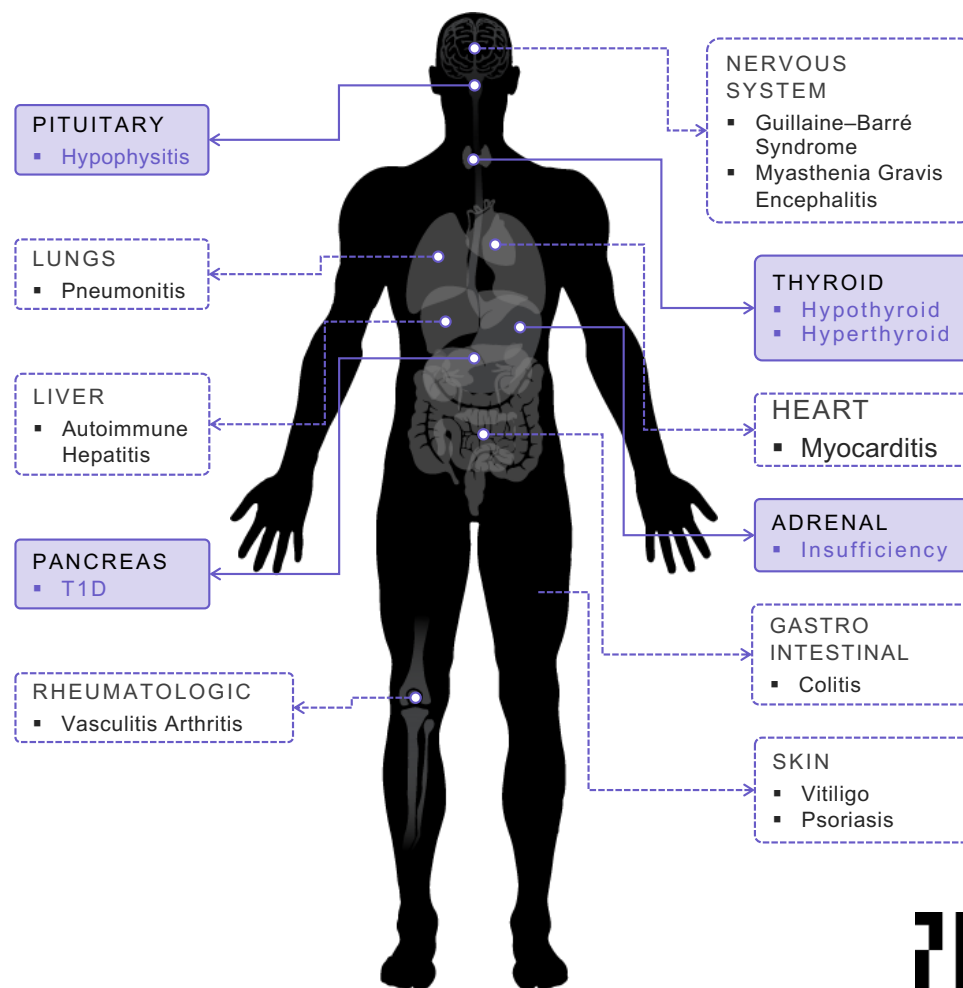
- Treatments can lead to autoimmune disease

## CONSORTIUM APPROACH:

- PICI, academic labs, cancer centers, foundations, pharma and government institutions

## GOALS:

- **Identify at-risk patients** early to reduce the incidence and/or severity of such events
- **Understand the mechanisms** behind autoimmunity following therapy
- **Determine the overlap** in mechanism with “classic” forms of autoimmune disease







LOOKING FORWARD