Sparkathon Project TimIOs: A Pooled Analysis of Durable vs. Transient Responders on Immunotherapy Trials

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- **On behalf of Team TimIOs**

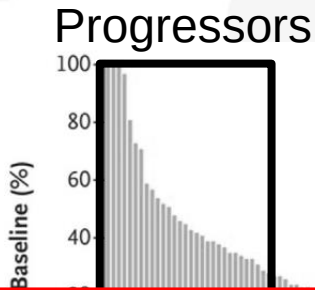
Disclosures

- Research funding: Merck (YGN), Bayer (RFS), BMS (RFS)
- Consulting: Array BioPharma (YGN), Puma (RFS), BMS (RFS), Eisai (RFS), Exelixis (RFS)
- Honoraria: BMS (RFS), Exelixis (RFS), Medscape (RFS)

Background

- Immunotherapy is standard of care for many solid tumor types
- 20-40% of patients respond to anti-PD-1
- The majority of patients do not respond
- Little is understood about distinct differences between responders and non-responders
- Compartmentalization of clinical and tissue-derived data
- Need for a unified platform to pool and analyze existing data

Responses to anti-PD-1 are heterogeneous



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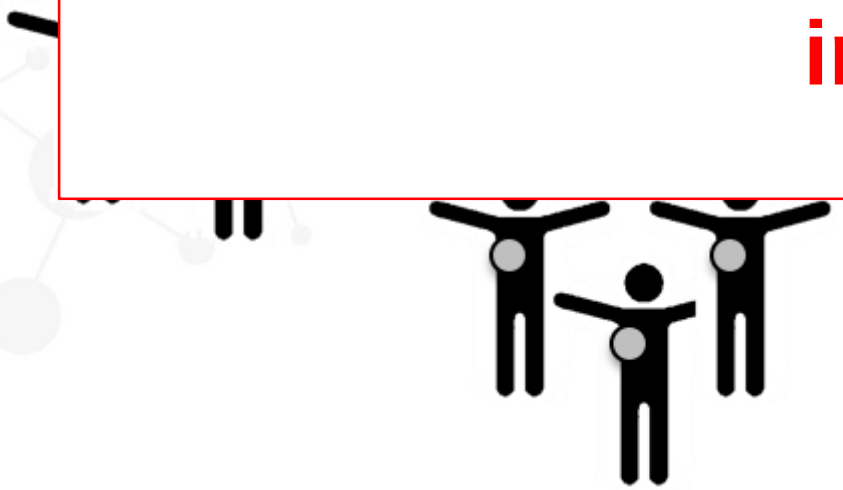
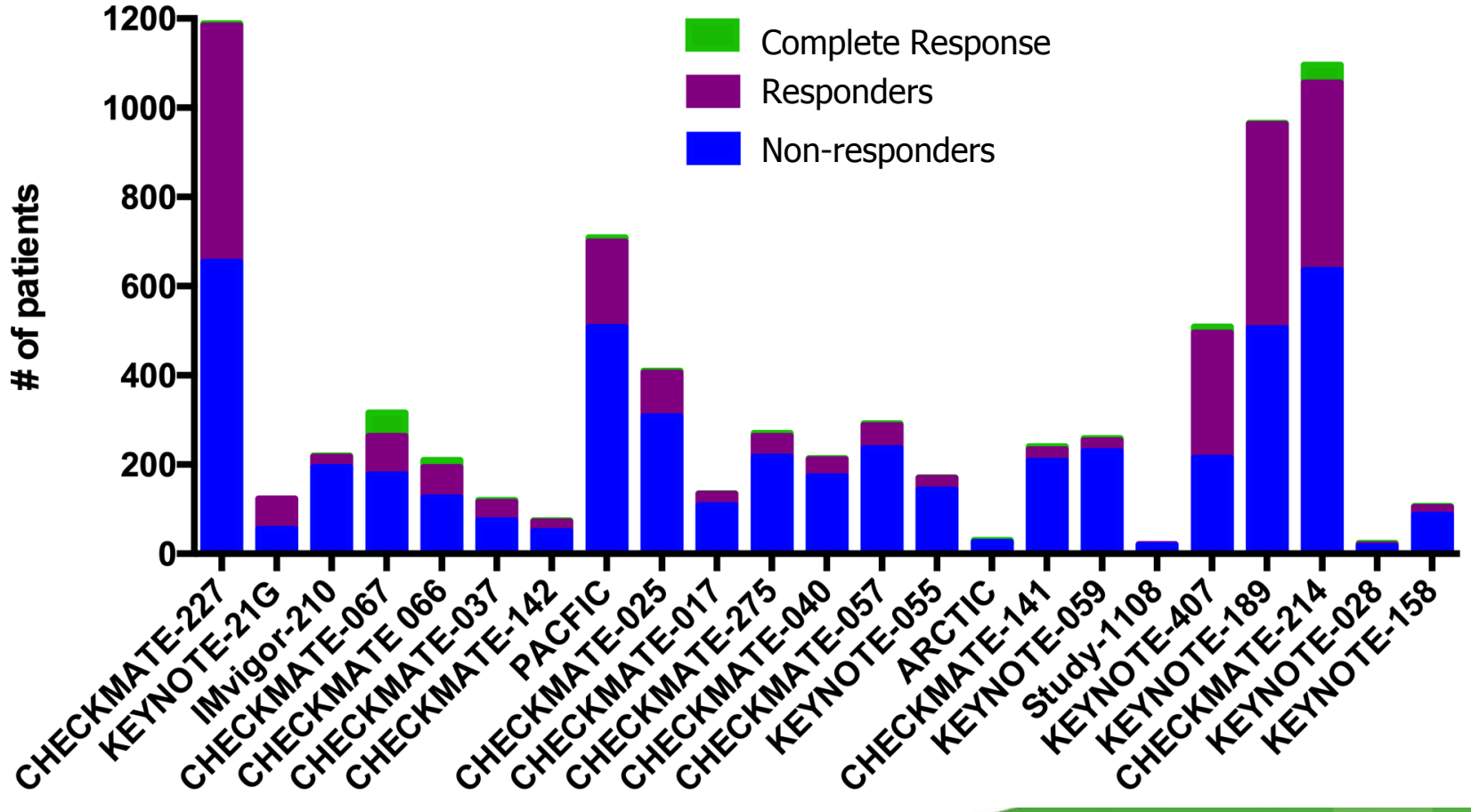
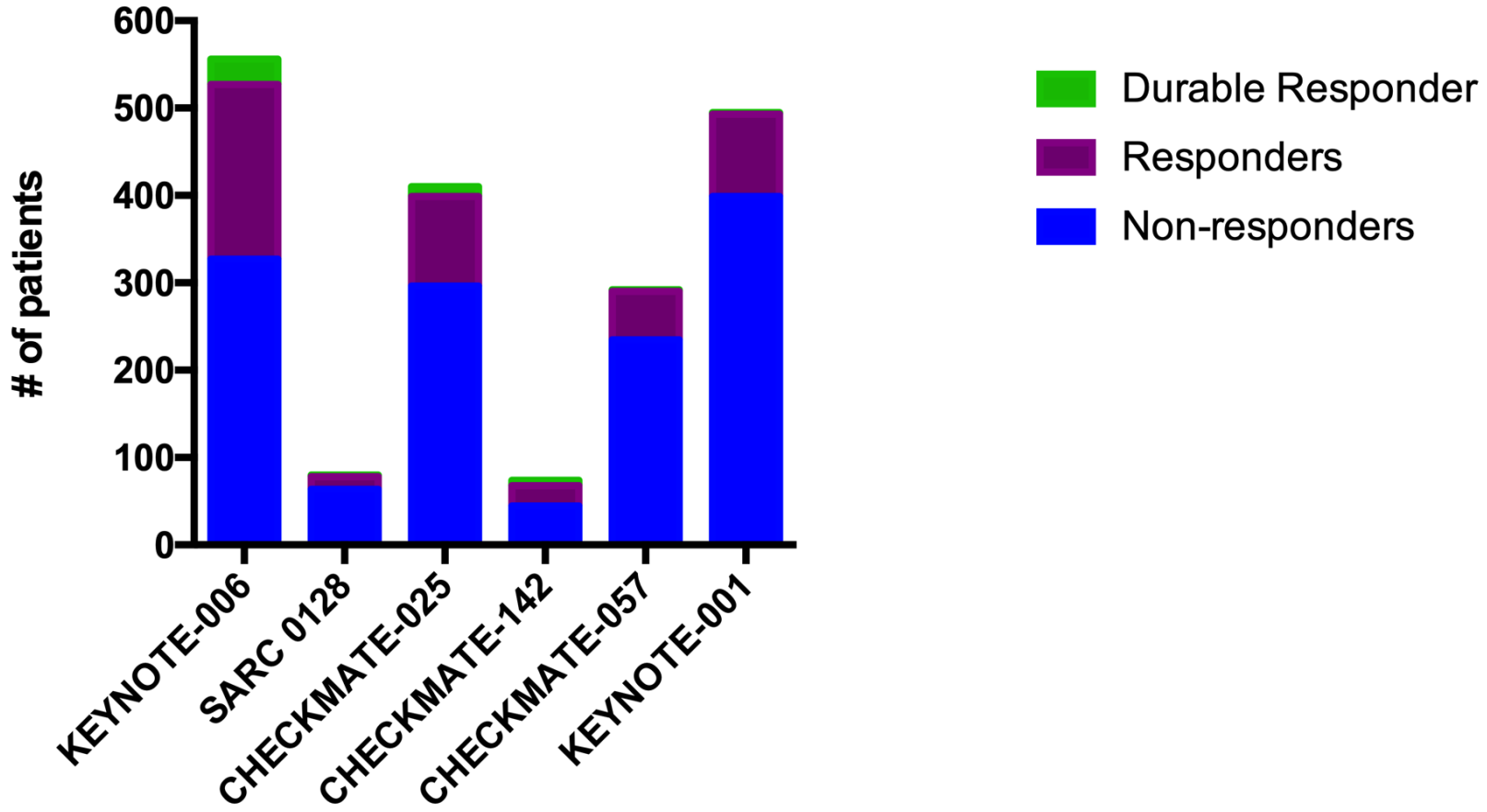


Understanding tumor heterogeneity is critical for developing the tools to predict clinical response to immunotherapy

Responses to anti-PD-1 across studies



Responses to anti-PD-1 across studies



Innovative Solution

- A unified public/private consortium
- An honest broker to facilitate cross-institutional collaboration
- To develop a platform identifying fundamental differences between:

  Durable responders vs. **Transient responders**

  Elite responders vs. **Rapid progressors**

Definitions

Standard (RECIST 1.1):

- Complete Response CR (100%↓)
- Partial response PR (≥30%↓)
- Stable disease SD (29%↑ - 19%↓)
- PD (≥20%↑)

Non-Standard:

- Rapid PD (≥50%↑) by 12 weeks
- Transient response (PR/CR < 6 months)
- Durable response (PR/CR > 2 years)

Comparative populations to analyze:

1- Transient vs. durable response

2- CR (‘elite’ responders) vs. rapid PD

Core Teams

Project Lead: Yana Najjar/Project Co-Lead: Randy Sweis

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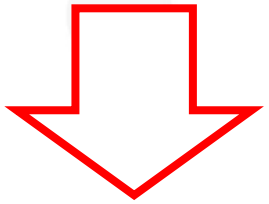
Project Goal

Define gene expression signatures associated with resistance to PD-1 blockade



- Inform on potential mechanisms of resistance
- Develop novel rational combination strategies
- Spare toxicity in patients less likely to benefit

Study Design

1A) Unsupervised approach using existing RNA-seq datasets from pretreatment biopsies to identify immune gene expression signatures distinguishing:

- Transient responders vs. durable responders (primary analysis)
- Elite responders vs. rapid progression of disease (secondary analysis)

Hypothesis: Tumors from durable vs. transient responders have different immune gene expression profiles, which can be used as biomarker of response, patient selection, and novel therapeutic targets.

Study Design

1B) <u>Supervised</u> approach using existing RNA-seq datasets from pretreatment biopsies to determine the impact of known immunosuppressive molecules on the outcome of PD-1 blockade:

- Focus on: PD-1, LAG3, TIM3, IDO1, PD-L1, PD-L2, TIGIT, ITGAM, ARG1, ADORA2A, CD39, CD73 and TGFB1, Foxp3

<u>Hypothesis:</u> Negative immune regulators are overexpressed by tumor and immune cells in the TME of transient vs. durable responders, and in patients with CR vs. rapid PD.

Data Elements

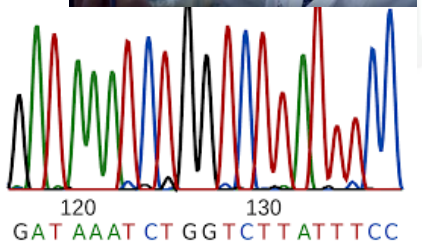
Clinical:

- Primary diagnosis
- Age, sex, race
- Date of metastatic diagnosis
- DFS, PFS, OS on trial
- date of biopsy, biopsy site
- Treatment on trial
- Number of cycles
- Prior therapies

Bioinformatic:

- Summarized gene level expression data
- Raw gene expression data
- Date of sequencing

Proposed Analysis Workflow



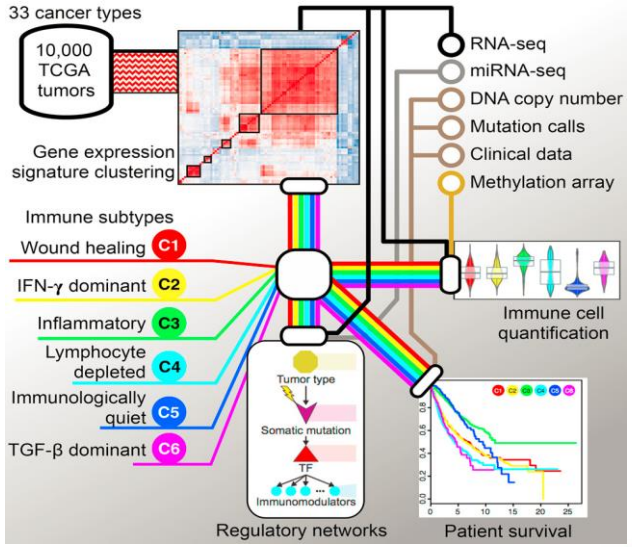
Transfer data

Sequencing QA/QC

Harmonize data

Clinical QA/QC

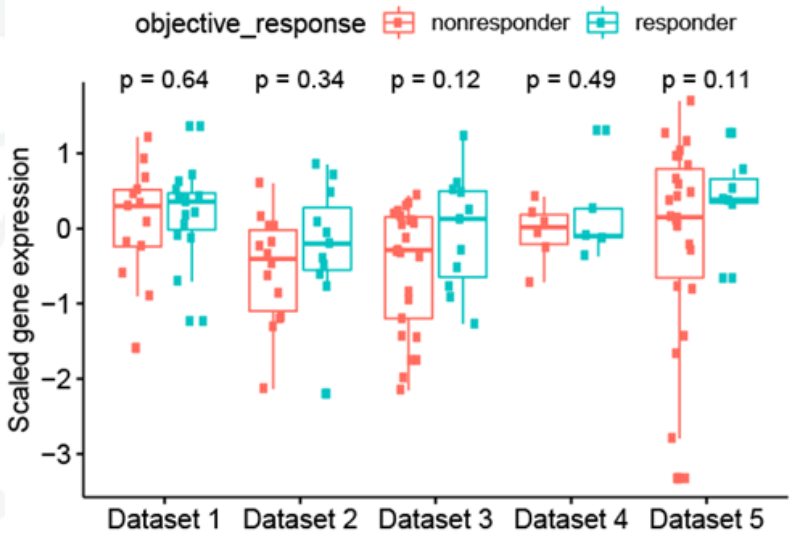
Institute for Systems Biology



Thorsson, V. et al, Immunity. 2018 Apr 17;48(4):812-830

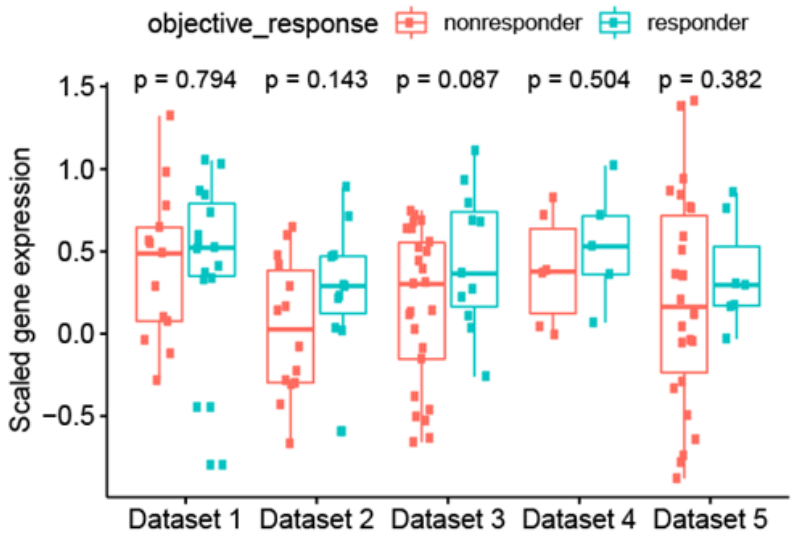
Selected Pilot Data (N = 170)

CD3



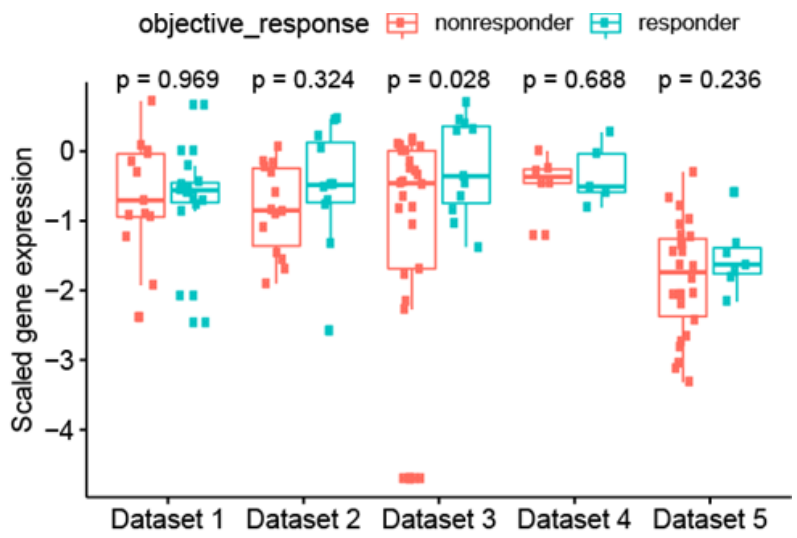
ANOVA, p=0.036

IRF1



ANOVA, p=0.042

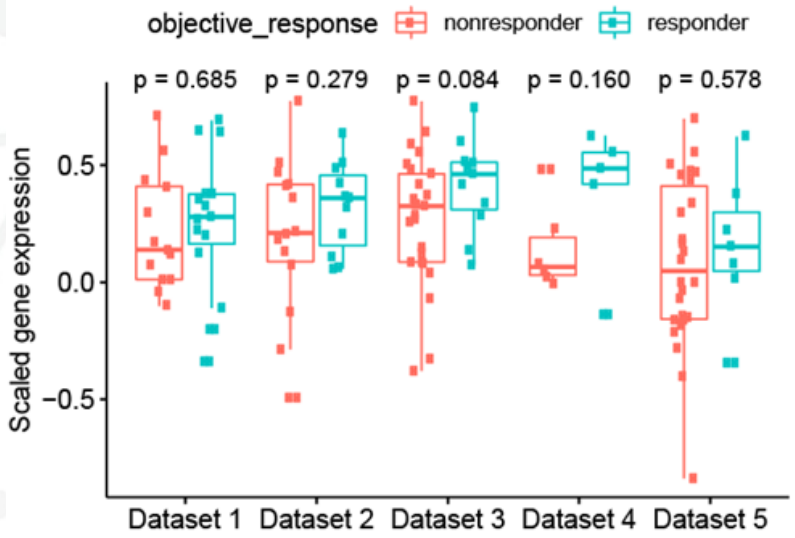
TIGIT



ANOVA, p=0.044

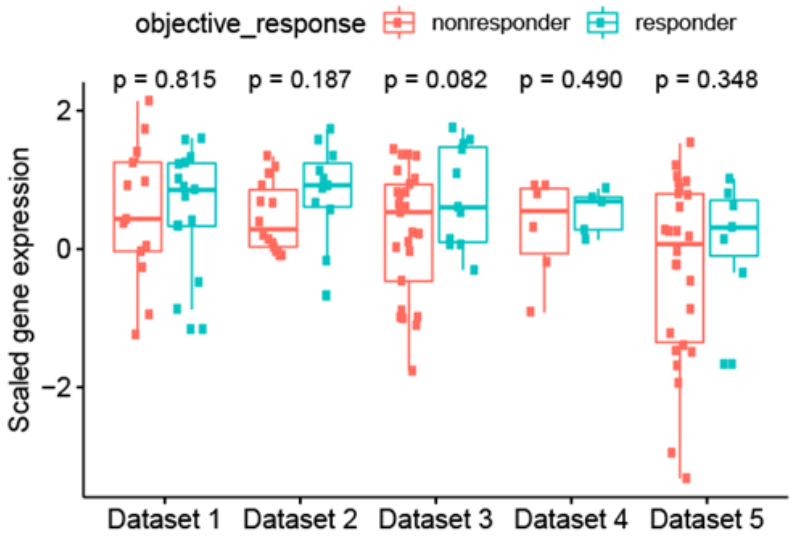
Selected Pilot Data N=170

BCL6



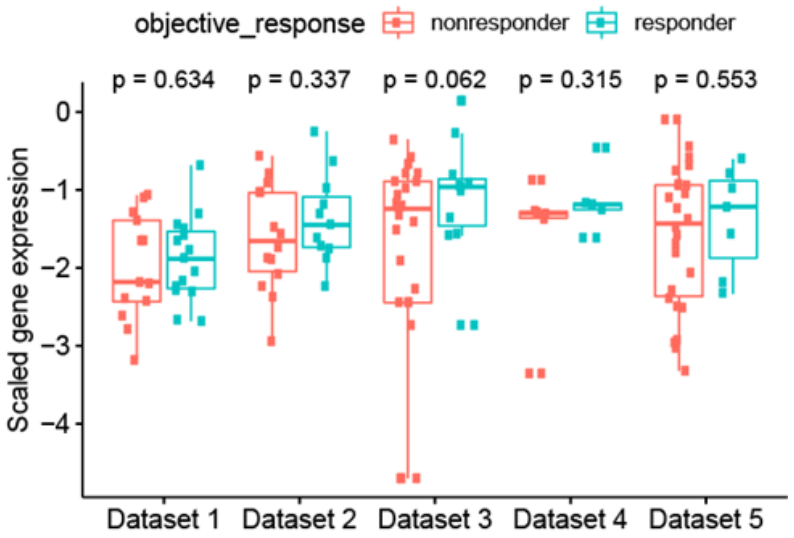
ANOVA, p=0.038

CXCL9



ANOVA, p=0.053

FLT3



ANOVA, p=0.041

Summary

- Pilot study demonstrates ability to integrate data across datasets in terms of clinical response
- Increasing the pool of harmonized datasets from individual onco-immunology trials is expected to increase power of analyses
- We continue to expand our collaborations with several partners
- Additional partners and datasets are needed and welcome

Acknowledgements - Thank you!

Advisory Committee

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Financial Support

AstraZeneca
Incyte
Amgen
Genentech
Anonymous Donor

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