Evaluating and Targeting Defects in DNA Damage Repair

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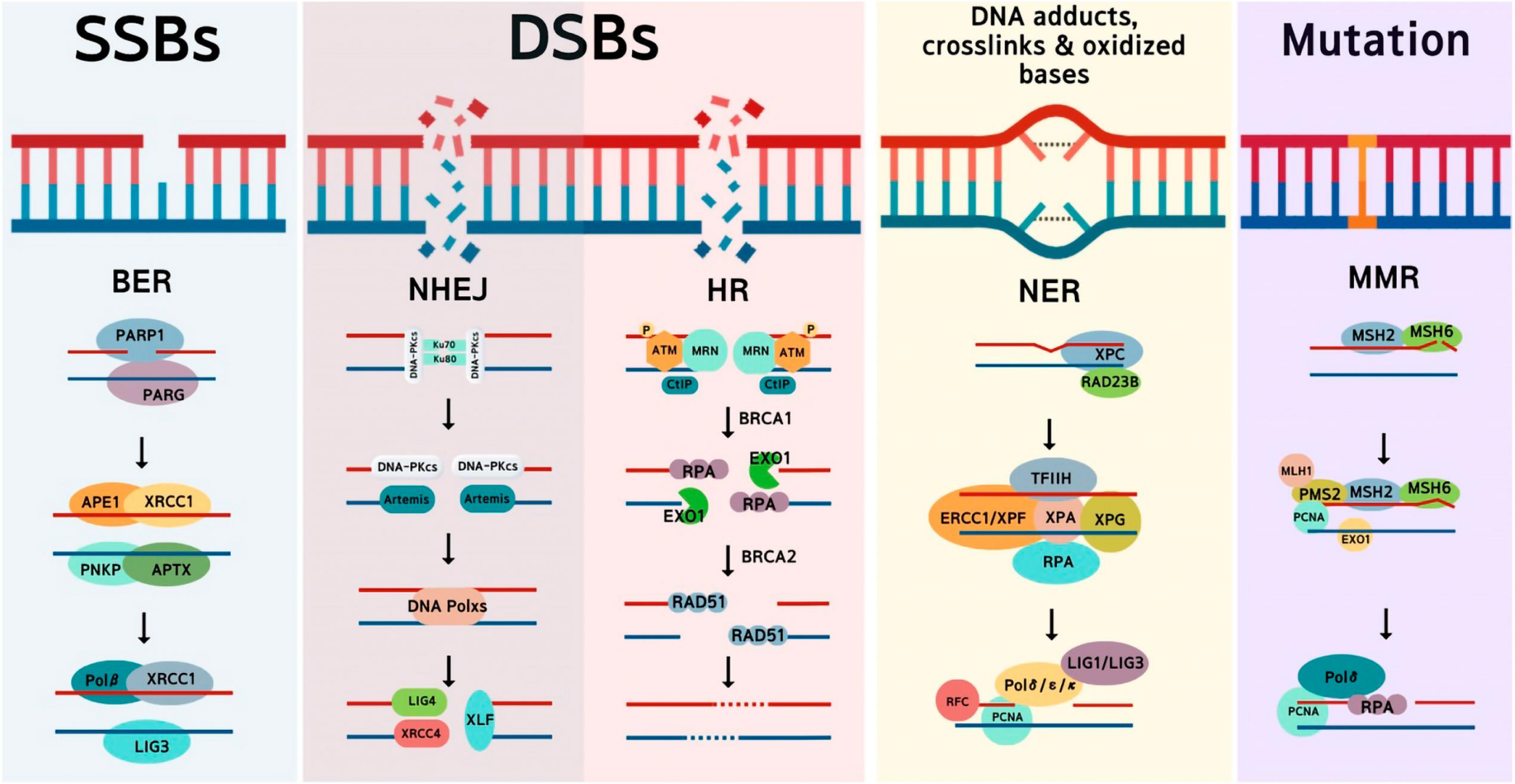
March 29, 2025

MaTOS Summit, Charlotte, NC

Memorial Sloan Kettering Cancer Center

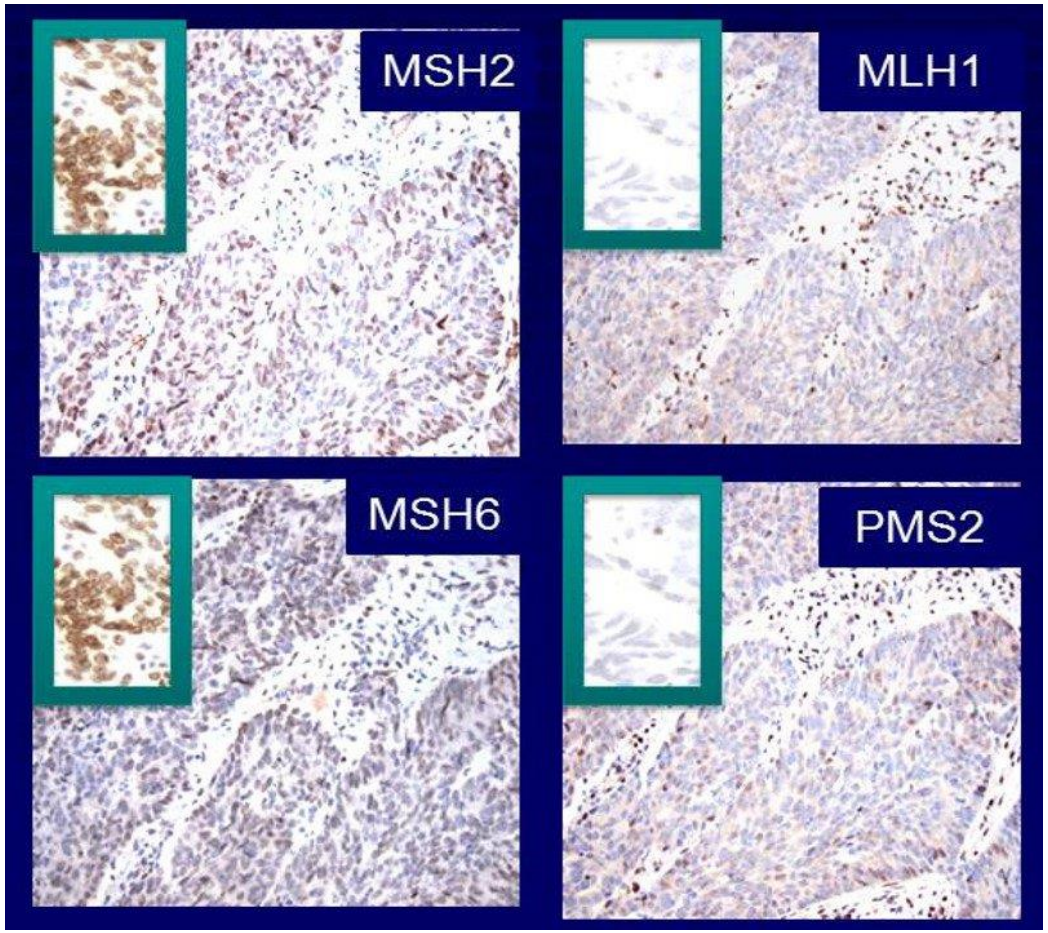
Point 1: Different Repair Pathways for Different Types of DNA Damage



Moon et al, https://doi.org/10.3390/ijms24054741

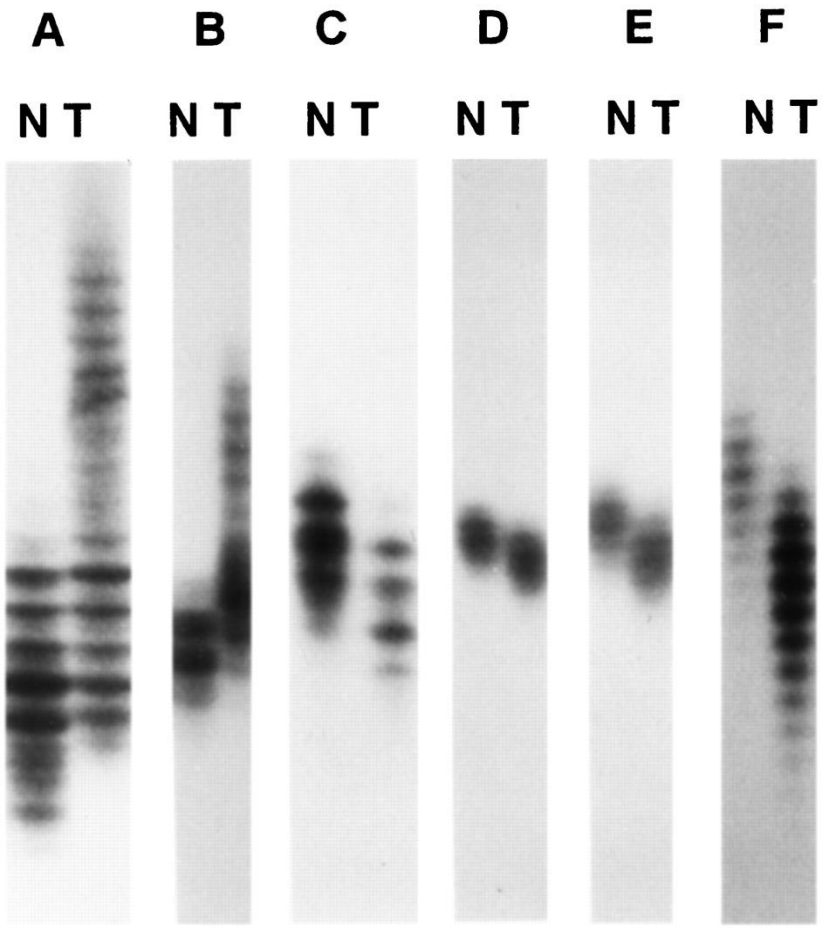
Point 2: Different DNA Damage Repair Defects Have Different “Phenotypes”

Mismatch Repair Protein Deficiency



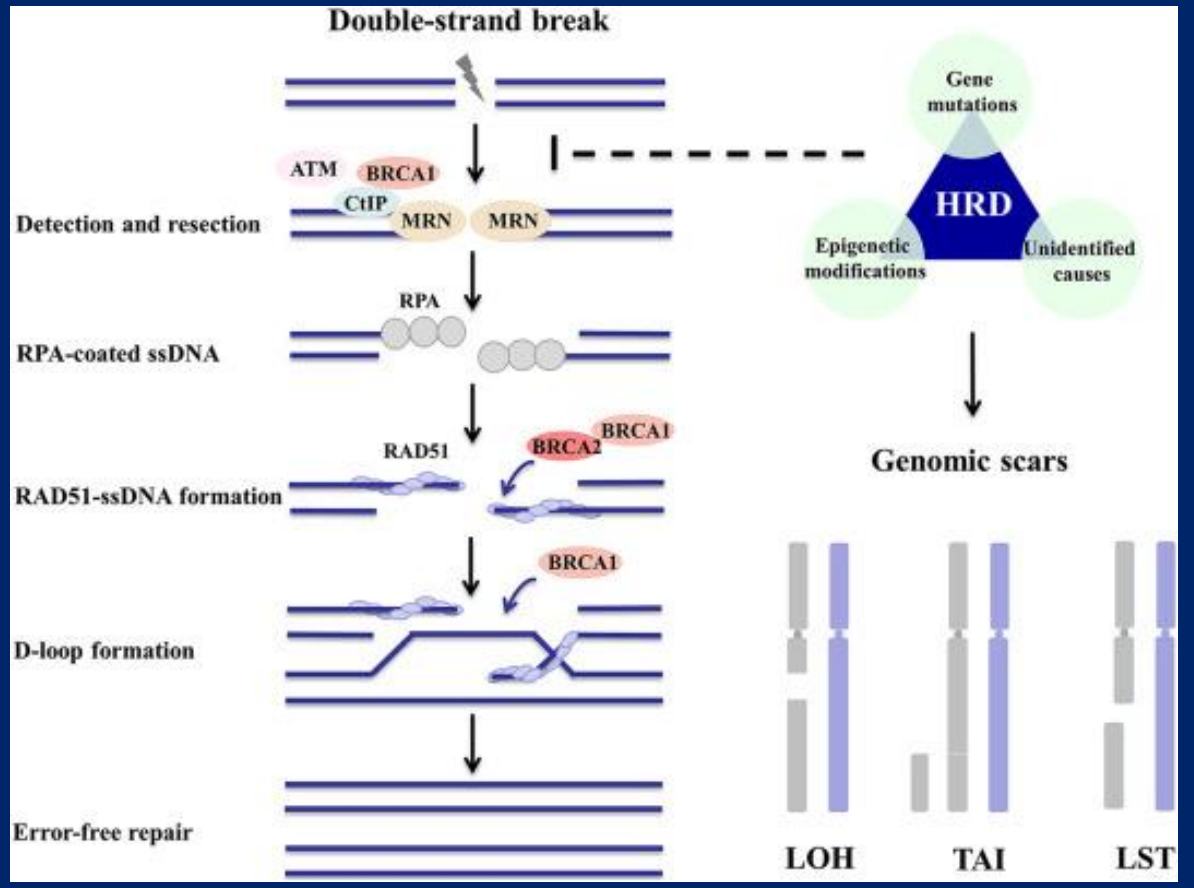
https://visualsonline.cancer.gov/details.cfm?imageid=11431

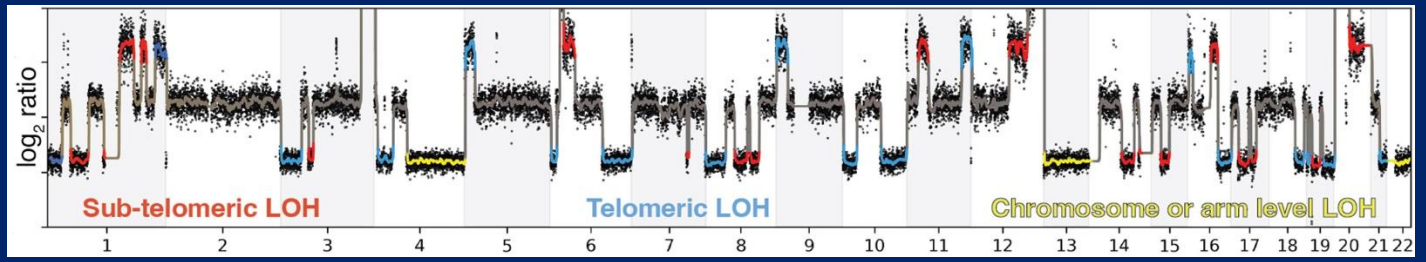
Microsatellite Instability



Point 2: Different DNA Damage Repair Defects Have Different "Phenotypes"

HRD leads to "genomic scars"

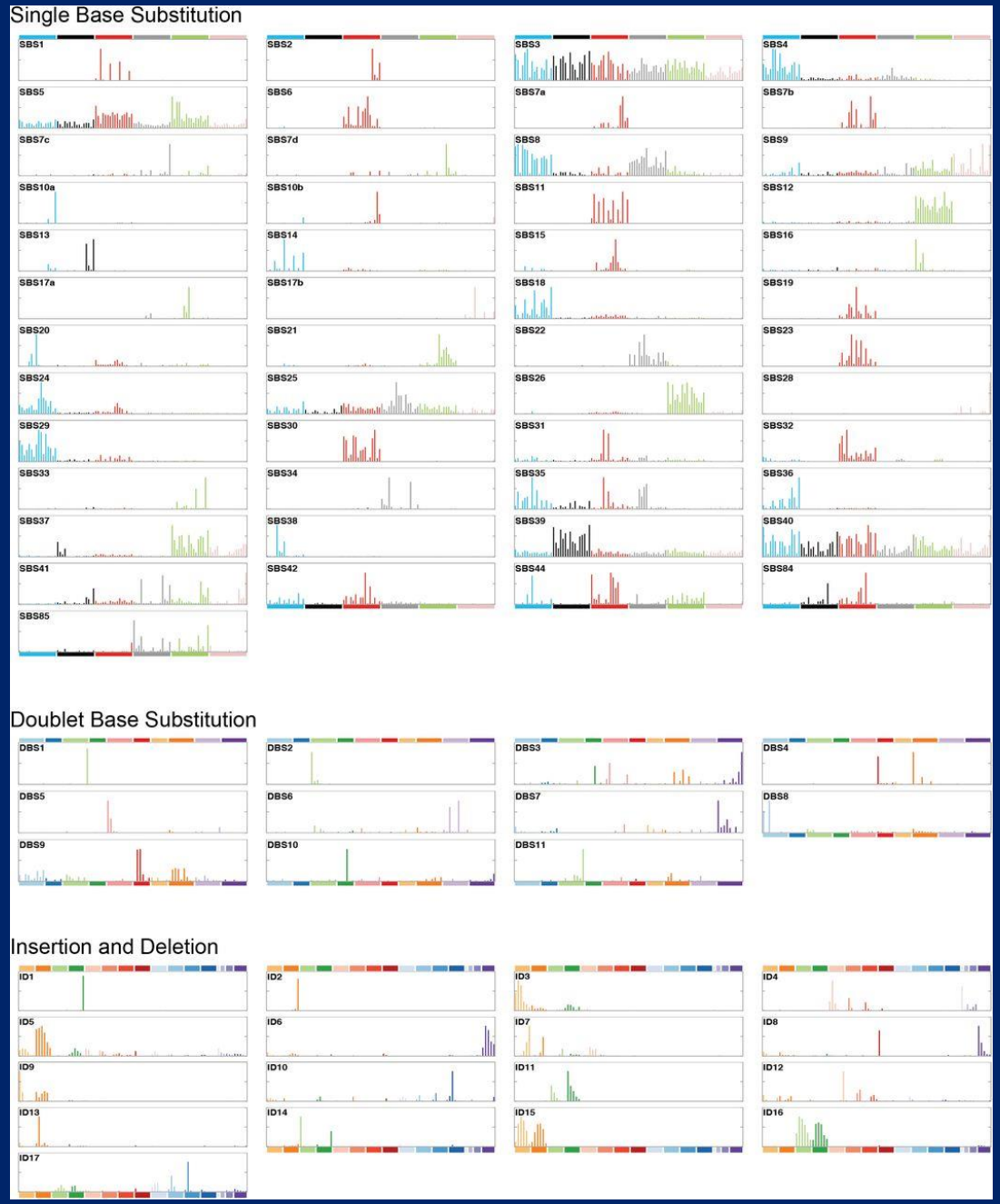




Gou et al, https://doi.org/10.1016/j.lfs.2020.118434

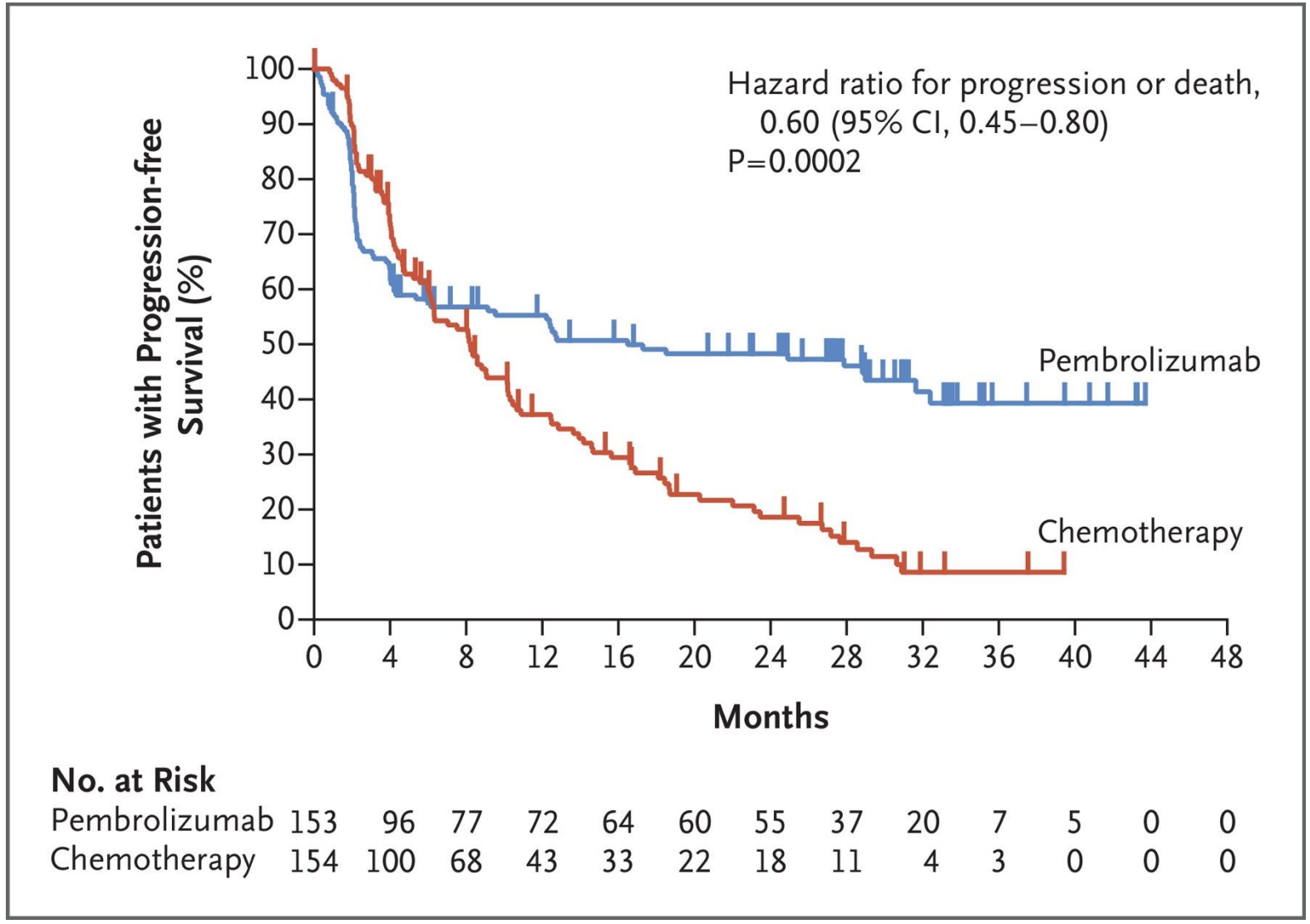
Mutational Signatures Reflect Mechanism of Carcinogenesis

Some mutational signatures reflect specific DNA damage repair defects (e.g. HRD)



Alexandrov et al, https://doi.org/10.1101/322859

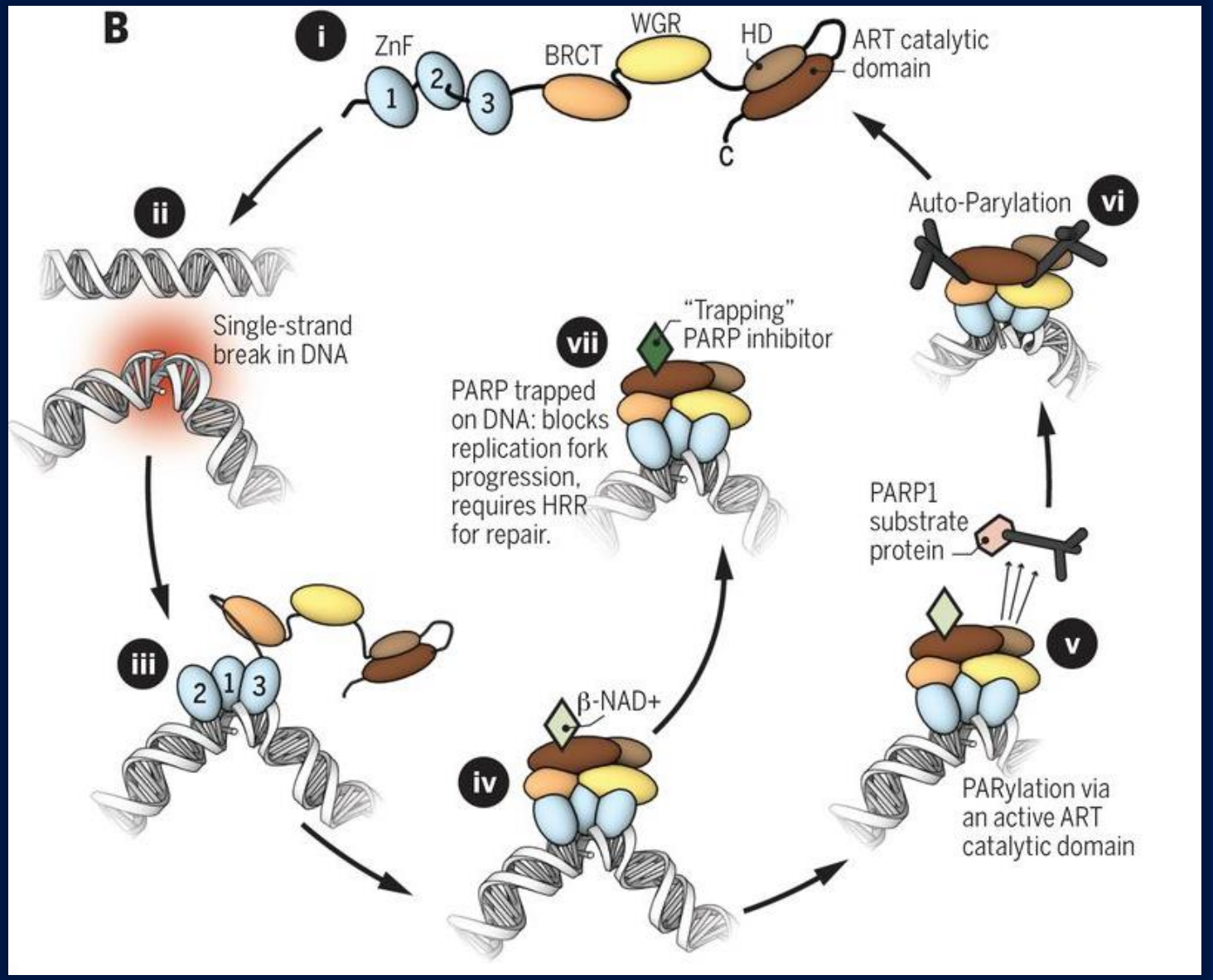
Treatment May Target the Result ("Phenotype") of Repair Defect



Andre et al, **DOI: 10.1056/NEJMoa2017699**M

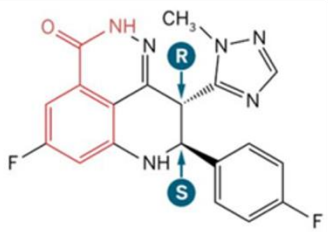
Treatment may target the PROCESS of repair deficiency

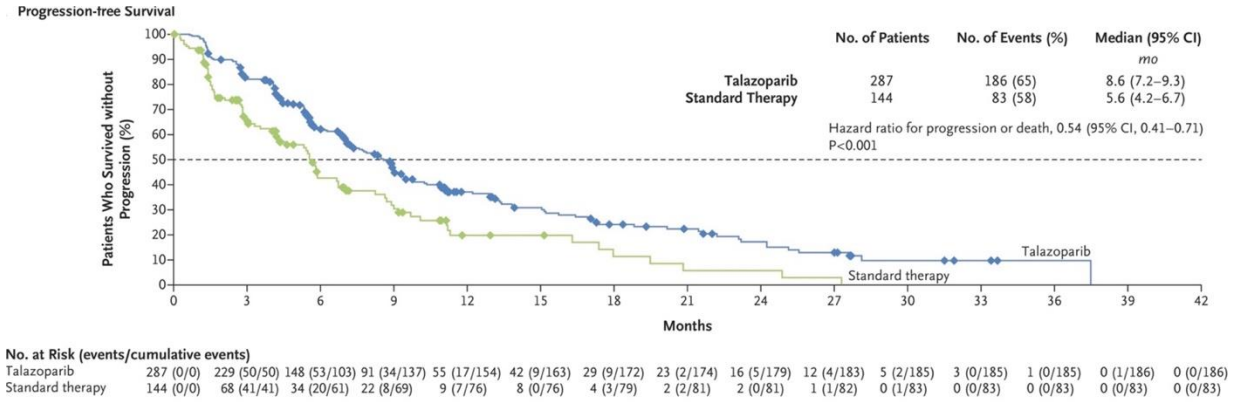
Example: Synthetic lethality of PARPi in HR-deficient cells



Treatment May Target the PROCESS of Repair Deficiency

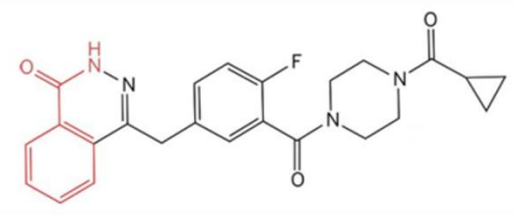
Talazoparib

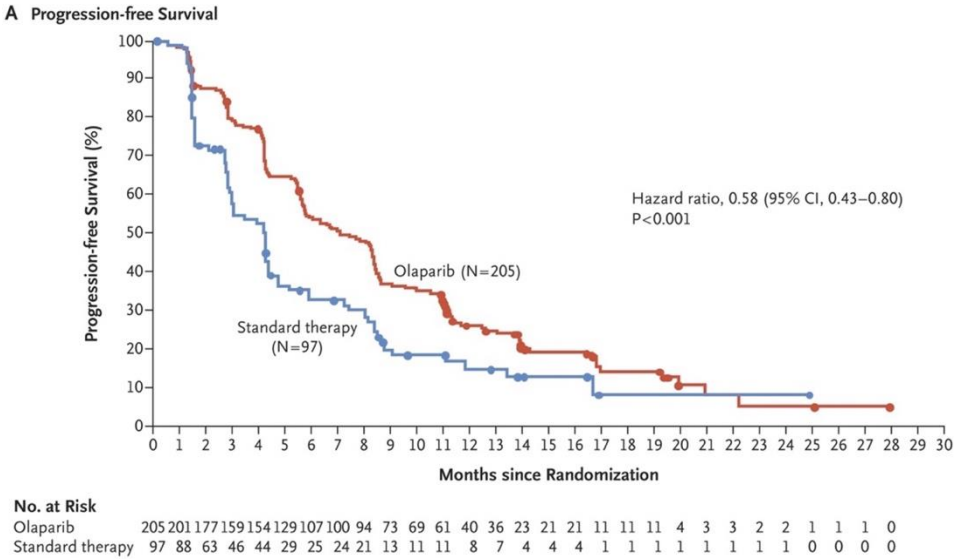




Litton et al, NEJM 2018

Olaparib

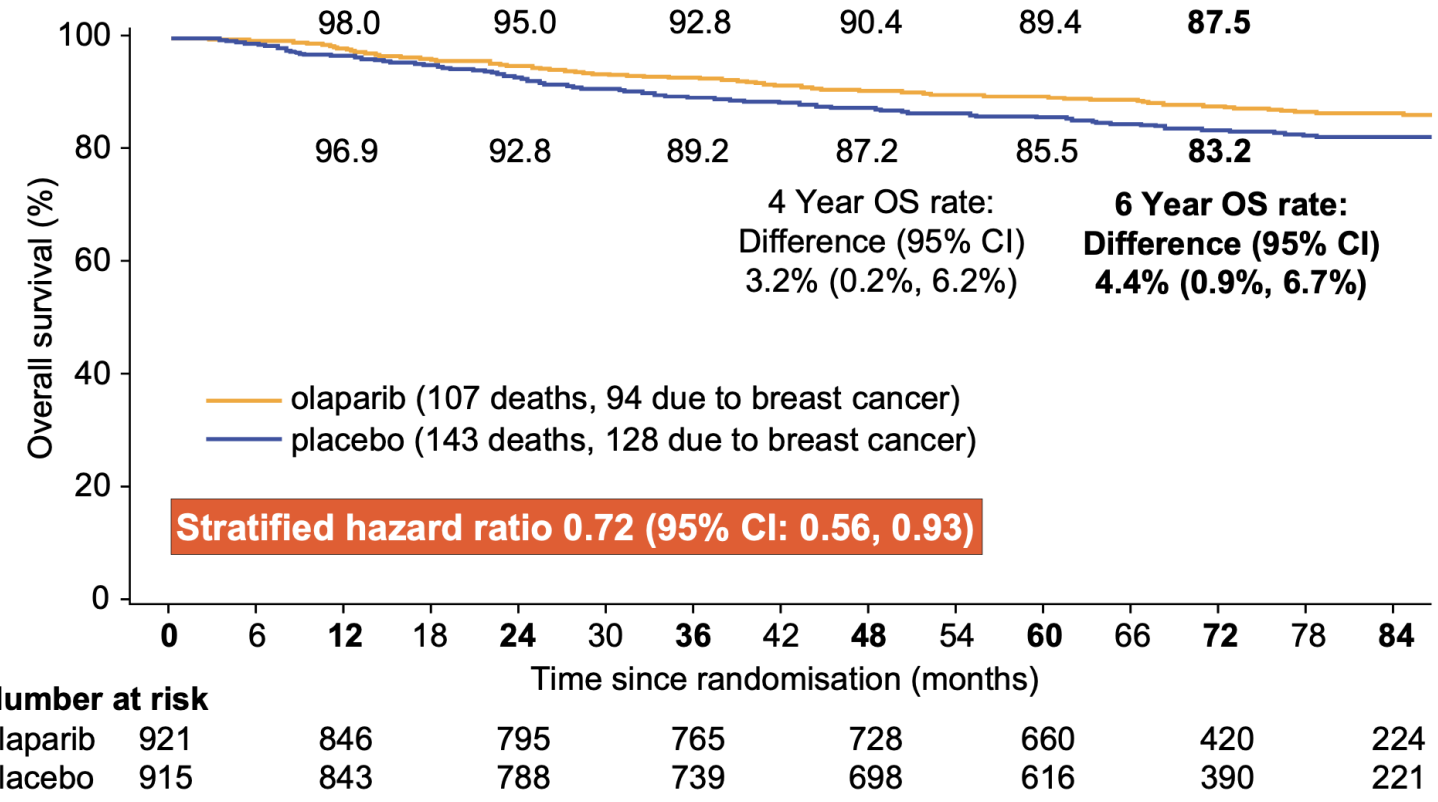




Robson et al, NEJM 2017

Outcomes of OlympiA 10 years after FPI

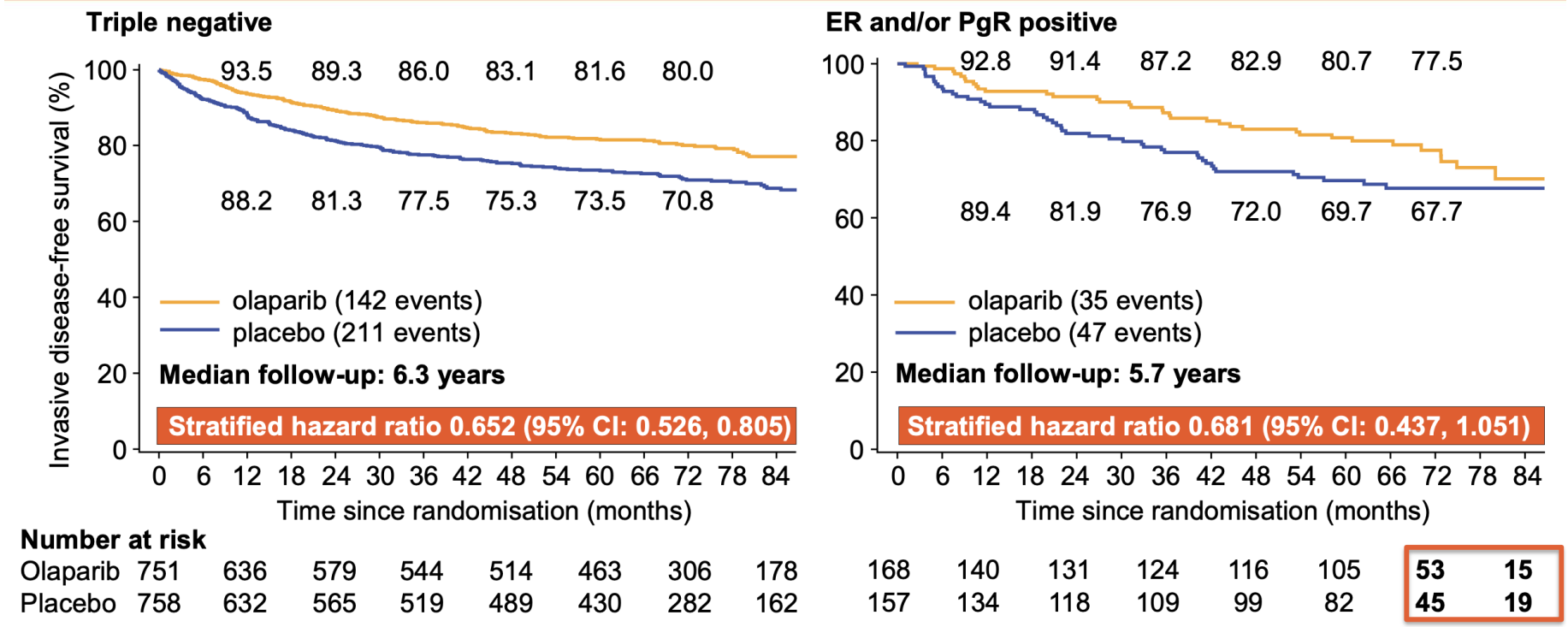
Analysis of OS (ITT)



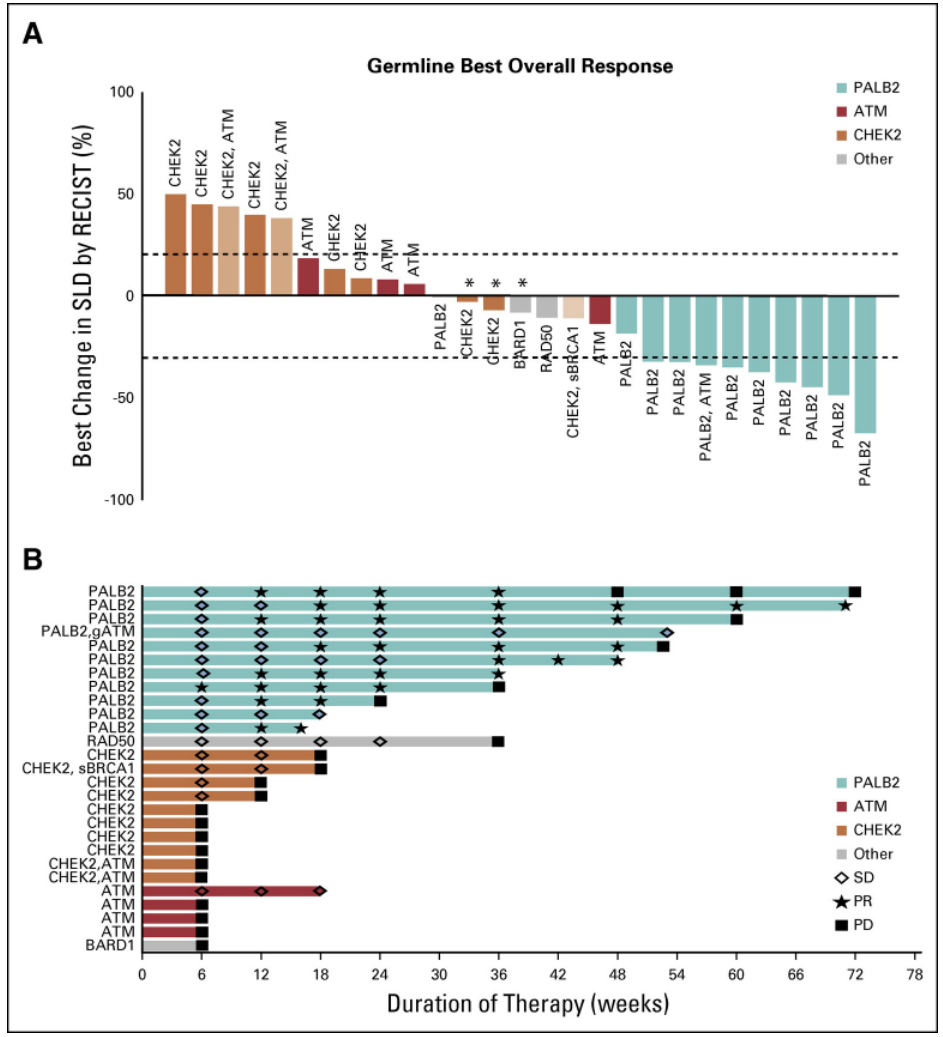
Garber et al, SABCS 2024

Outcomes of OlympiA 10 years after FPI

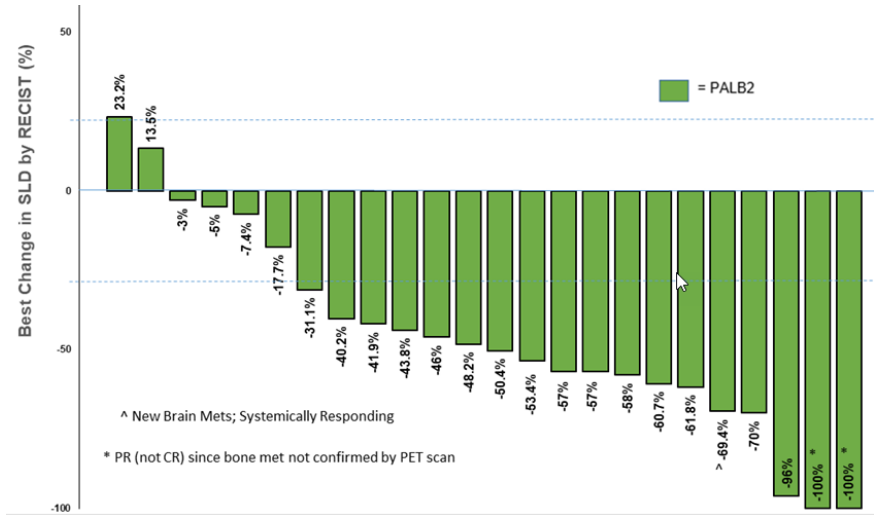
Analysis of IDFS by HR status



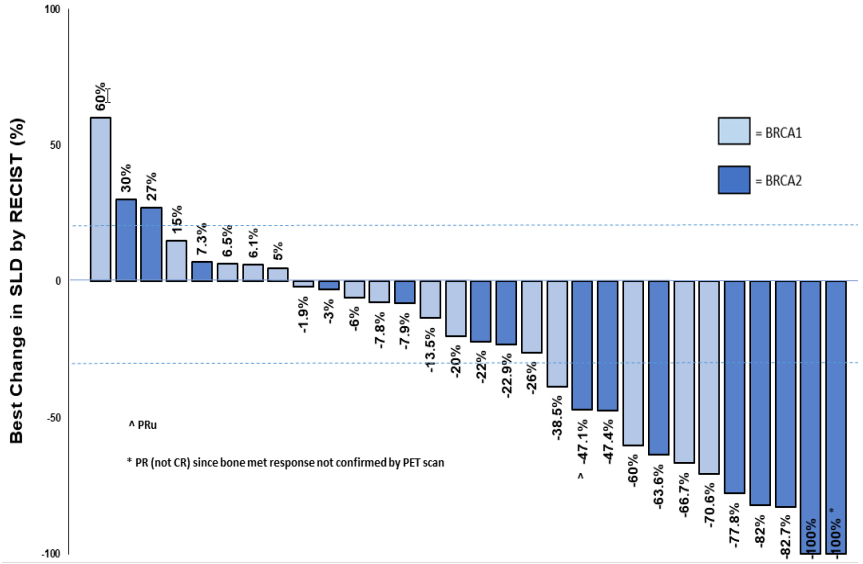
Garber wt al SABCS 2024



Tung N, Robson M et al, JCO 2021

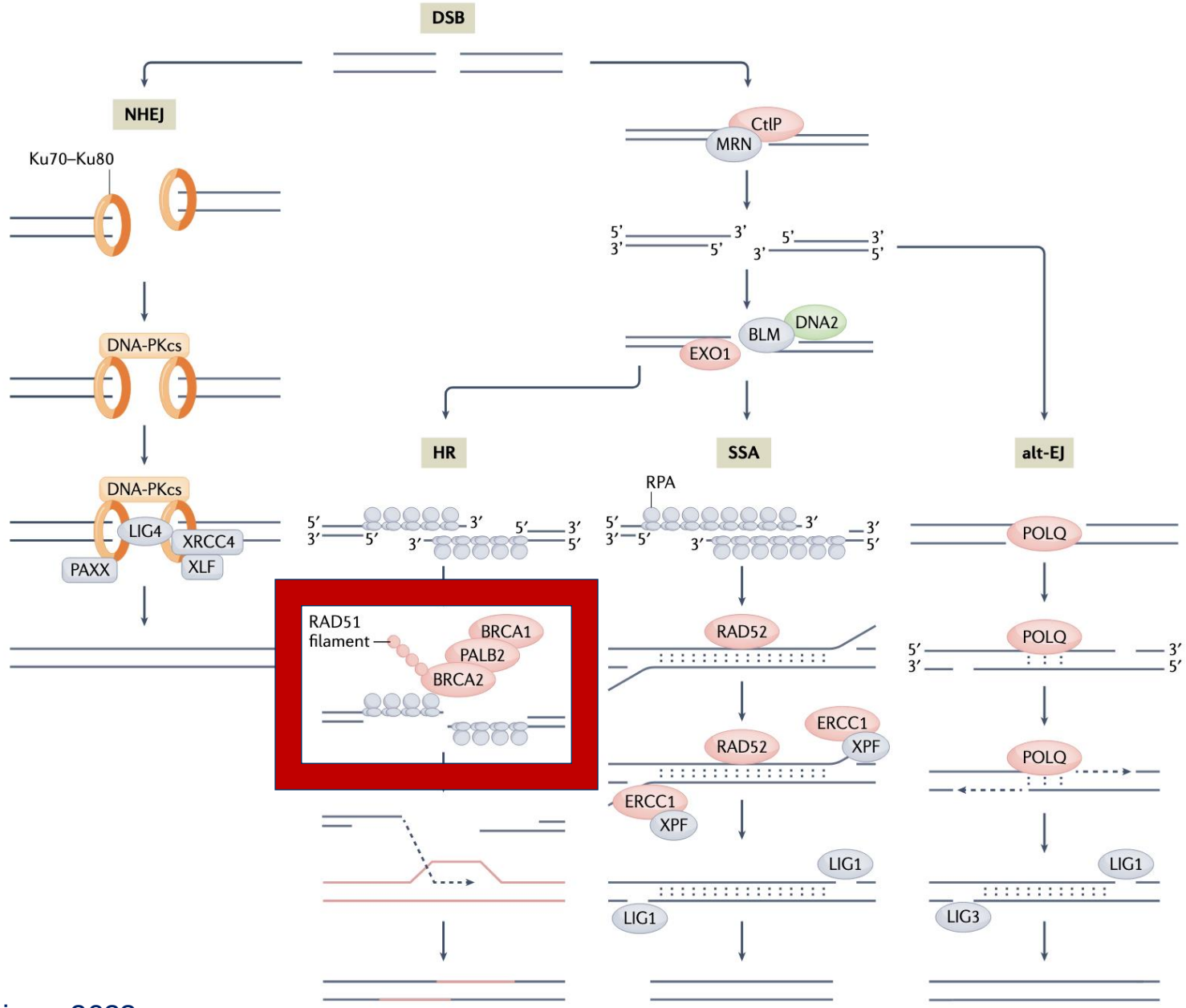


ORR 75%



ORR 37%

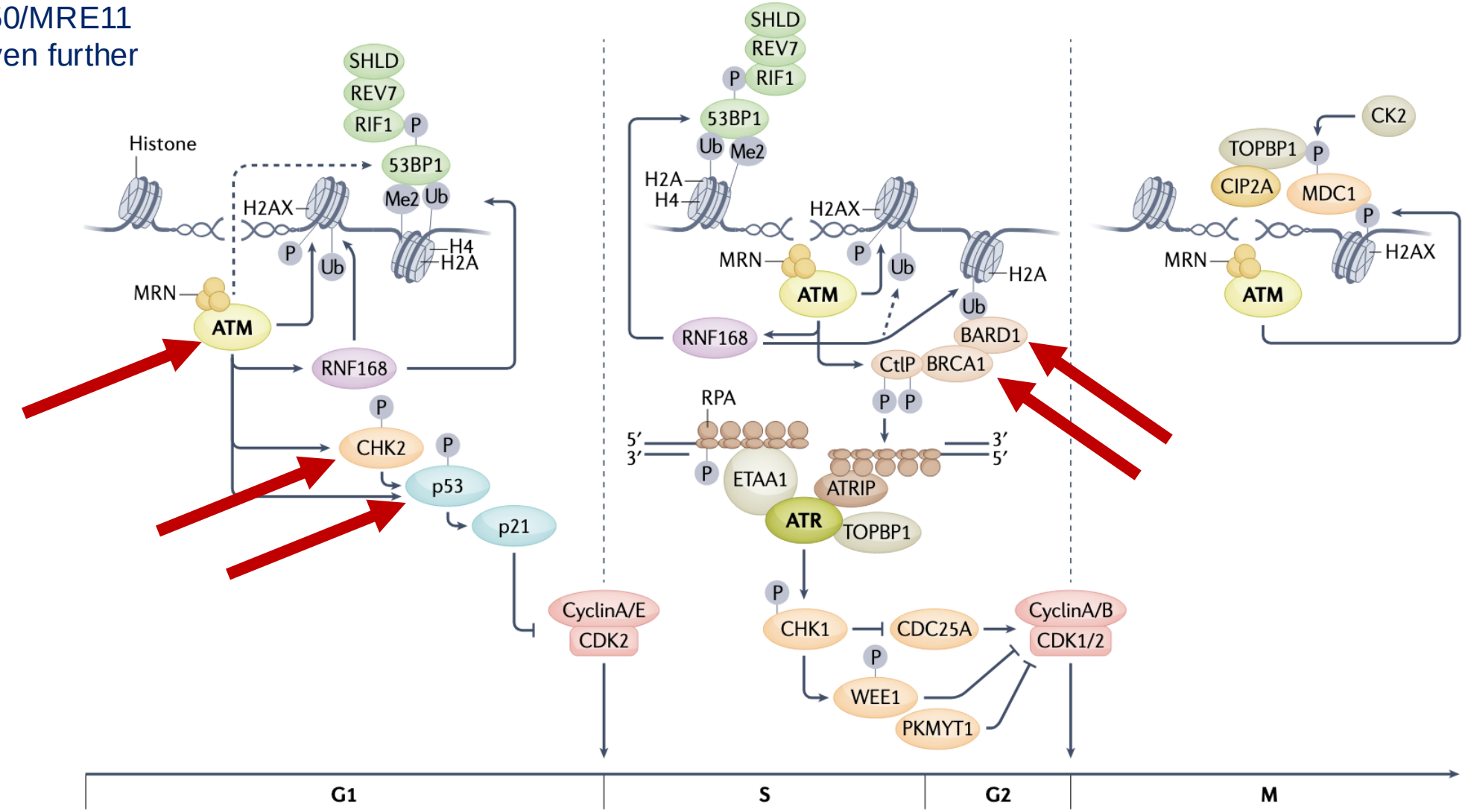
Tung N, Robson M et al, ASCO 2024



Groelly et al, Nature Cancer Reviews 2023

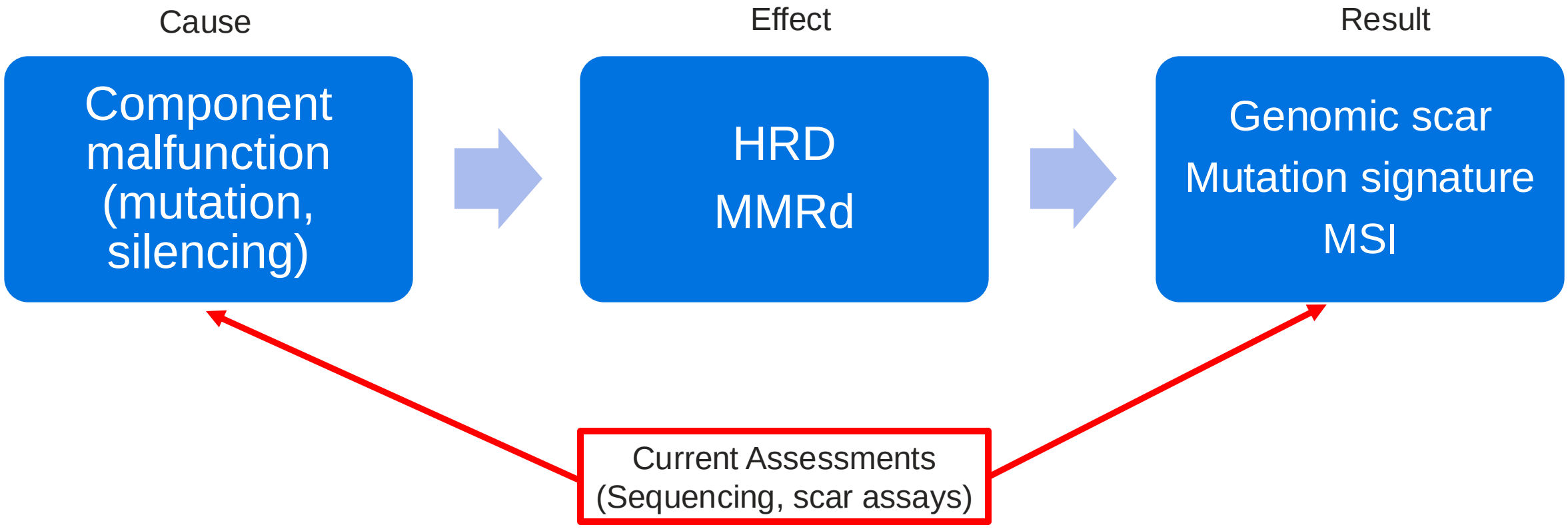
Mark Robson, MD, FASCO

NBN/RAD50/MRE11 complex even further “upstream”



Groelly et al, Nature Cancer Reviews 2023

Problem: How to measure the process

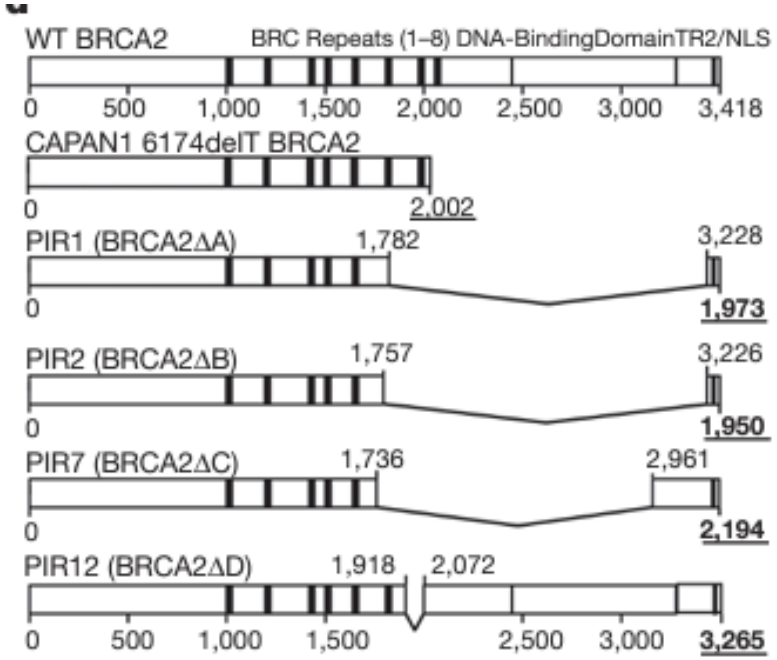


Multiple mechanisms of PARPi resistance

Resistance to therapy caused by intragenic deletion in *BRCA2*

Stacey L. Edwards[1], Rachel Brough[1], Christopher J. Lord[1], Rachael Natrajan[1], Radost Vatcheva[1], Douglas A. Levine[2], Jeff Boyd[3], Jorge S. Reis-Filho[1] & Alan Ashworth[1]

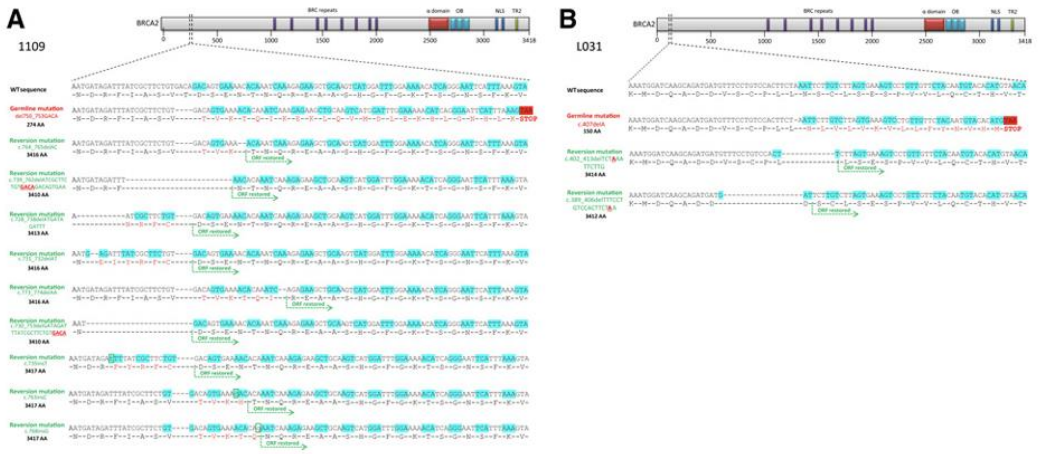
Nature 2008



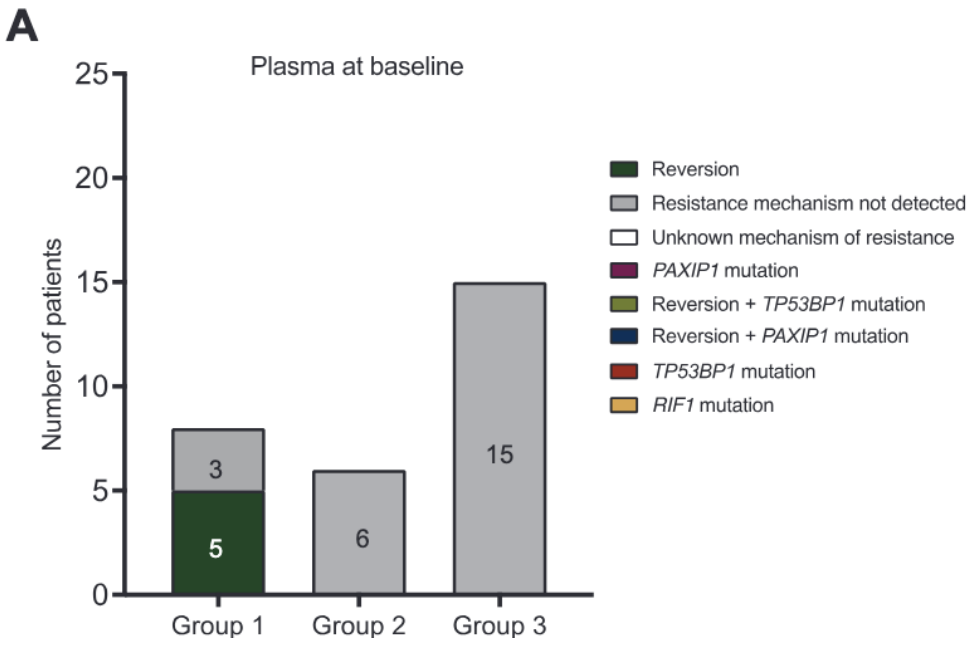
Diverse *BRCA1* and *BRCA2* Reversion Mutations in Circulating Cell-Free DNA of Therapy-Resistant Breast or Ovarian Cancer

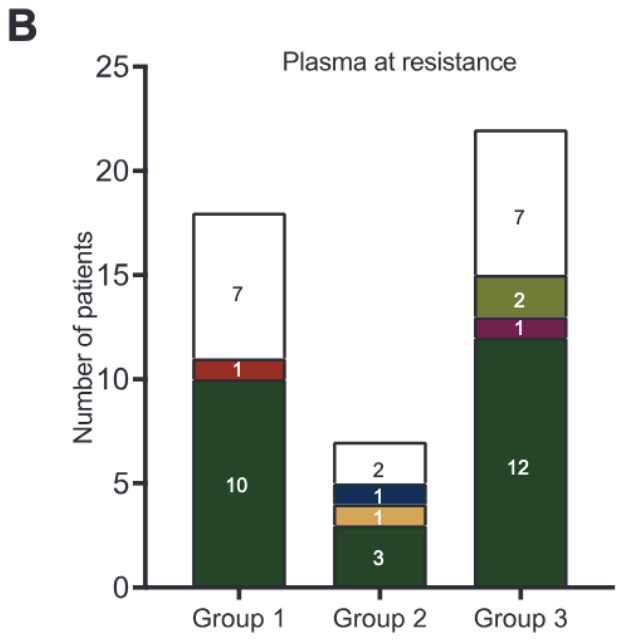
Britta Weigelt[1], Iñaki Comino-Méndez[2], Ino de Bruijn[1], Lei Tian[3], Jane L. Meisel[4,5], Isaac García-Murillas[2], Charlotte Fribbens[2,6], Ros Cutts[2], Luciano G. Martelotto[1], Charlotte K.Y. Ng[1,7,8], Raymond S. Lim[1], Pier Selenica[1], Salvatore Piscuoglio[1,7], Carol Aghajanian[4], Larry Norton[4], Rajmohan Murali[1], David M. Hyman[4], Laetitia Borsu[1], Maria E. Arcila[1], Jason Konner[4], Jorge S. Reis-Filho[1], Roger A. Greenberg[3], Mark E. Robson[4], and Nicholas C. Turner[2,6]

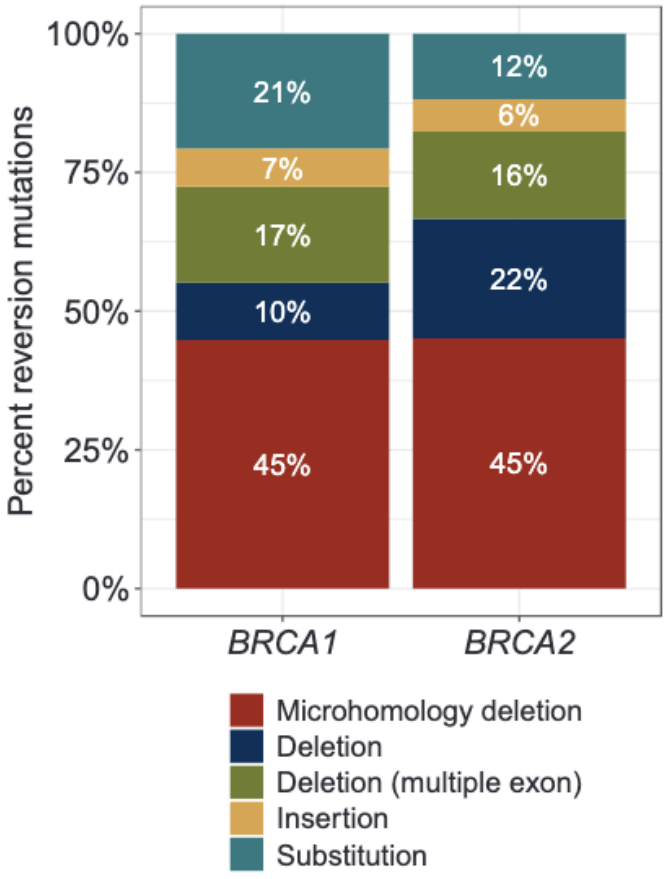
Clin Cancer Res 2017



PARPi resistance mechanisms







Group 1: de novo resistant
Group 2: minimal response
Group 3: response, then progression

Harvey-Jones et al, Ann Oncol 2024

Scars may remain …

Summary

- Not all defects in DNA damage repair are the same (DDR is a *very* broad term)
- Not all defects in DNA damage repair are (currently) targetable
- The results of some defects are targetable (e.g. MSI, TMB)
- The process of some defects are targetable (e.g. HRD)
- Current assays are largely measuring results, not process
- Dynamic measurement of process may maximize benefit of certain treatments

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