PARPi Resistance – Mechanisms, Diagnosis and Solutions

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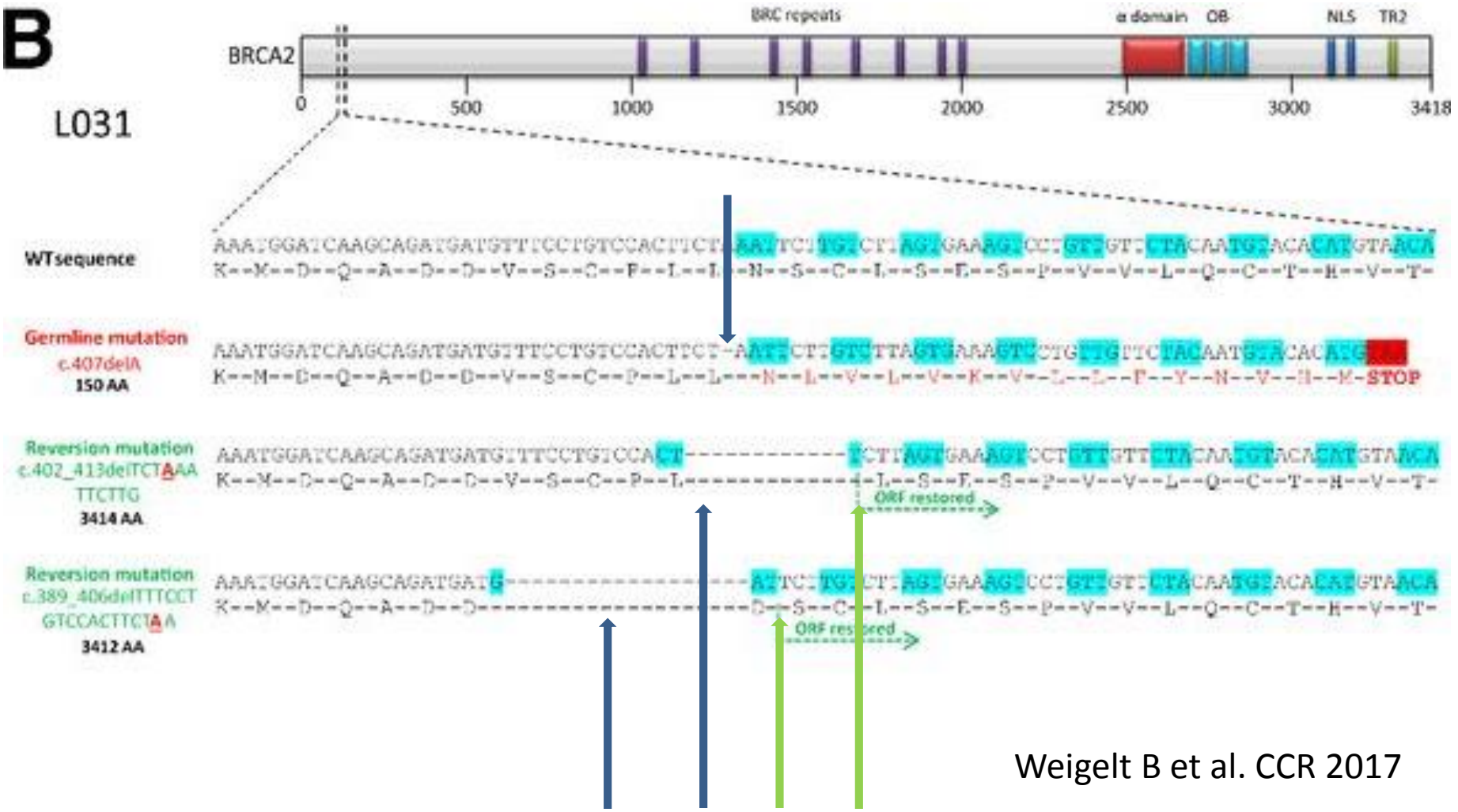
March 9, 2018

Emergence of PARPi resistance

	PFS – BRCA mut	DOR – BRCA mut	PFS – BRCA WT / LOH high	DoR – BRCA WT / LOH high
Olaparib / rec. OvCa	7mo	7.4-8.0mo		
Olaparib / maintenance	11.2mo		7.4mo	
Rucaparib / rec. OvCa	12.8mo	9.2mo	5.7mo	10.8mo
Rucaparib / maintenance	16.6mo		13.6mo	

gBRCA mut OvCa – RR ranges from 30% to 60%, depending on platinum resistance status and # of previous treatment lines

Mechanisms – *BRCA* reversion mutations

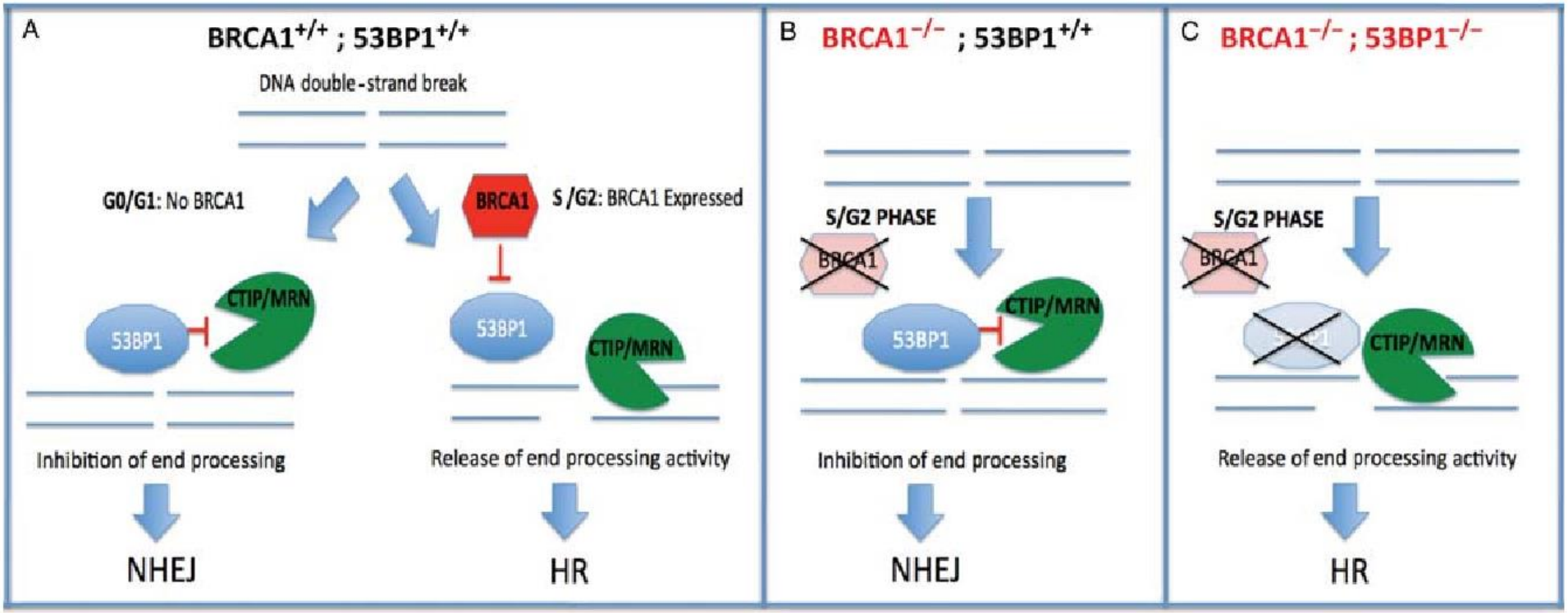


Weigelt B et al. CCR 2017

BRCA reversion mutation - facts

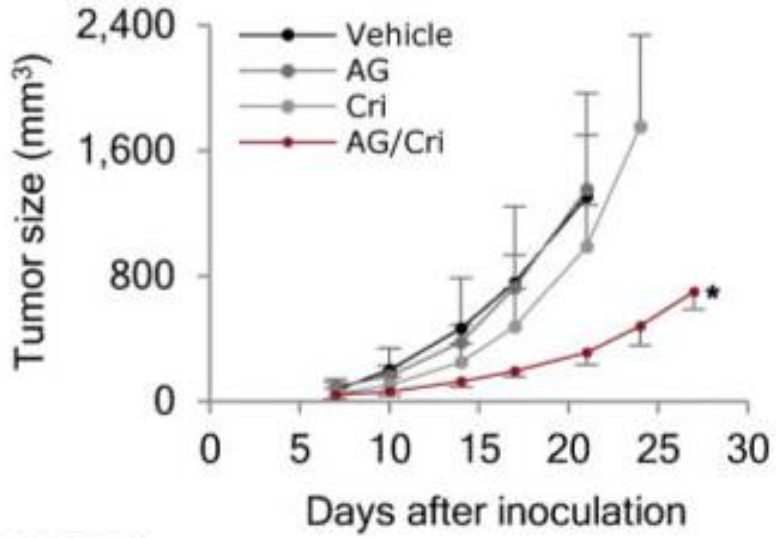
- Occurs in ~30% of recurrent OvCa
- 95% are platinum-resistent
- More common in BRCA2 carriers (46%) than BRCA1 (19%).
- Occurs in 10% of primary OvCa tumors of women who had previous breast cancer and treated with chemo
- Probably induced by DNA-damaging agents.

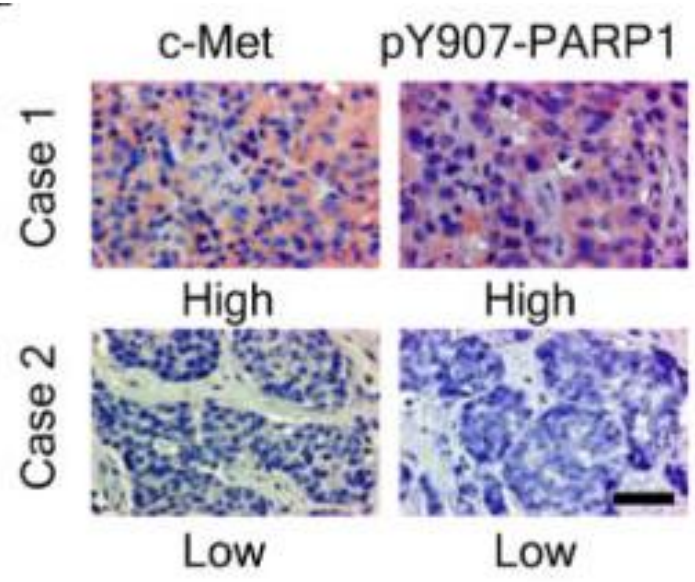
Other mechanisms – 53BP1 inactivation

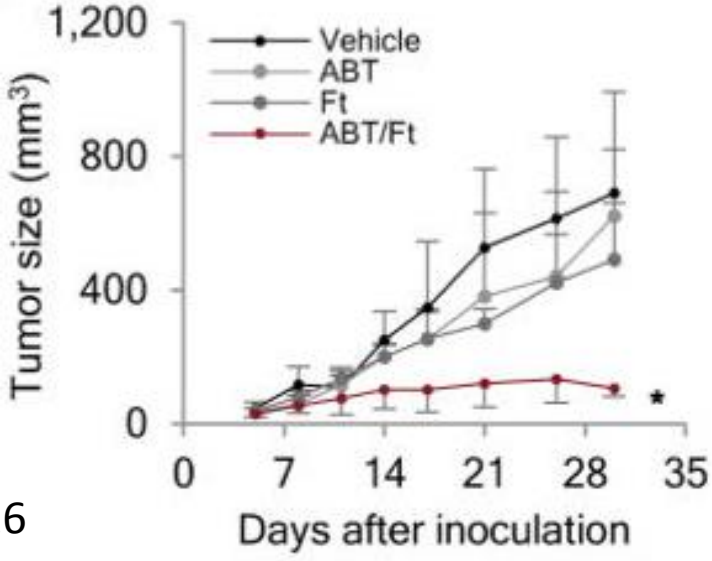


Aly et al. JMCB 2011

Other mechanisms – c-MET activation







Du et al. Nat Med 2016

Additional mechanisms of PARPi resistance

- wt BRCA retention and copy number gain (Maxwell et al. Nat Comm 2017; Lheureux et al. JCO 2017)
- Loss of wtBRCA allele promoter methylation (Ter Brugge et al. JNCI 2016)
- p-glycoprotein drug efflux transporter (Durmus et al. Phar Res 2014)
- mTOR pathway activation and S6 phosphorylation (Sun et al. Oncotarget 2014)
- miRNA-622 OE and restriction of NHEJ (Choi et al. Cell Reports 2016)

Predictive biomarkers for PARPi resistance

- *BRCA* reversion mutations can be detected using cfDNA in 20% of platinum-resistant OvCa patients, 40% of platinum and/or PARPi pre-treated BrCa patients and in PrCa patients previously treated with PARPi (and no platinum-based chemo).
- Multiple sub-clonal variants → requires NGS techniques of detection

Long-term PARPi response

- Study 19 – 37/136 OvCa patients are LT responders (>2y)
- 32/37 received Olaparib
- *BRCA* mut , HRD-score >42, and Olaparib treatment were significantly associated with LT response.
- No molecular biomarker identified

Possible solutions for PARPi resistance?

- Improve predictive biomarkers
- Avoid platinum before PARPi- is that possible?
- Combination therapy trials with:
  - mTOR pathway inhibitors
  - HDAC inhibitors
  - HSP90 inhibitors
  - c-MET inhibitors
  - WEE1 inhibitors

Thank you