

PARP inhibitors in SCLC

Charles Rudin MD PhD



Memorial Sloan Kettering
Cancer Center

PARP inhibitors in SCLC



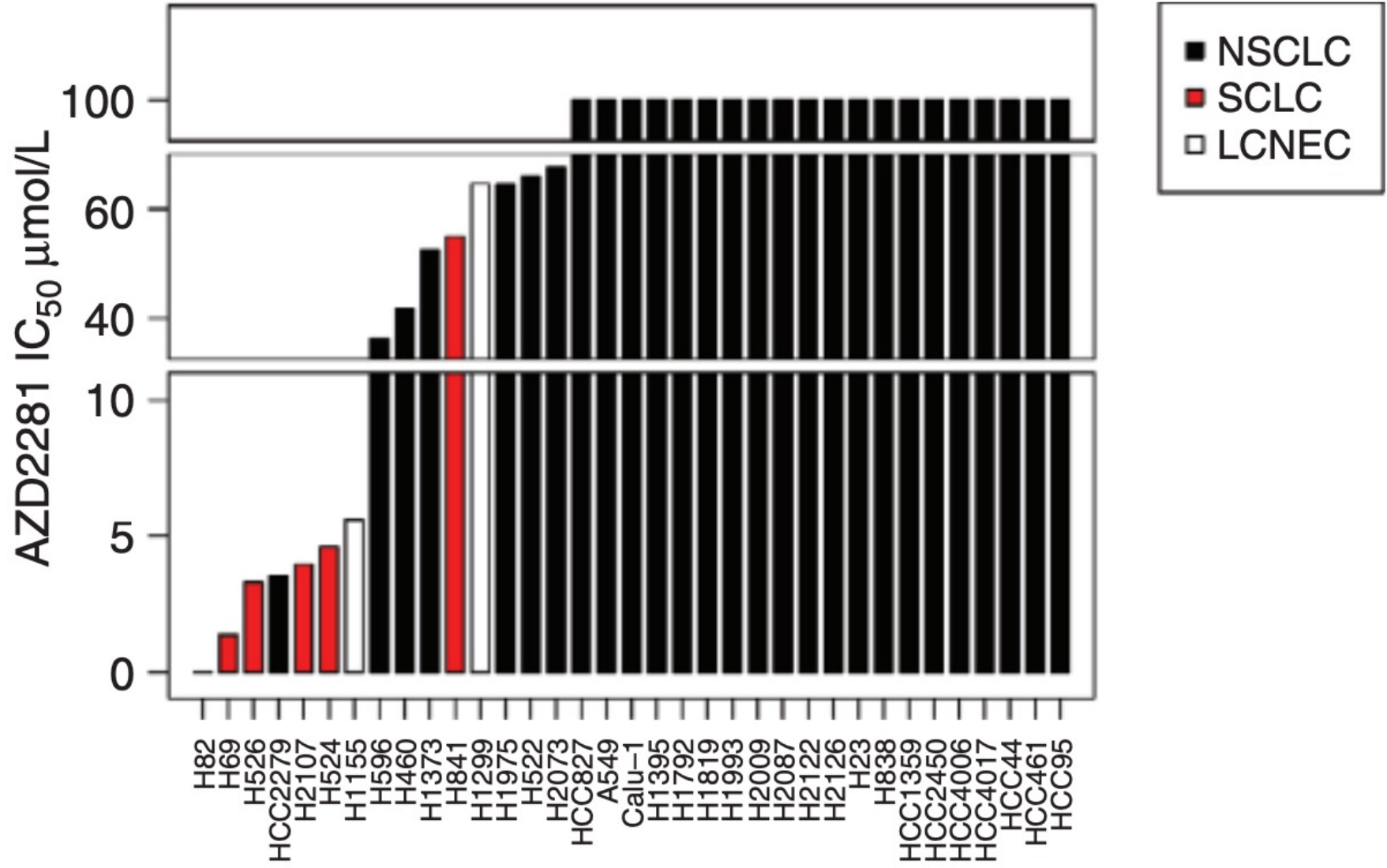
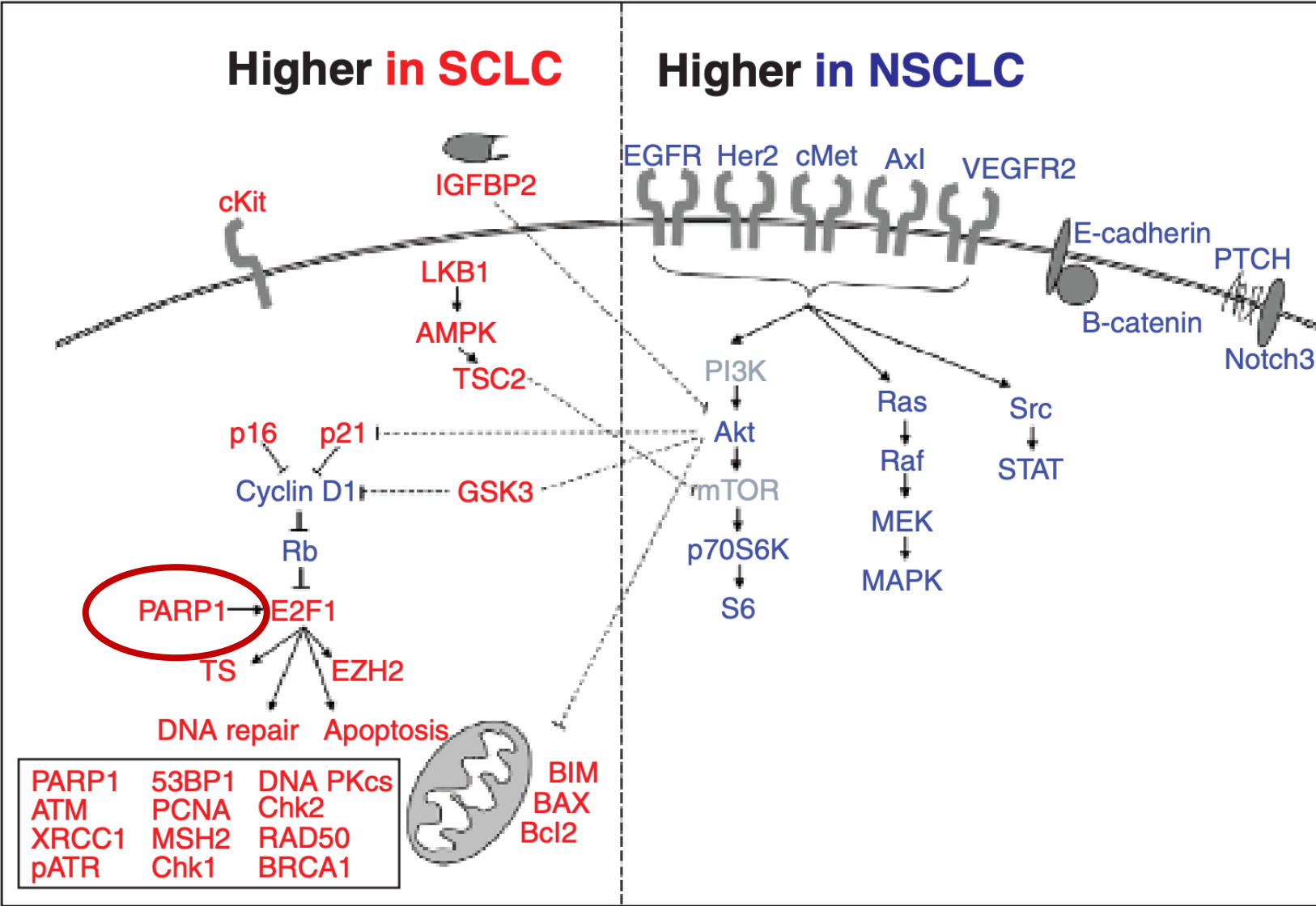
... ever the bridesmaid, never the bride

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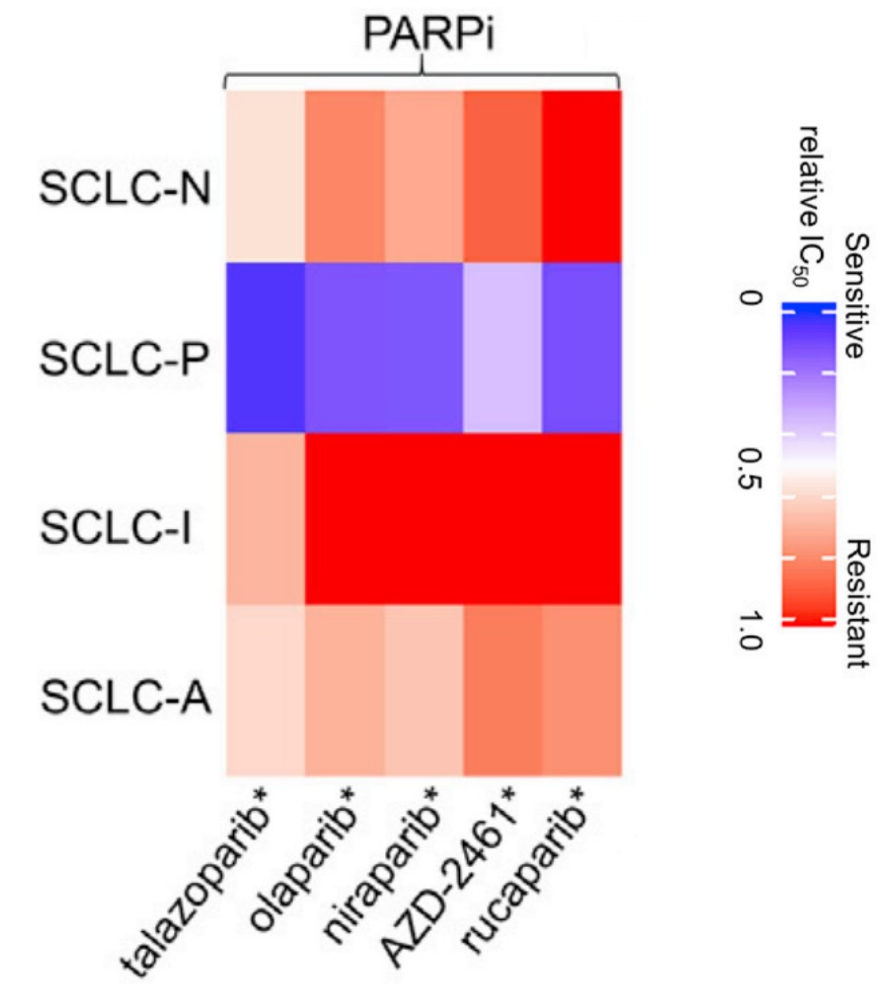
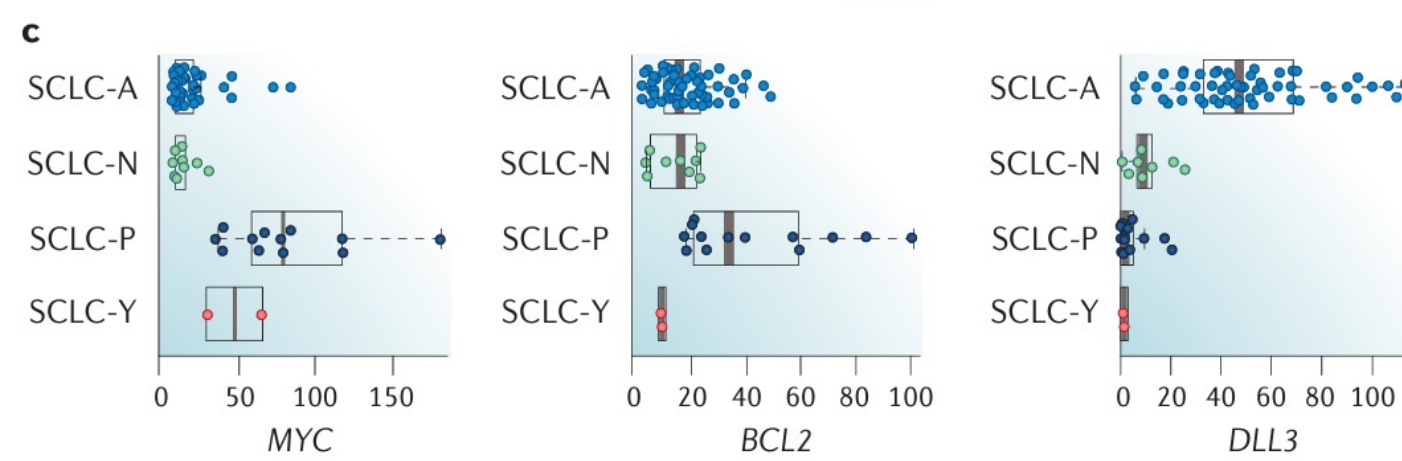
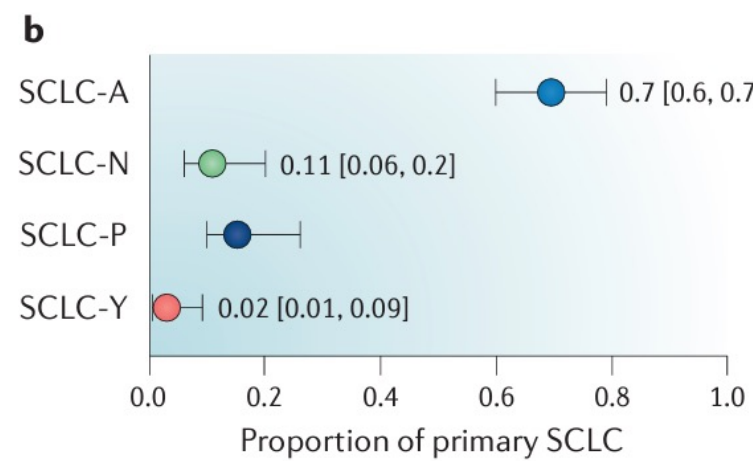
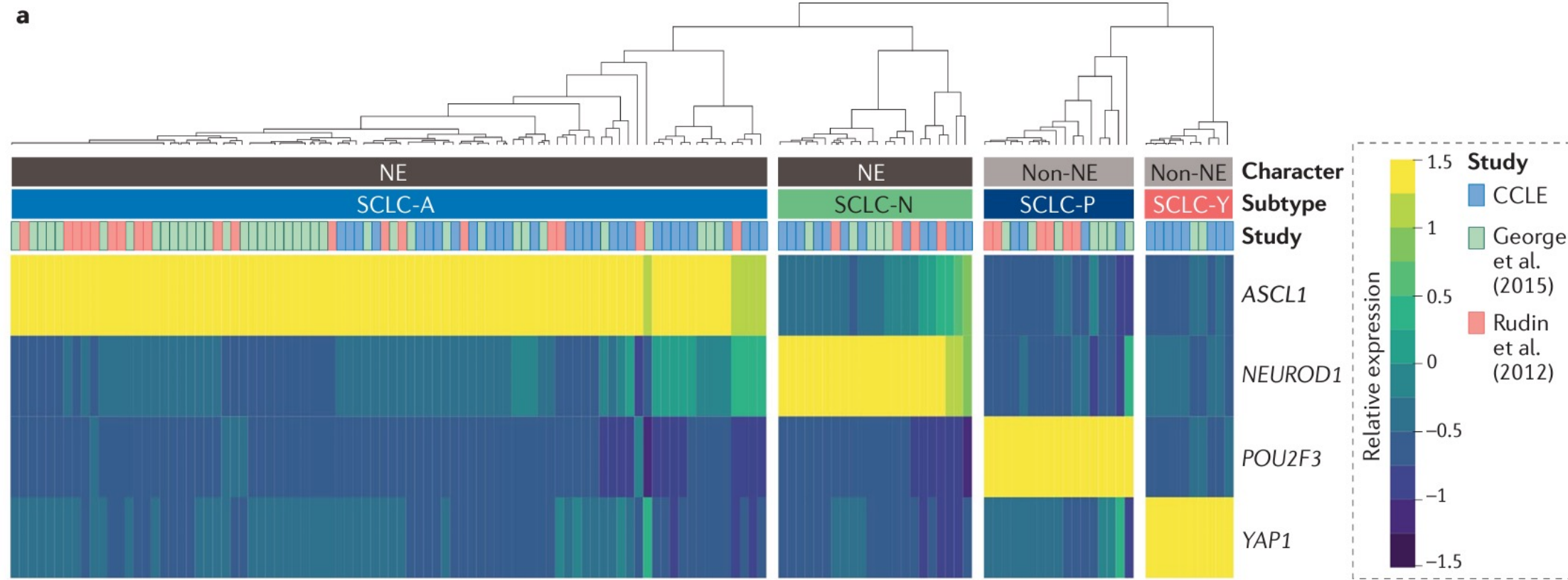


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How did we get here?



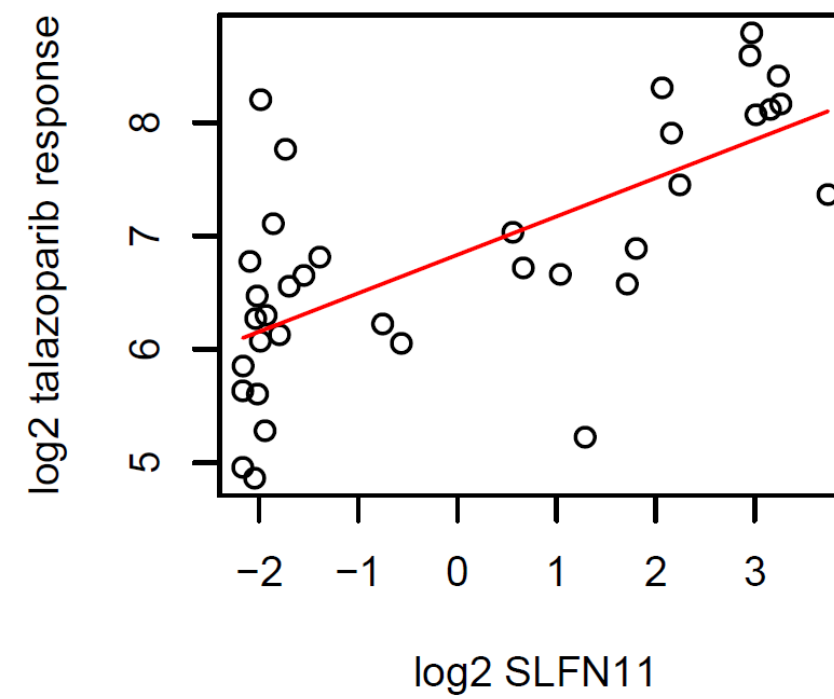
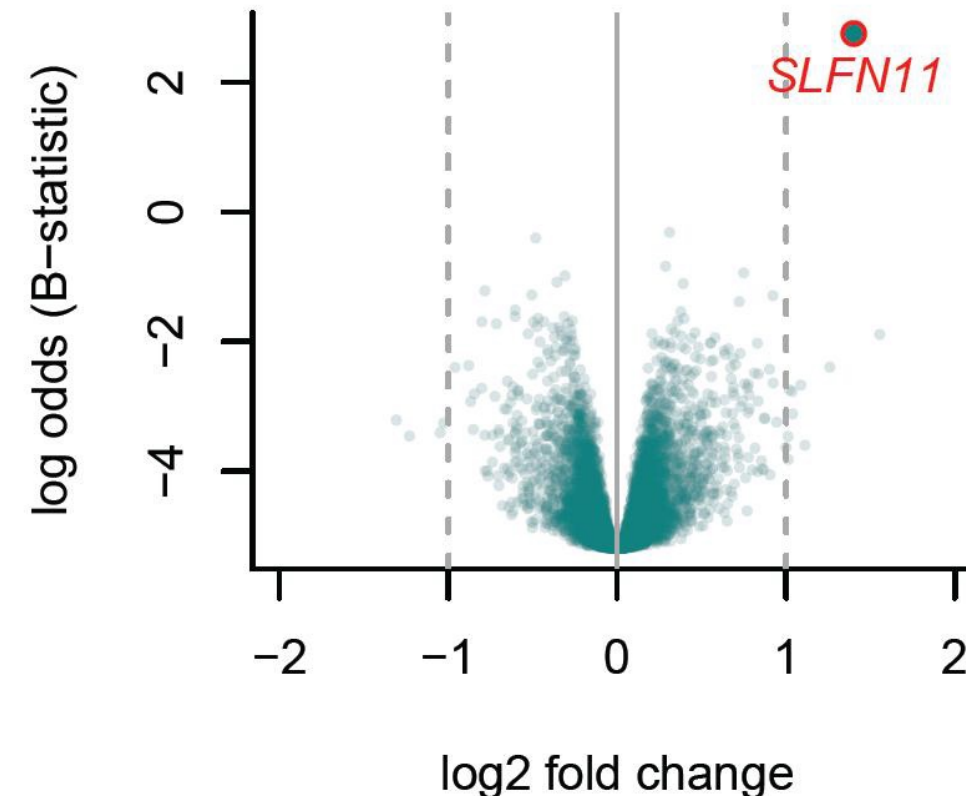
Subtyping SCLC to search for biomarkers



SLFN11 expression predicts PARPi sensitivity in SCLC



Ben Lok

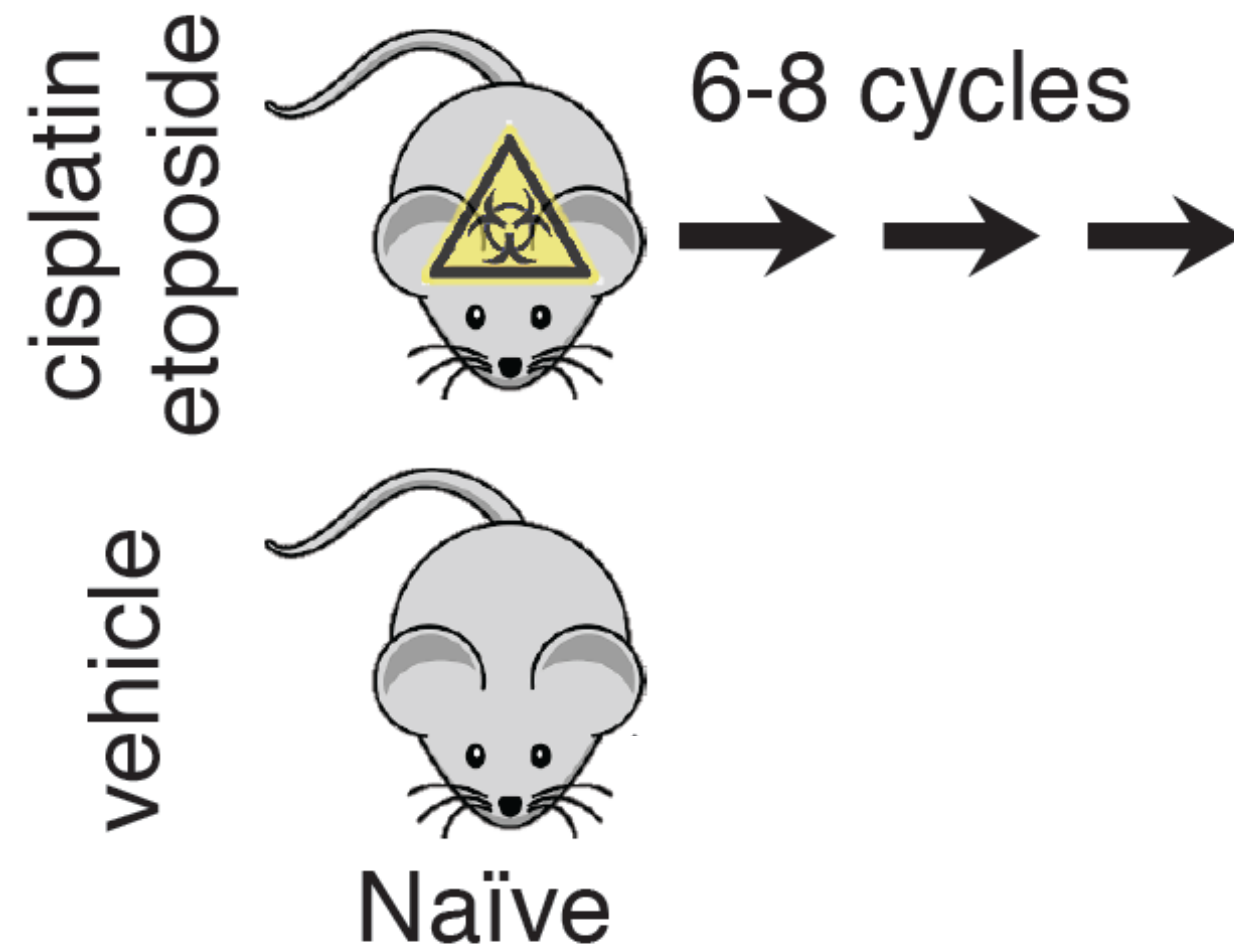


FDR $p < 0.008$

How did we get to SLFN11?



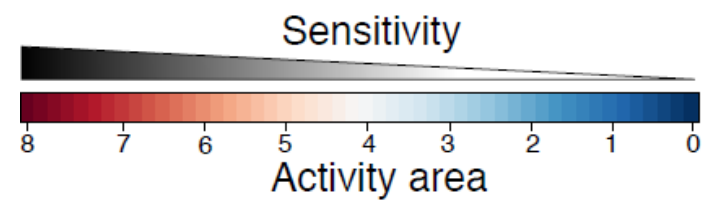
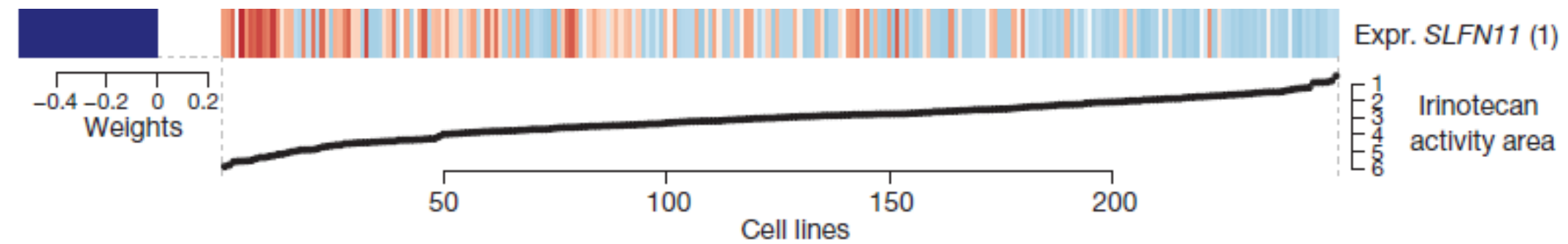
Eric Gardner



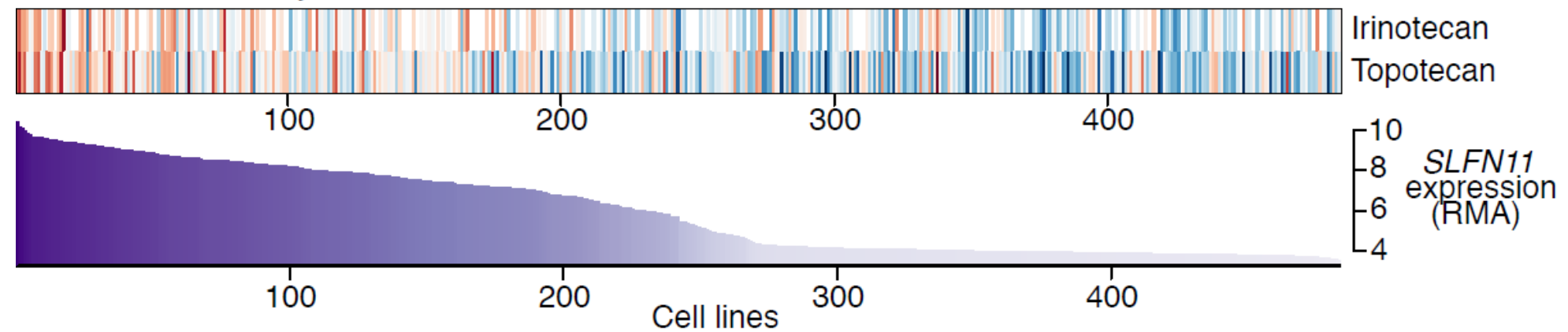
In 4 of 10 models, silencing of SLFN11 expression occurred with acquired chemoresistance

SLFN11 is also the strongest single gene correlate of TOP1 inhibitor sensitivity across cancer cell lines

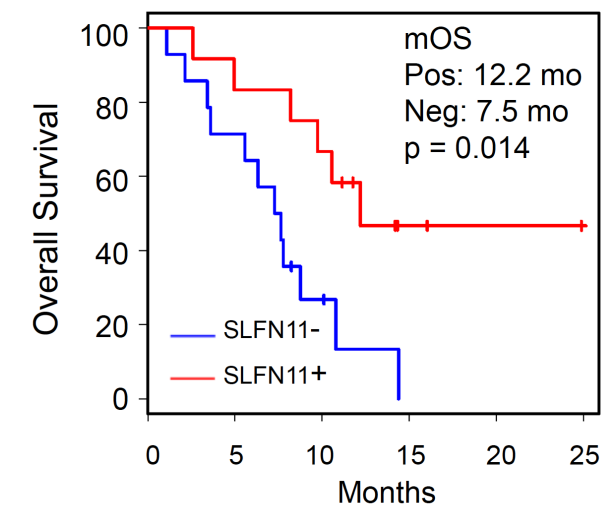
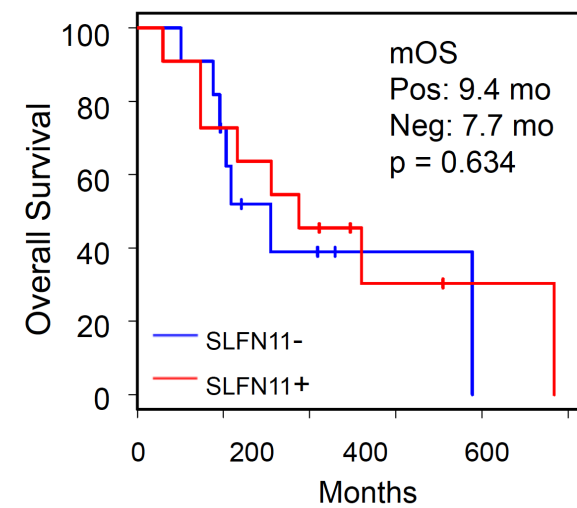
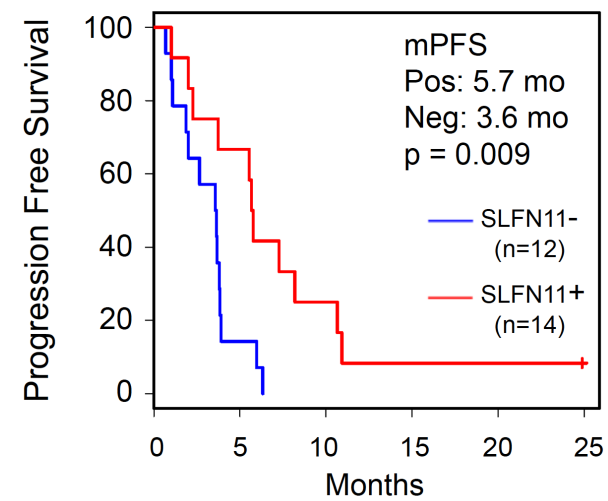
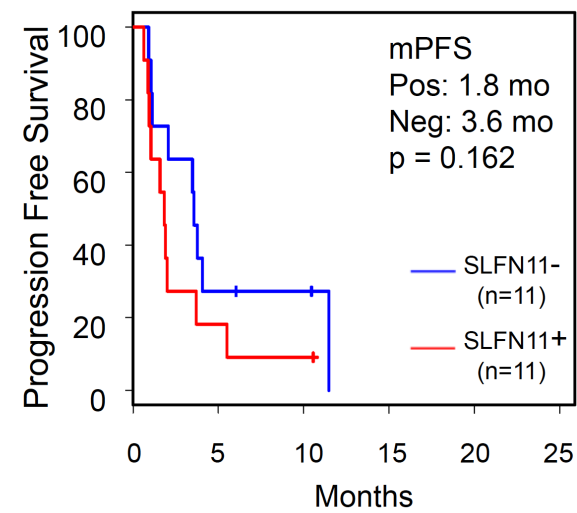
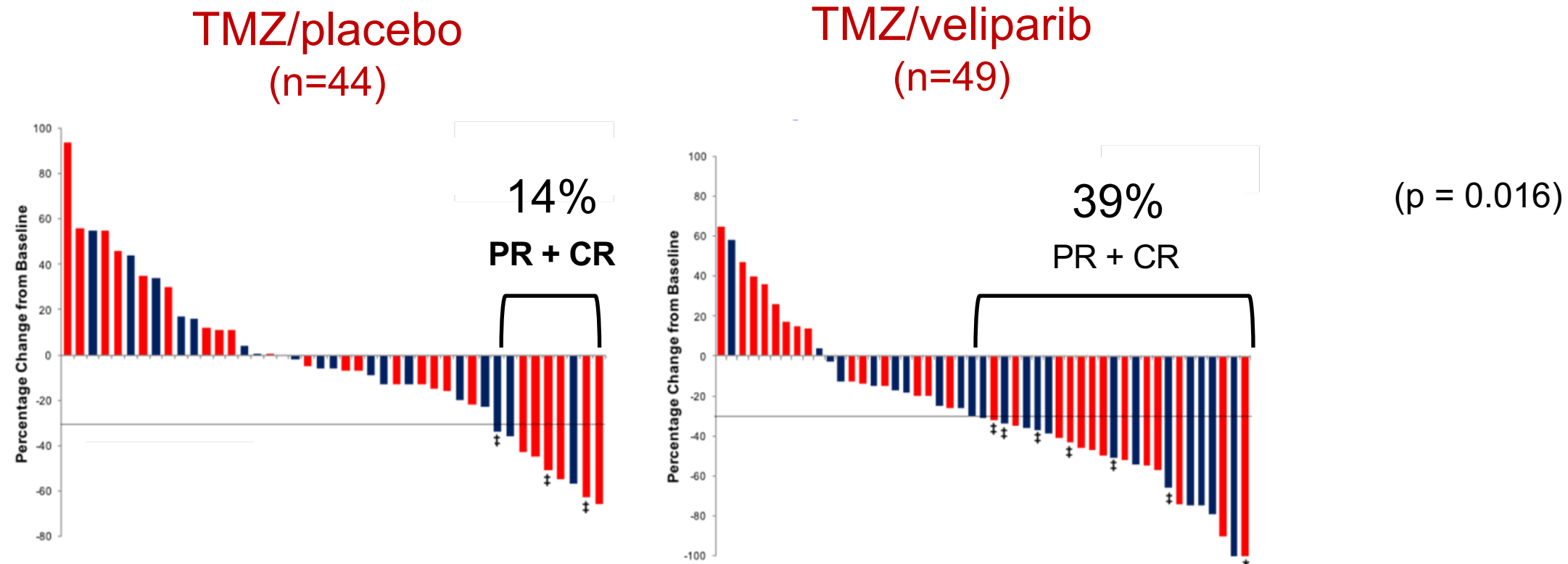
CCLE



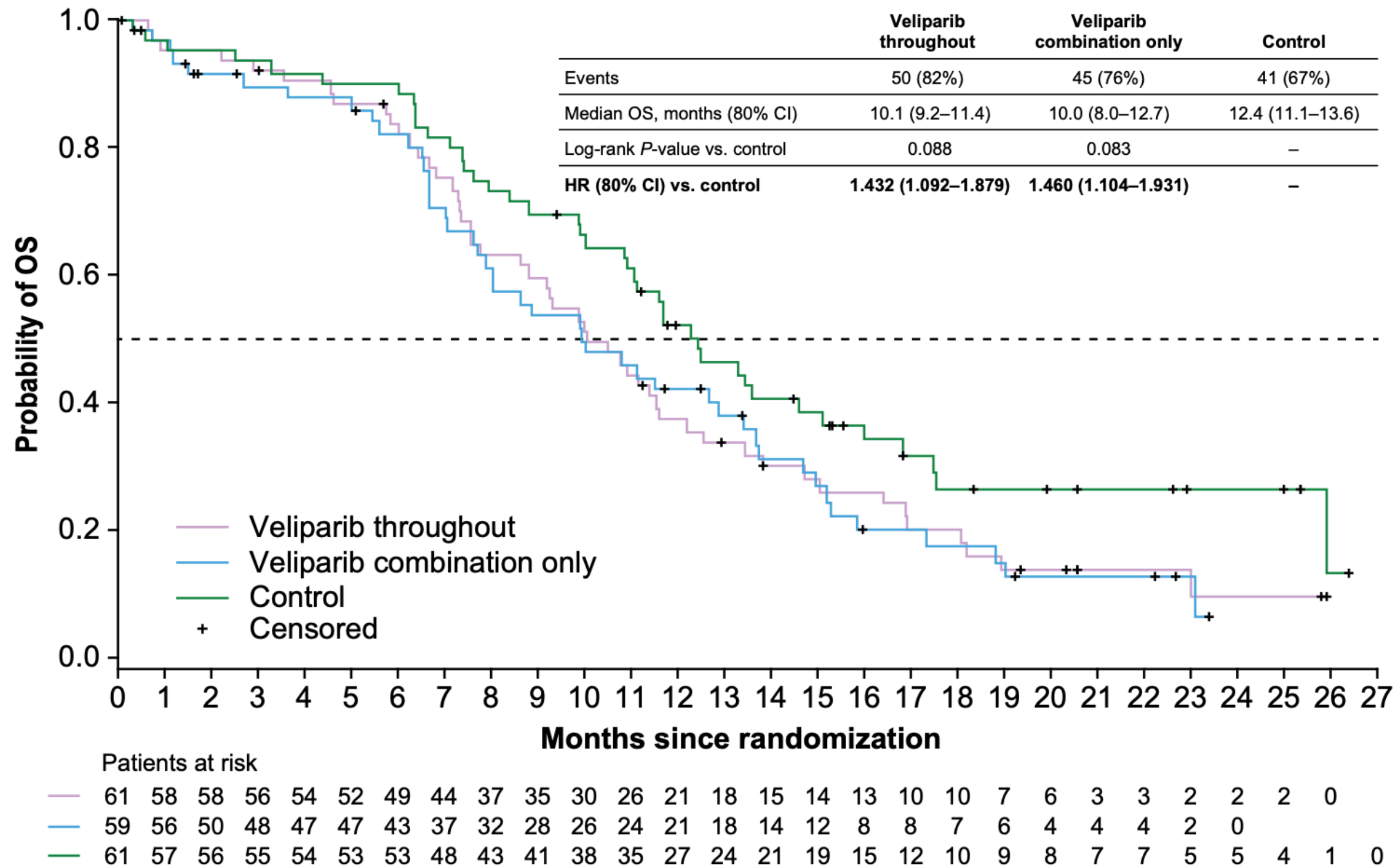
NCI 60



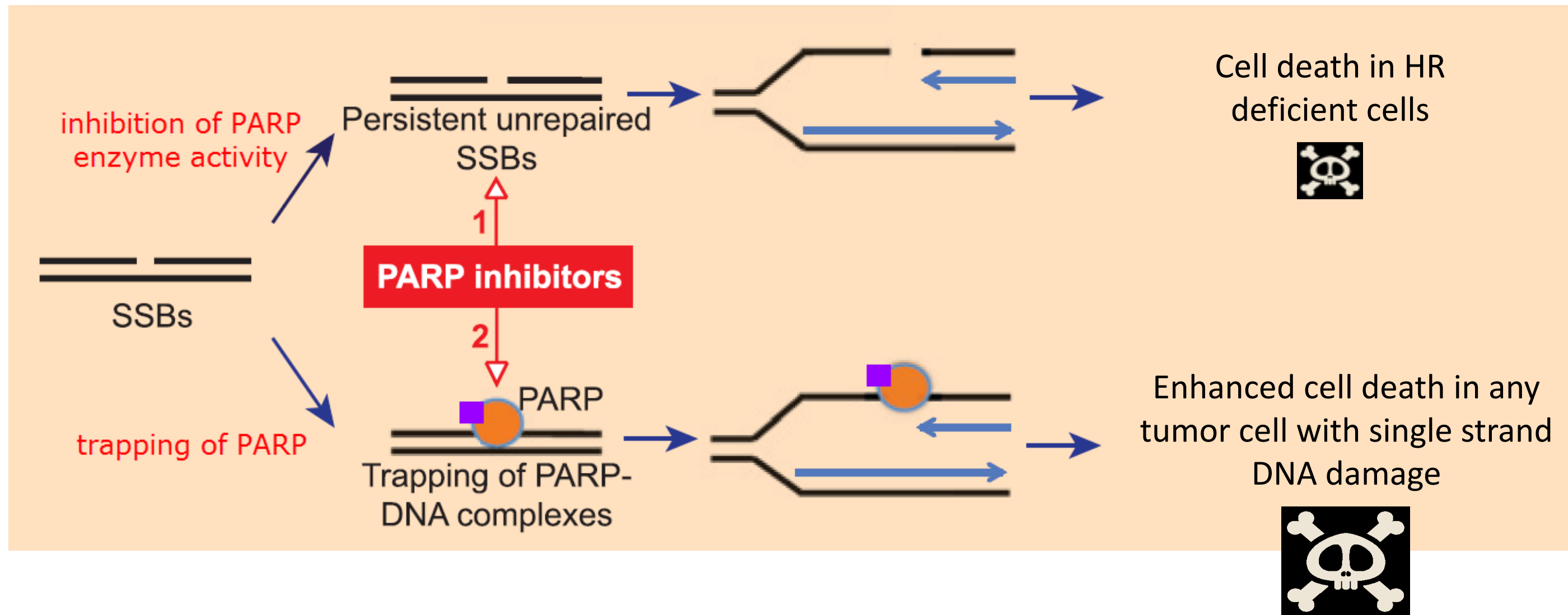
Clinical validation – phase 2 temozolomide +/- veliparib



Veliparib added to first line chemotherapy +/- maintenance... *harm??*



PARP inhibitors work through (at least) 2 mechanisms



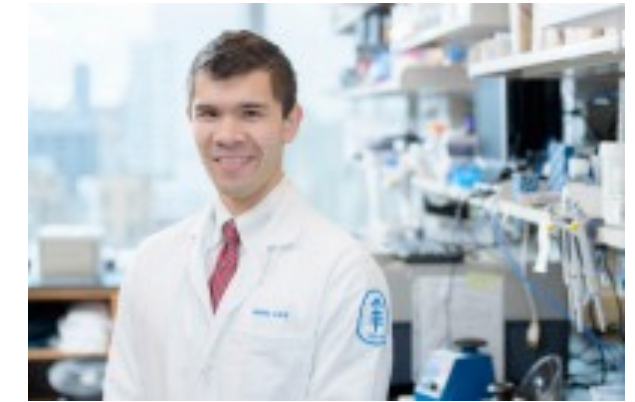
Trapping potency

Talazoparib > Neraparib > Olaparib = Rucaparib > Veliparib

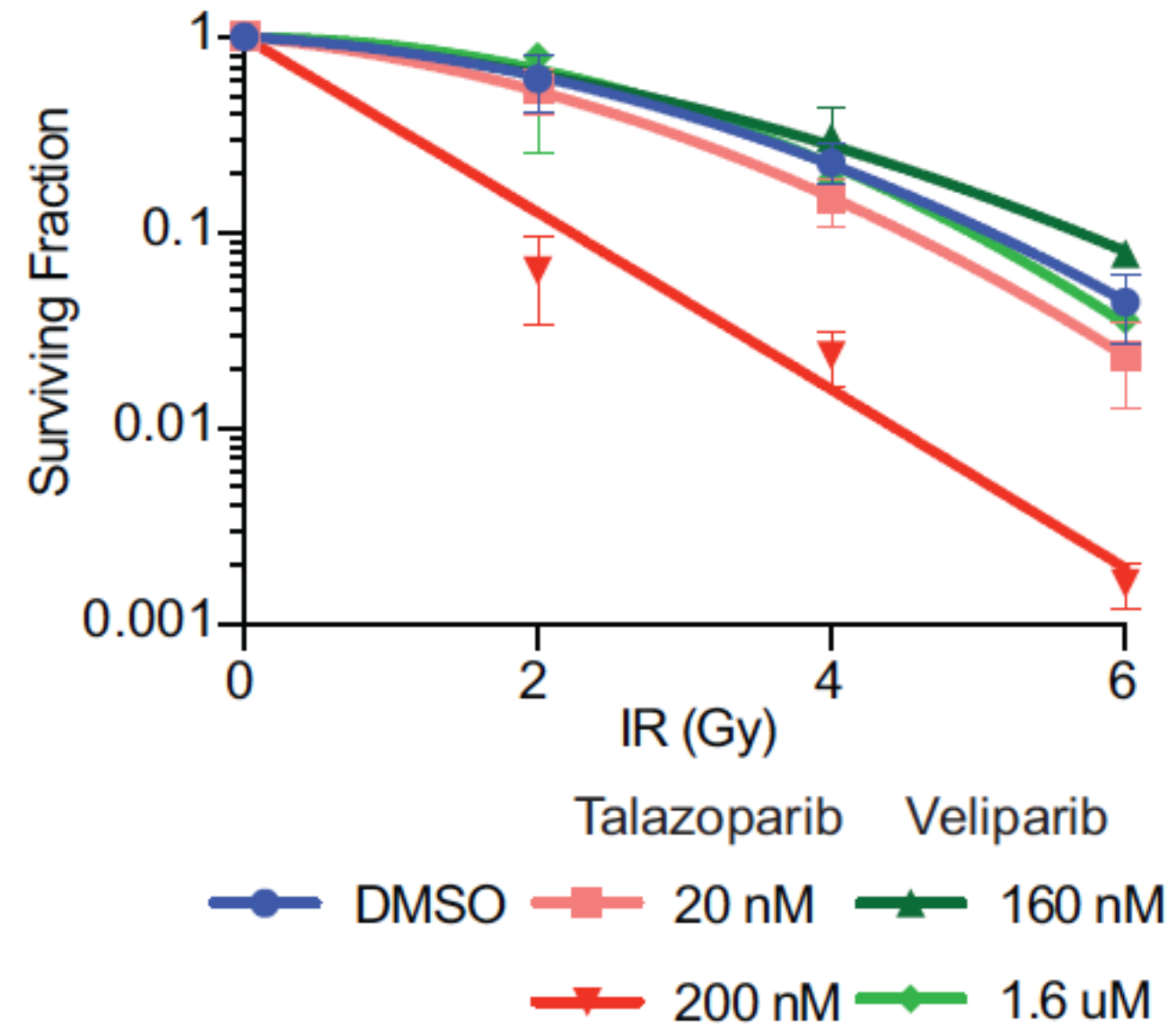
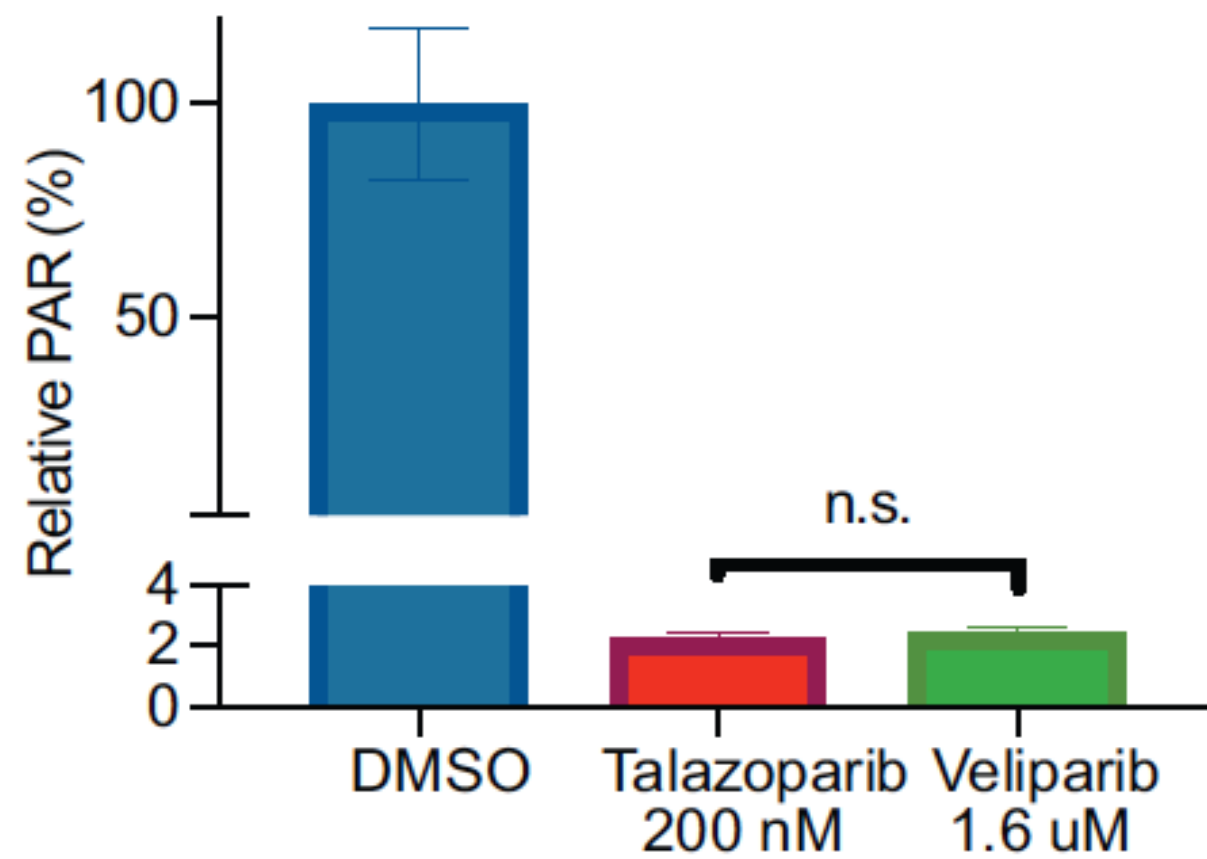
PARP inhibitors and radiosensitization in SCLC

Trapping potency

Talazoparib > Neraparib > Olaparib = Rucaparib > Veliparib

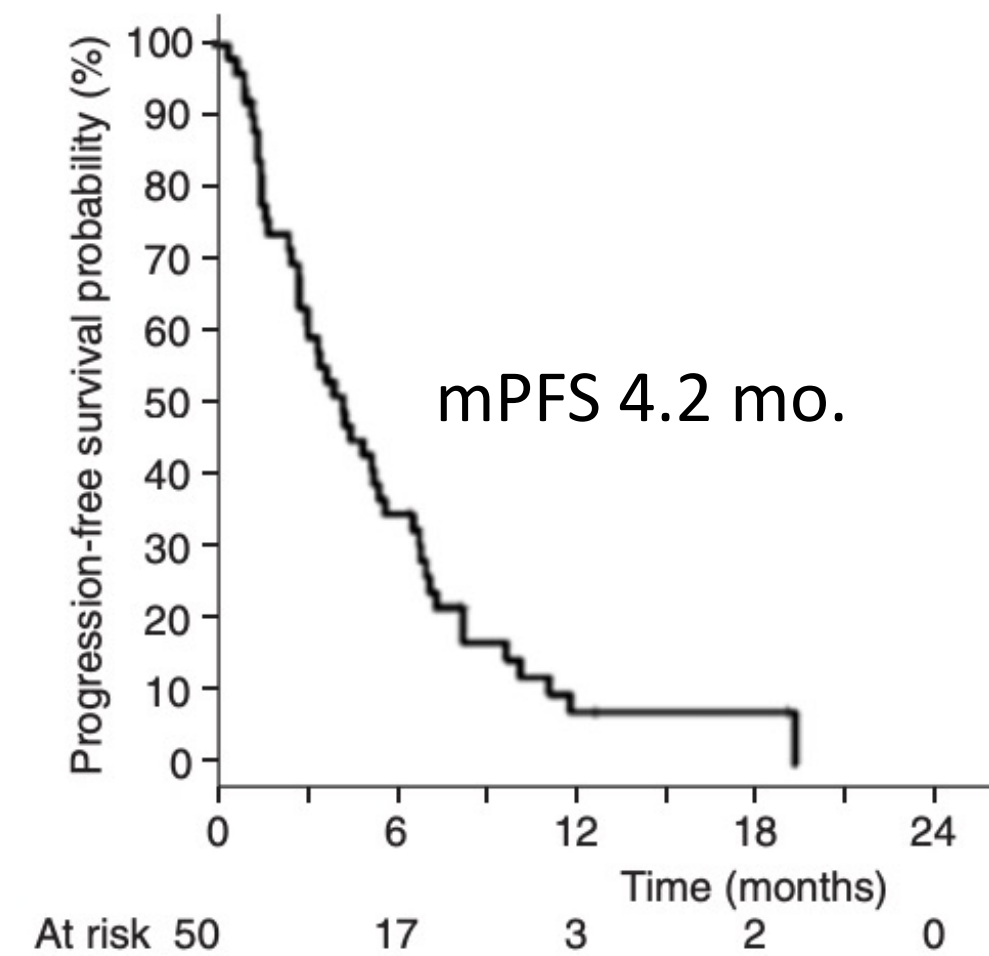
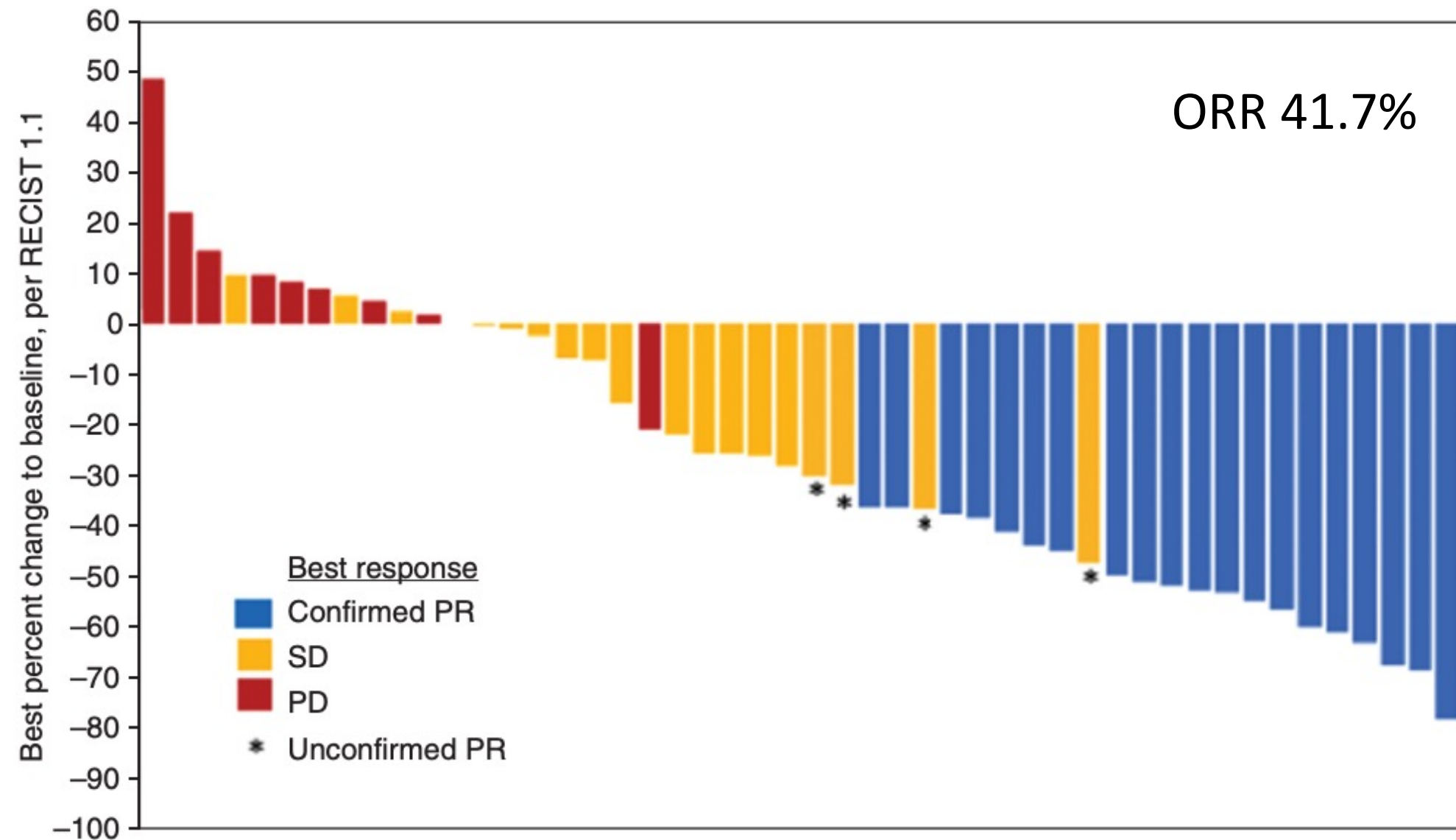


James Laird

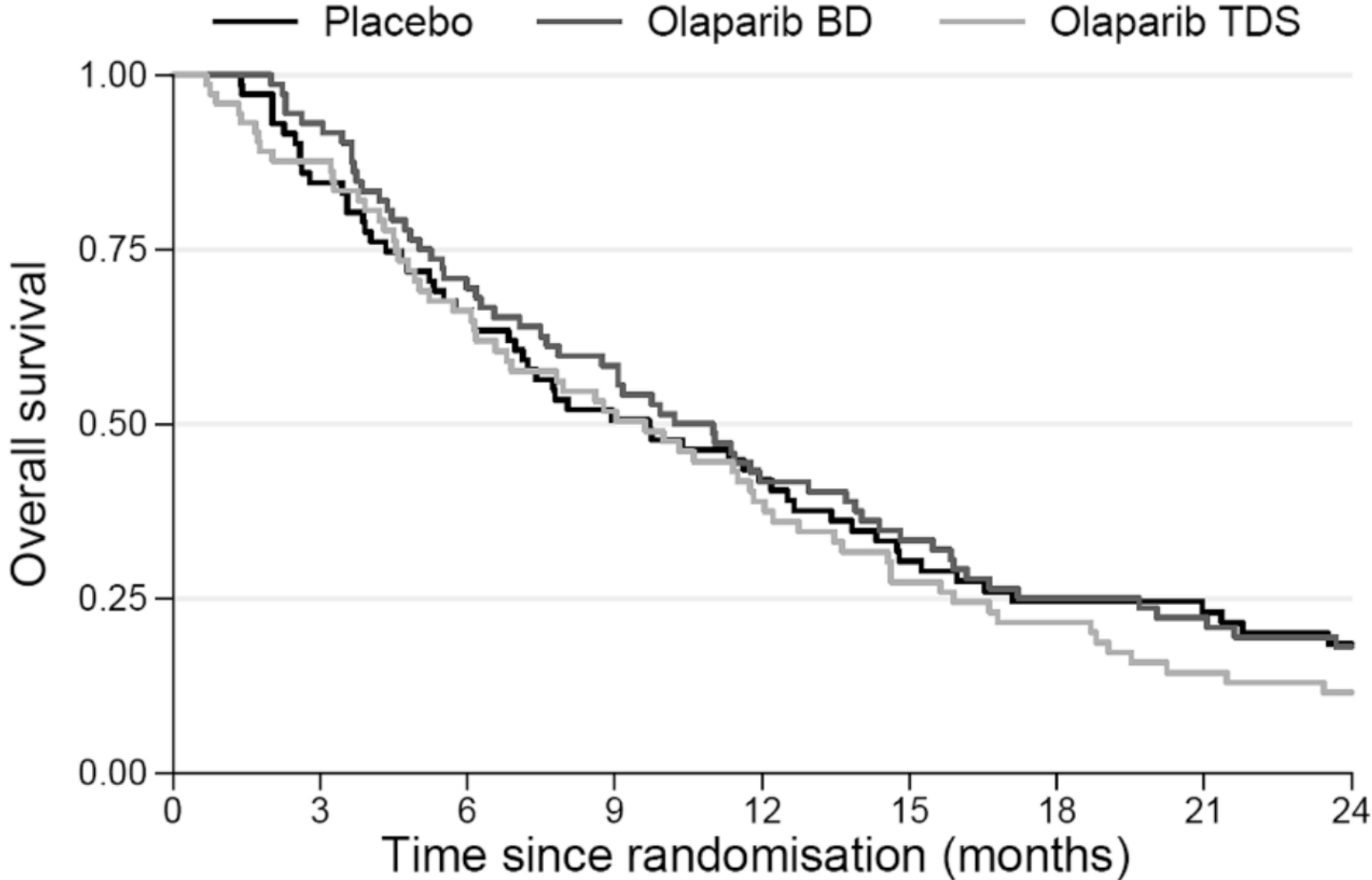


Olaparib and temozolomide in patients with SCLC

Perhaps the most promising data to date – but durability is modest



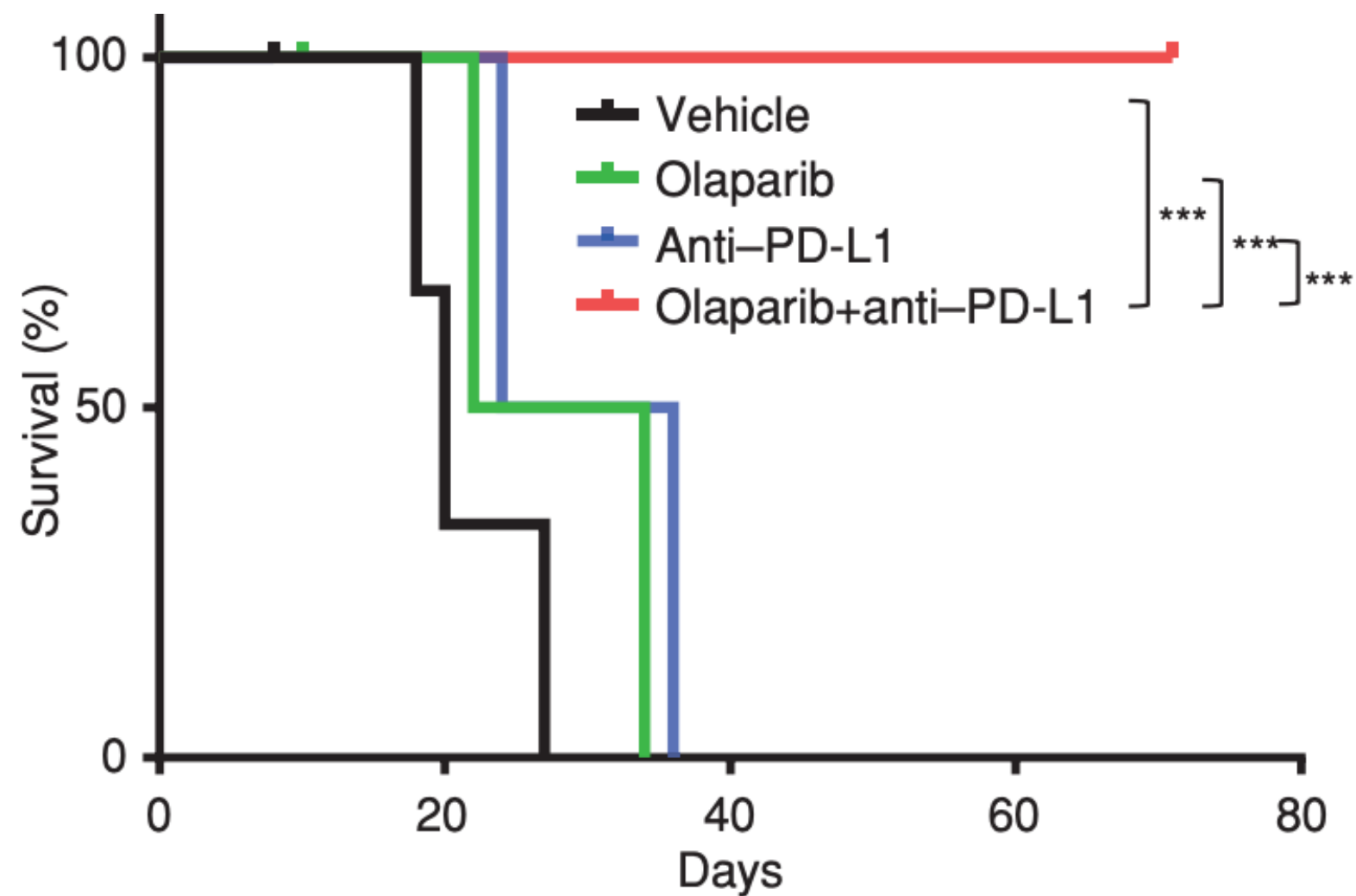
Olaparib maintenance? No.



Number at risk		0	3	6	9	12	15	18	21	24
Placebo	74	60	47	35	29	21	17	15	12	
Olaparib BD	73	67	50	42	30	24	18	16	13	
Olaparib TDS	73	63	46	36	27	19	15	10	8	

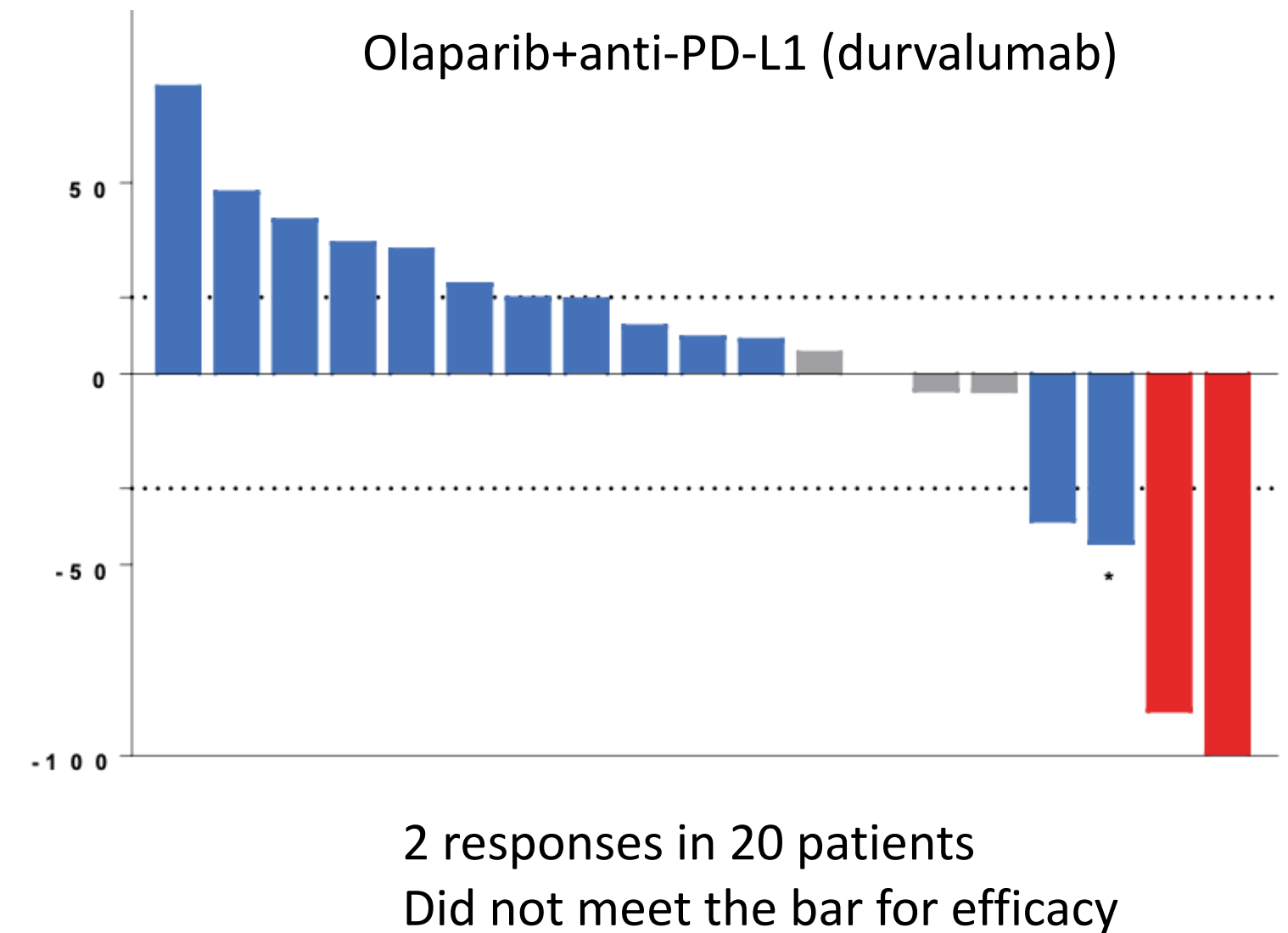
Could PARP inhibitors inflame SCLC and lead to IO response?

Looked great in mice!



Sen et al. *Cancer Discov* 2019

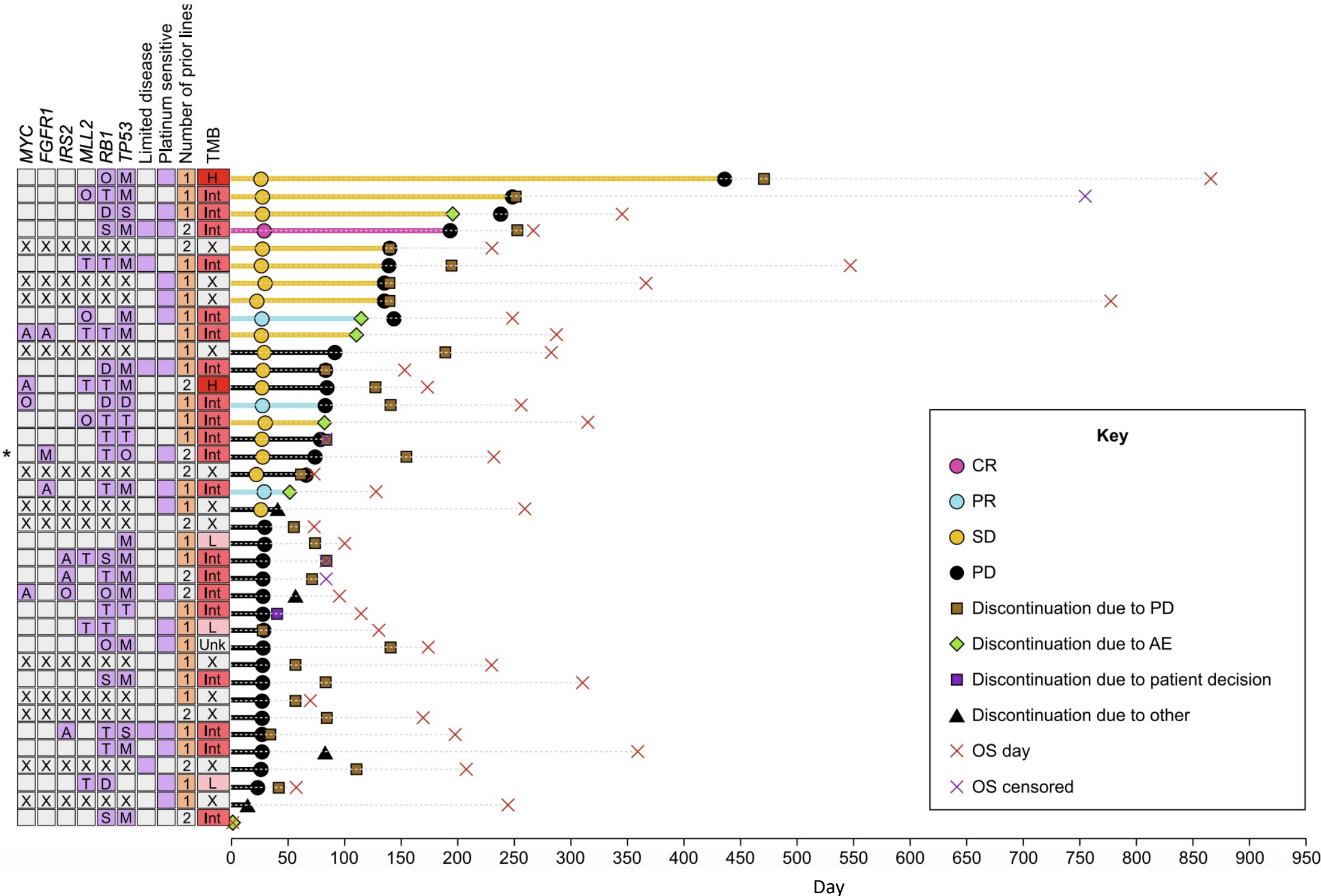
... but disappointing in patients...



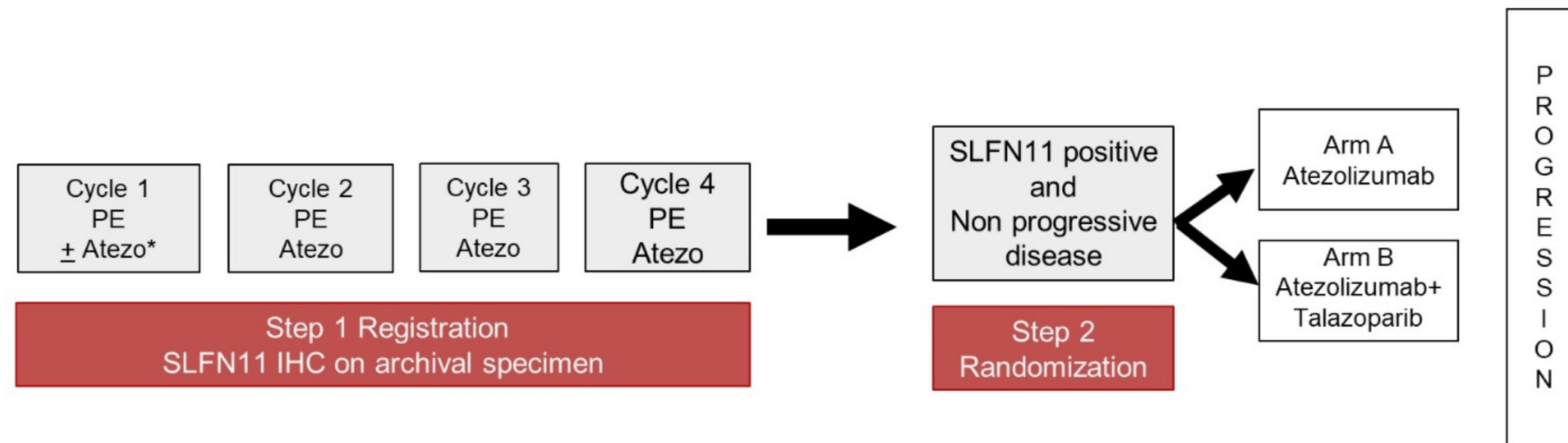
Thomas et al. *J Thor Oncol* 2019

This combo did not look any better in phase II

MEDIOLA phase II study of olaparib + durvalumab



Maintenance atezo vs. atezo + talazoparib in SLFN11+ ES-SCLC

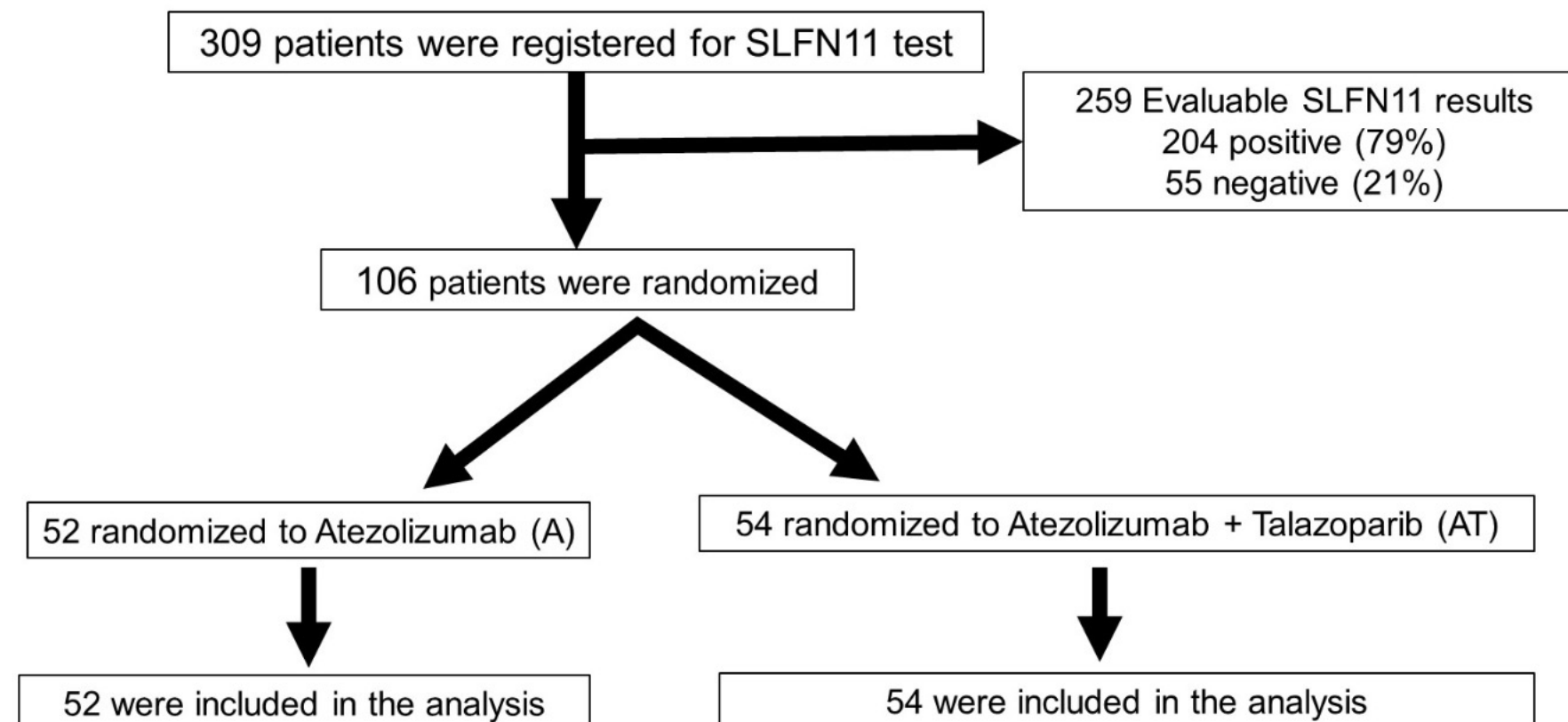


Hypothesis: The addition of talazoparib to maintenance atezolizumab will improve PFS in SLFN11+ SCLC.

Primary Endpoint: PFS

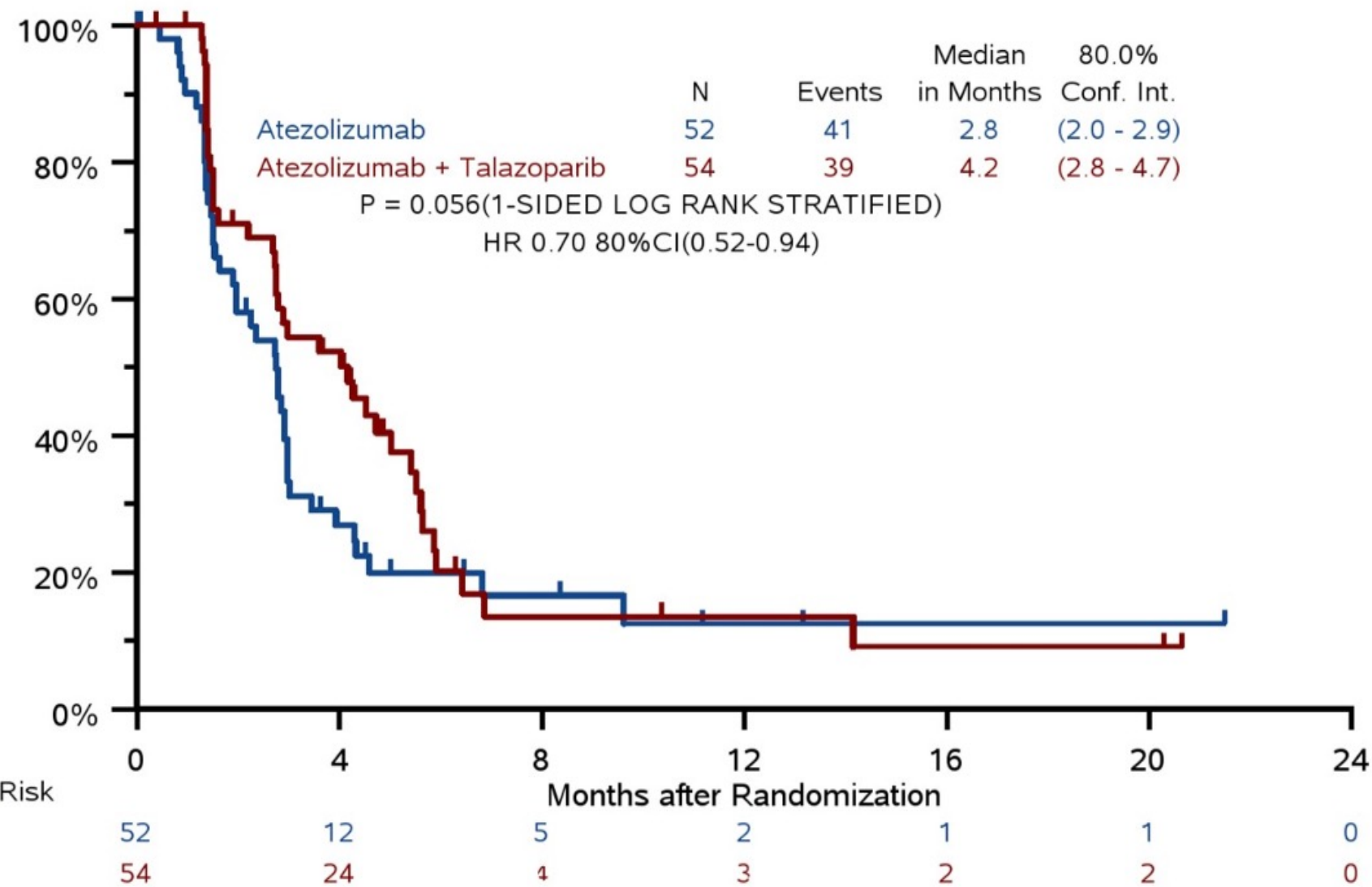
Secondary endpoints: OS, ORR, AE.

TM Objective: To bank specimens for future correlative studies.

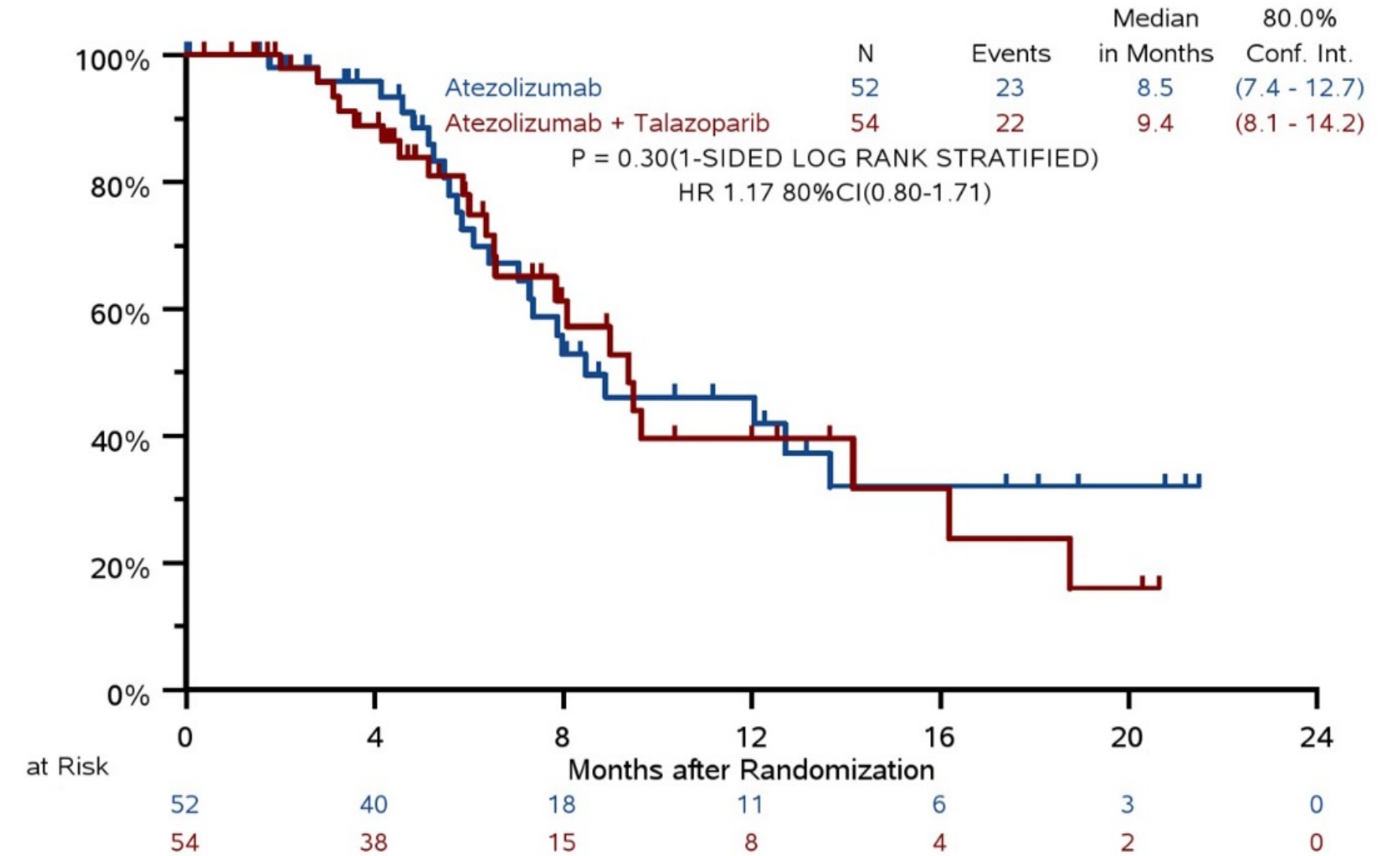


Maintenance atezo vs. atezo + talazoparib in SLFN11+ ES-SCLC

Progression-free survival

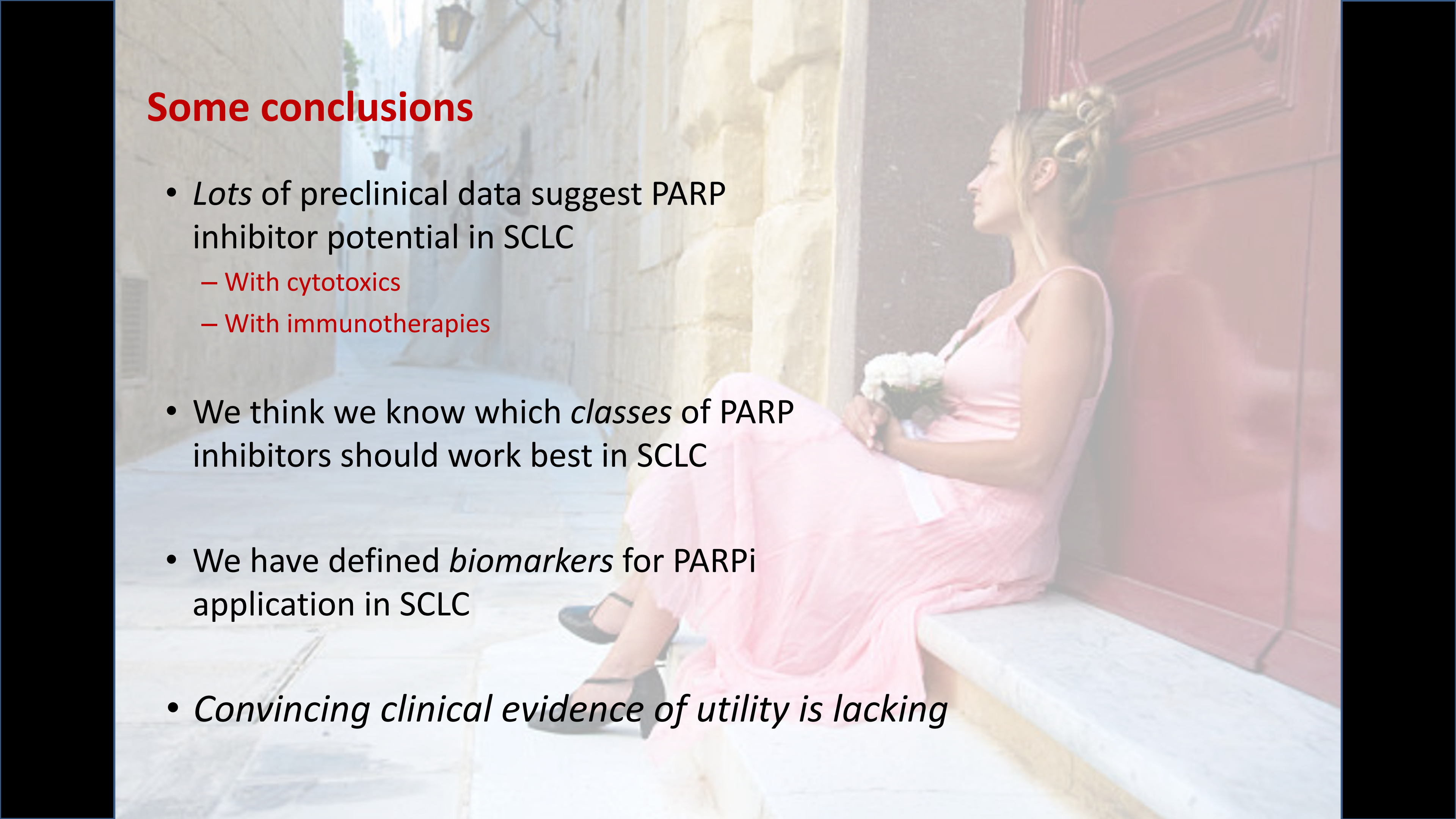


Overall survival



Even biomarker-selected, with a potent PARP trapper: *Not good enough.*

Some conclusions

- *Lots* of preclinical data suggest PARP inhibitor potential in SCLC
 - With cytotoxics
 - With immunotherapies
 - We think we know which *classes* of PARP inhibitors should work best in SCLC
 - We have defined *biomarkers* for PARPi application in SCLC
 - *Convincing clinical evidence of utility is lacking*
- 
- A woman with blonde hair styled in a bun, wearing a light pink sleeveless dress and black heels, sits on a stone ledge. She is holding a bouquet of white flowers and looking out over a narrow, stone-paved street. The background shows a stone wall with a small window and a street lamp.

Thanks!

