# Part II – paper discussion

Article

# Personalized RNA neoantigen vaccines stimulate T cells in pancreatic cancer

https://doi.org/10.1038/s41586-023-06063-y

Received: 10 January 2023

Accepted: 6 April 2023

Published online: 10 May 2023

Open access

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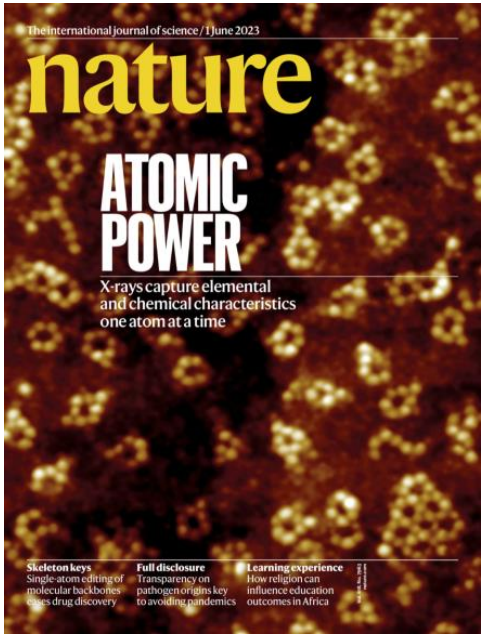
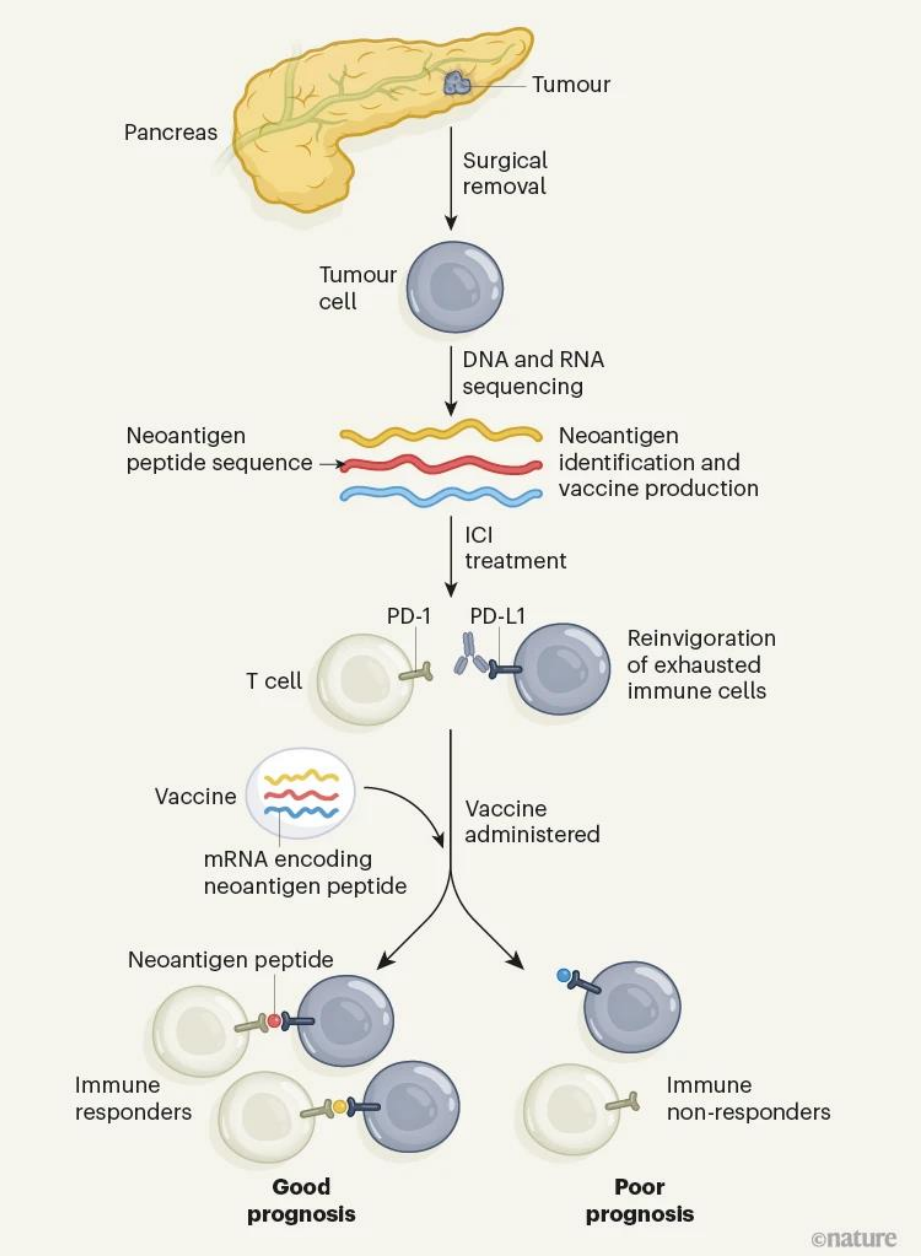



*Nature* 618, 144–150 (2023).

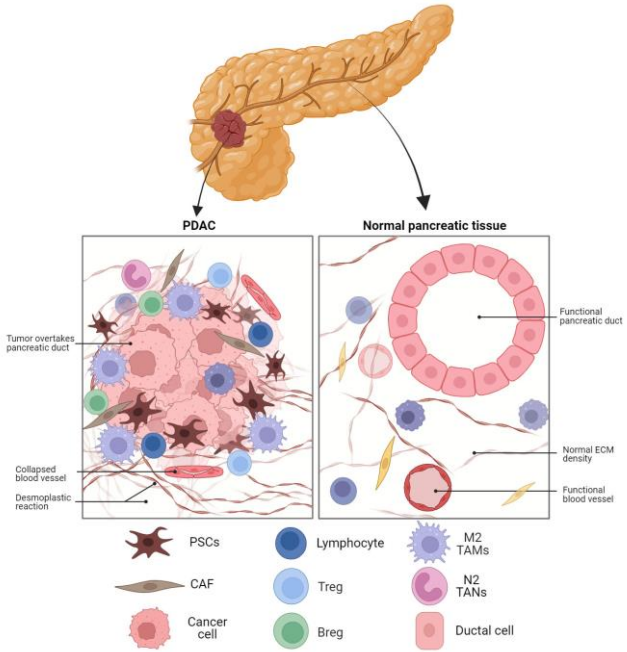
# Story at a glance






*Commentary: Huff AL and Zaidi N., 2023. Nature*

# Background



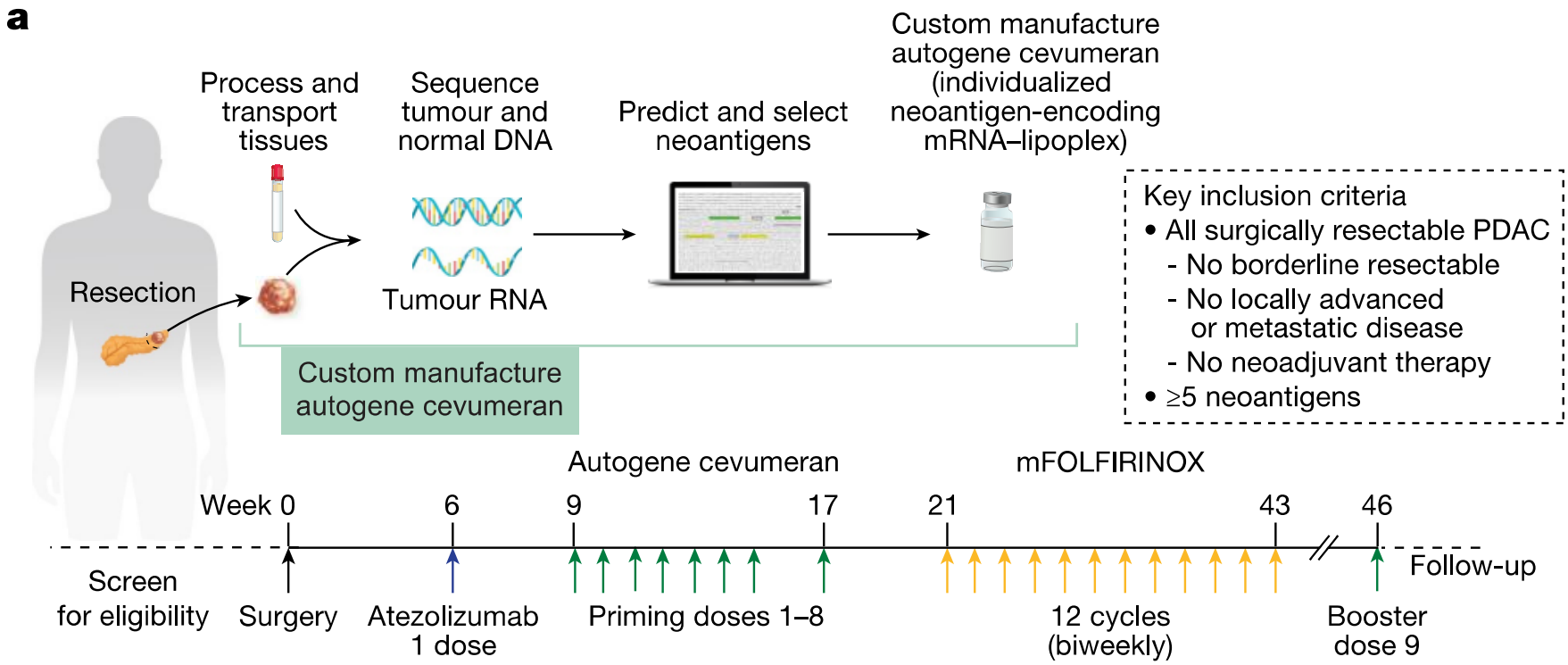

- **Pancreatic ductal adenocarcinoma (PDAC)**
  - only 20% operable
  - 90% recurrence after median 8 months
  - 5 year overall survival < 10%
  - 5 year OS after adjuvant chemotherapy < 30%

- KRAS mutation as driver mutation; but **low overall (*passenger*) mutation rate**
  - → usually non-responsive to immune checkpoint inhibitors
  - → but subset of patients known to have higher mutation rates and better prognosis

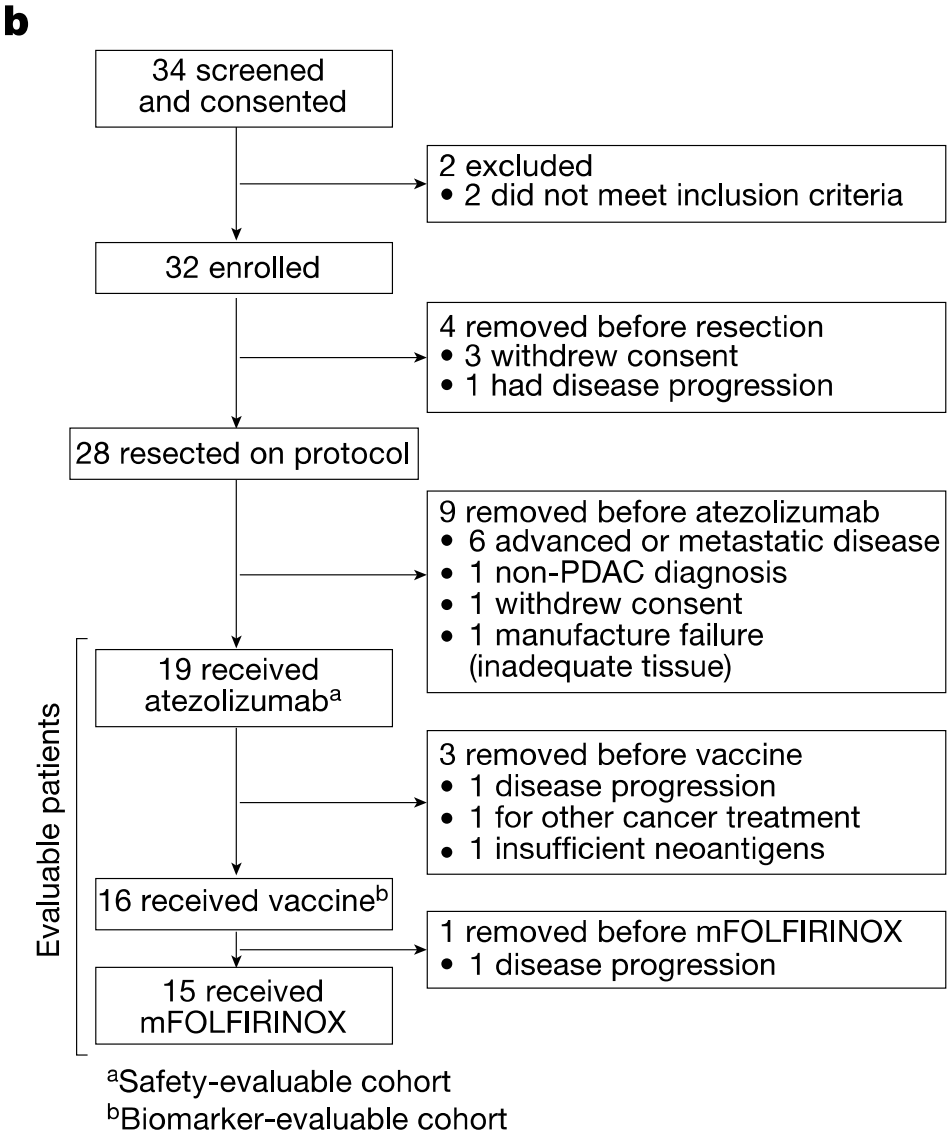
# Approach

- 16 pancreas cancer patients
- phase 1 clinical trial: adjuvant **personalized neoantigen mRNA cancer vaccine**
- **up to 20 neoantigens** per vaccine compound
- **co-treatment with checkpoint inhibitor** anti-PD-L1 (atezolizumab)
- co-treatment with four-drug chemotherapy
- Study endpoints:
  - Neoantigen-specific T cell immunogenicity assay
  - 18 month recurrence-free survival

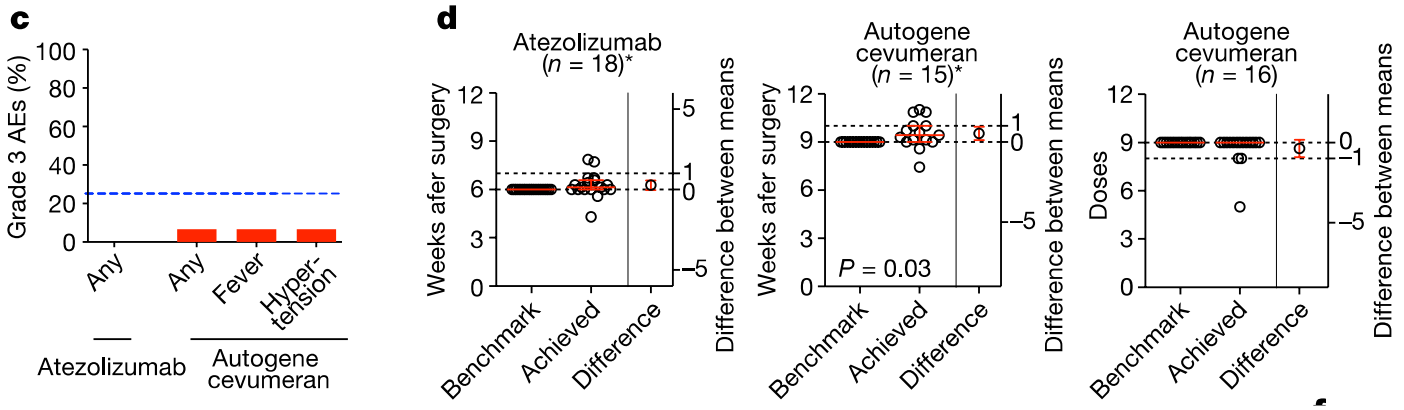
# Trial design



# Patient selection

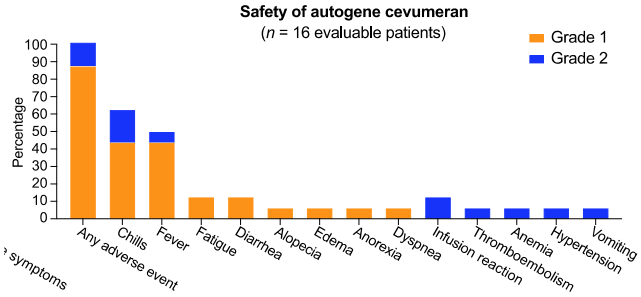


# Individualized mRNA neoantigen vaccines are safe and feasible

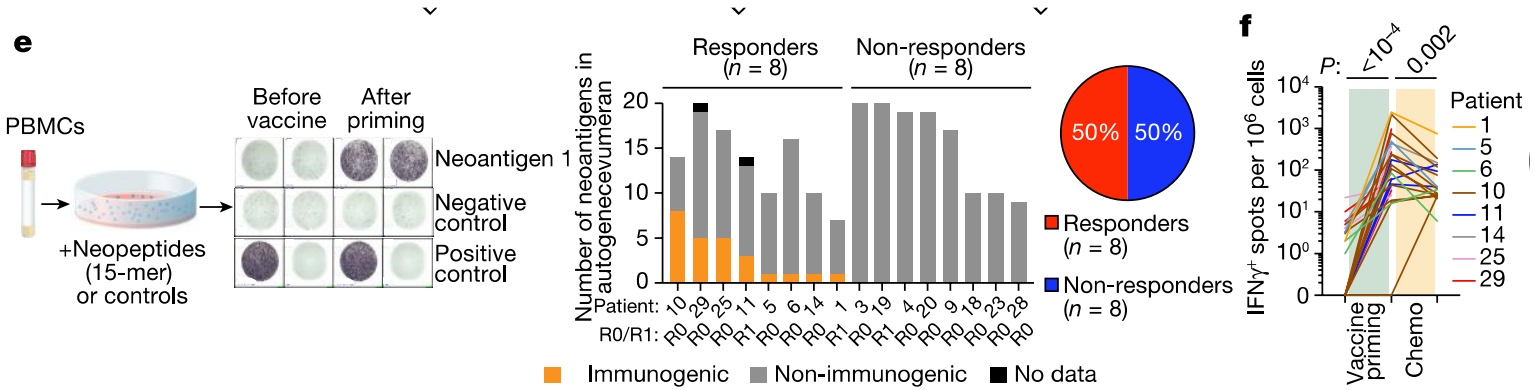



- Very **safe** (only 1/16 patient showed grade 3 adverse reaction to vaccine)
- "needle-to-needle" time **9-10 weeks**
- Most received **8 priming + 1 boosting doses** of mRNA vaccine

Suppl. Fig1



# Individualized mRNA neoantigen vaccines are immunogenic



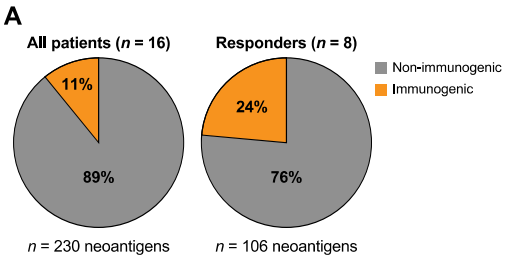

**Exemplary ELISpot**

**CAVE: Only minority of included neoantigens are immunogenic**

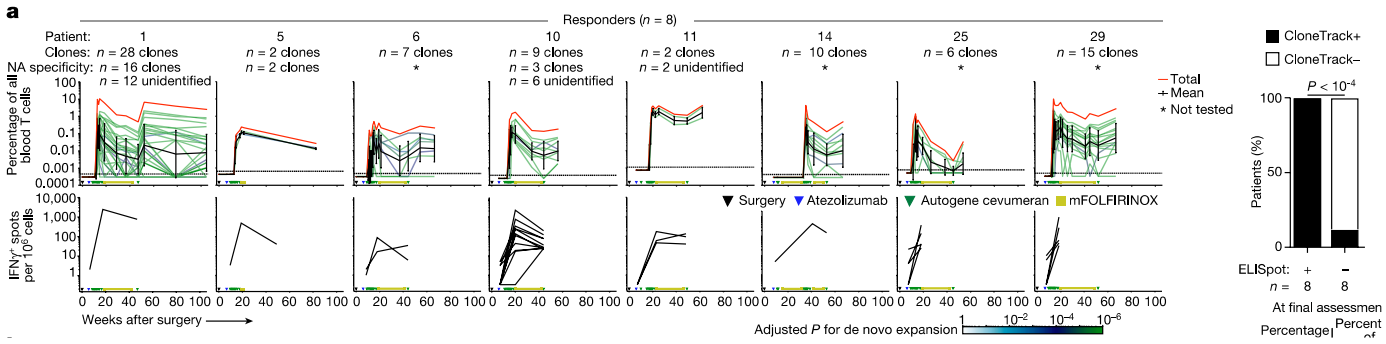
**de novo response**

**50% of patients showed measurable immune responses against neoantigens**

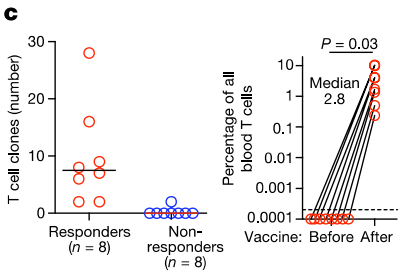
**But only minority of all neoantigens responded to!**



# mRNA vaccines expand effector CD8+ T cells

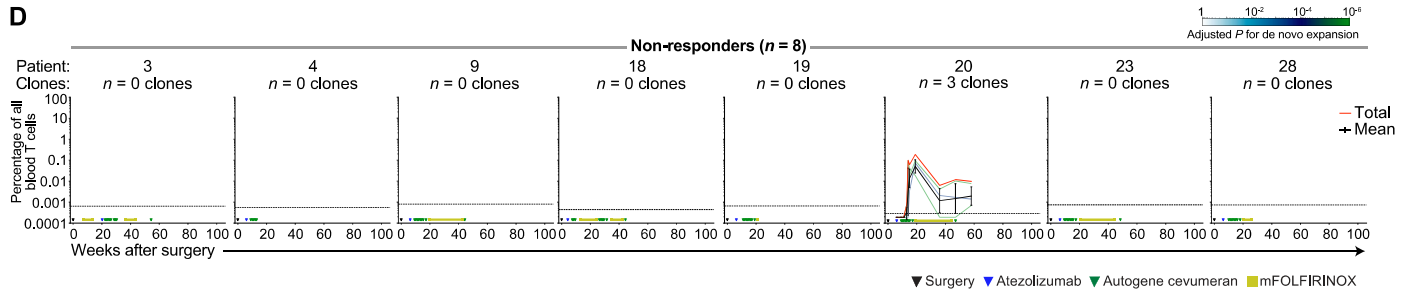



Upper: TCR sequencing ("CloneTrack")
Lower: ELISpot
Right correlation

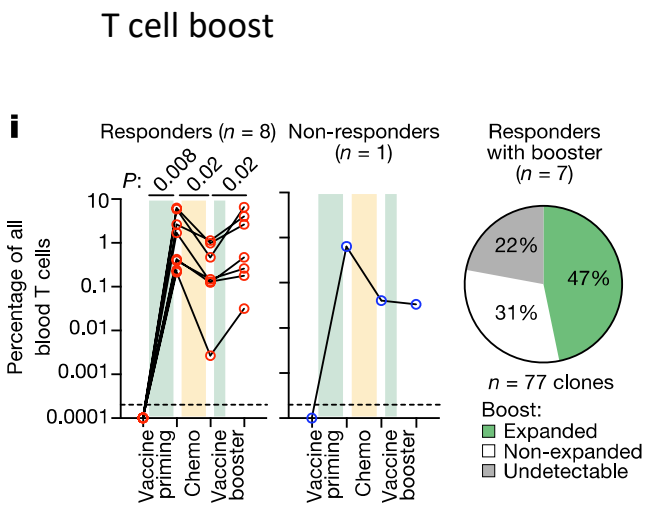



de novo TCR clone detection

## Compare TCR seq non-responders

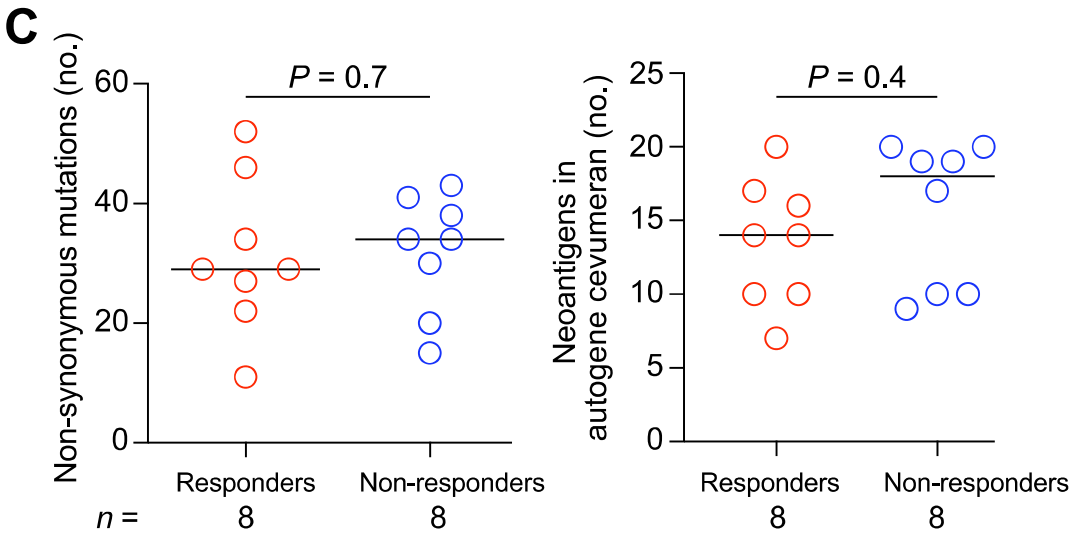


# Boost effect of mRNA vaccines after chemotherapy




**Important: maintained T cell functionality under chemotherapy (up to 2 years)!**

# Quantity of detected and selected mutations

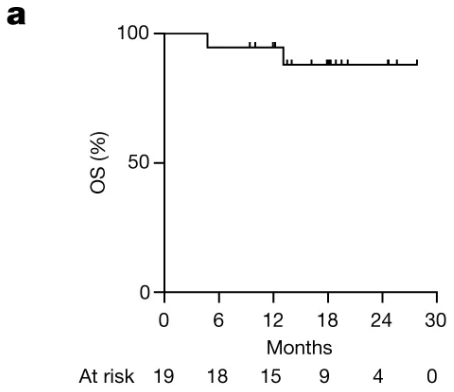



**Important: similar QUANTITY of mutations and neoantigens between reponders and non-reponders**

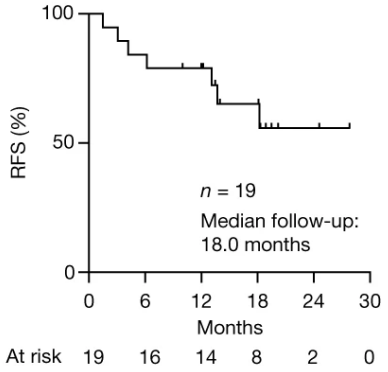
**→ neoantigen QUALITY correlates to vaccine response**

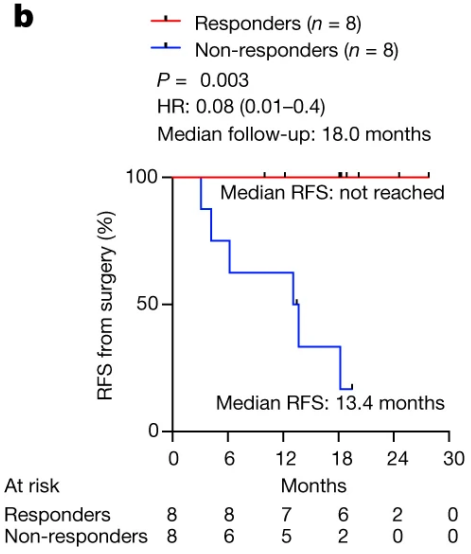
# mRNA vaccine response correlates with delayed PDAC recurrence

overall survival




Recurrence-free survival




← CAVE: treatment not synchroniced, some patients only short observation at time of reporting

# Summary

- mRNA vaccination showed **favorable safety profile**
- neoantigen specific immune responses can be induced in a tumor field normally **not responsive to immune therapies**
- even among responders, **half only showed monotope responses** (single antigen)
- TCRseq for clonal expansion correlates with antigen specific ELISpot
- indication that **neoantigen QUALITY** might impact response vs non-response
- preliminary indication that individualized neoantigen vaccine in combination treatment setting **may delay tumor recurrence**

# Consideration

- CAVE: eligibility for inclusion into a phase 1 is already a strong selection bias towards better course of disease

- standard flow cytometry can miss vaccine induced T cell expansion → TCR seq!

- CAVE: potential confounding factors:
  - 5/8 non-responders had SPLEENECTOMY!
  - non-responders had larger primary tumor sizes (3 vs 2 cm)!
  - responders had lower tumor stage (stage I vs stage III)