Module 5: Other Promising Novel Agents and Strategies Under Investigation

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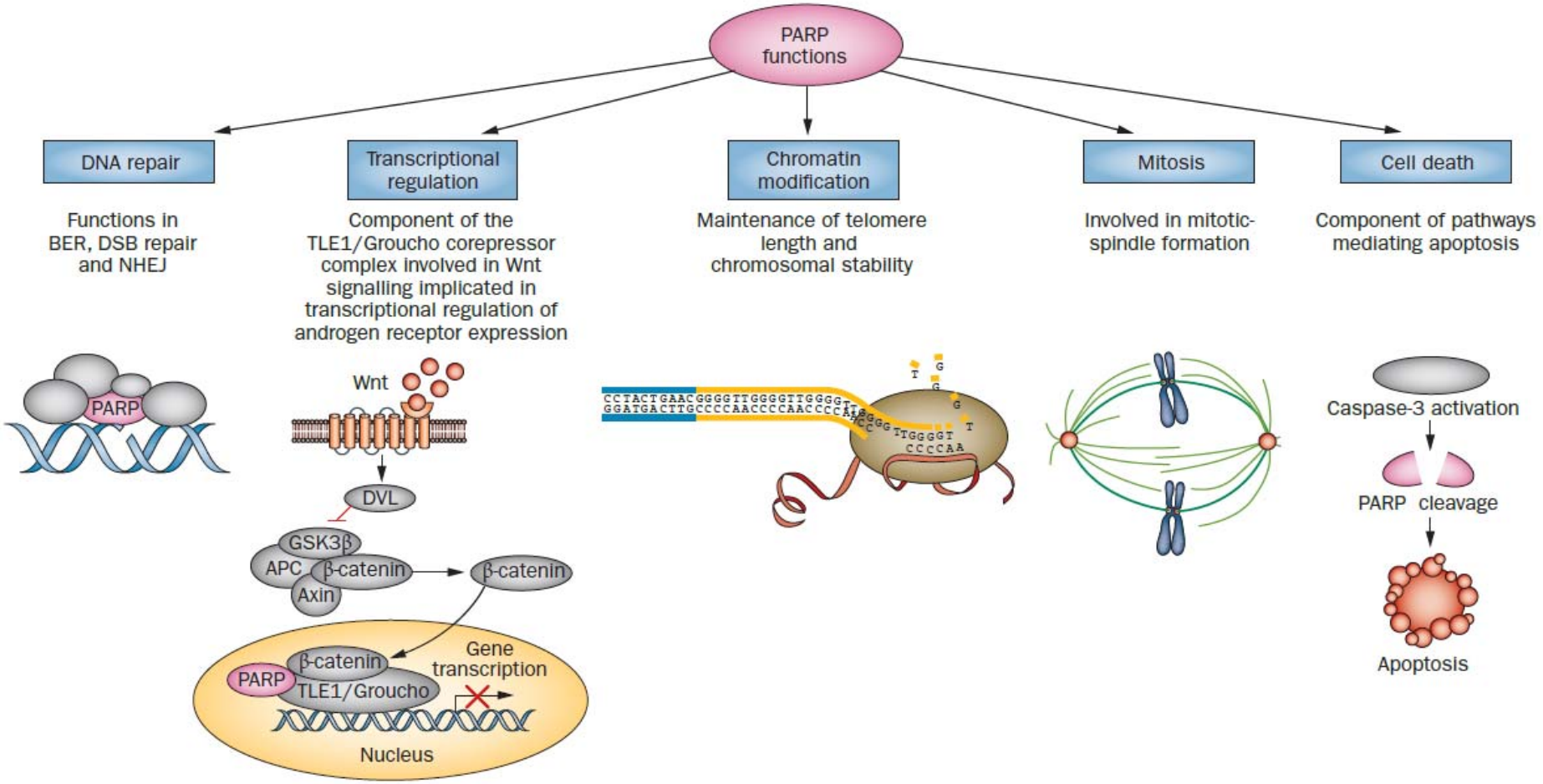
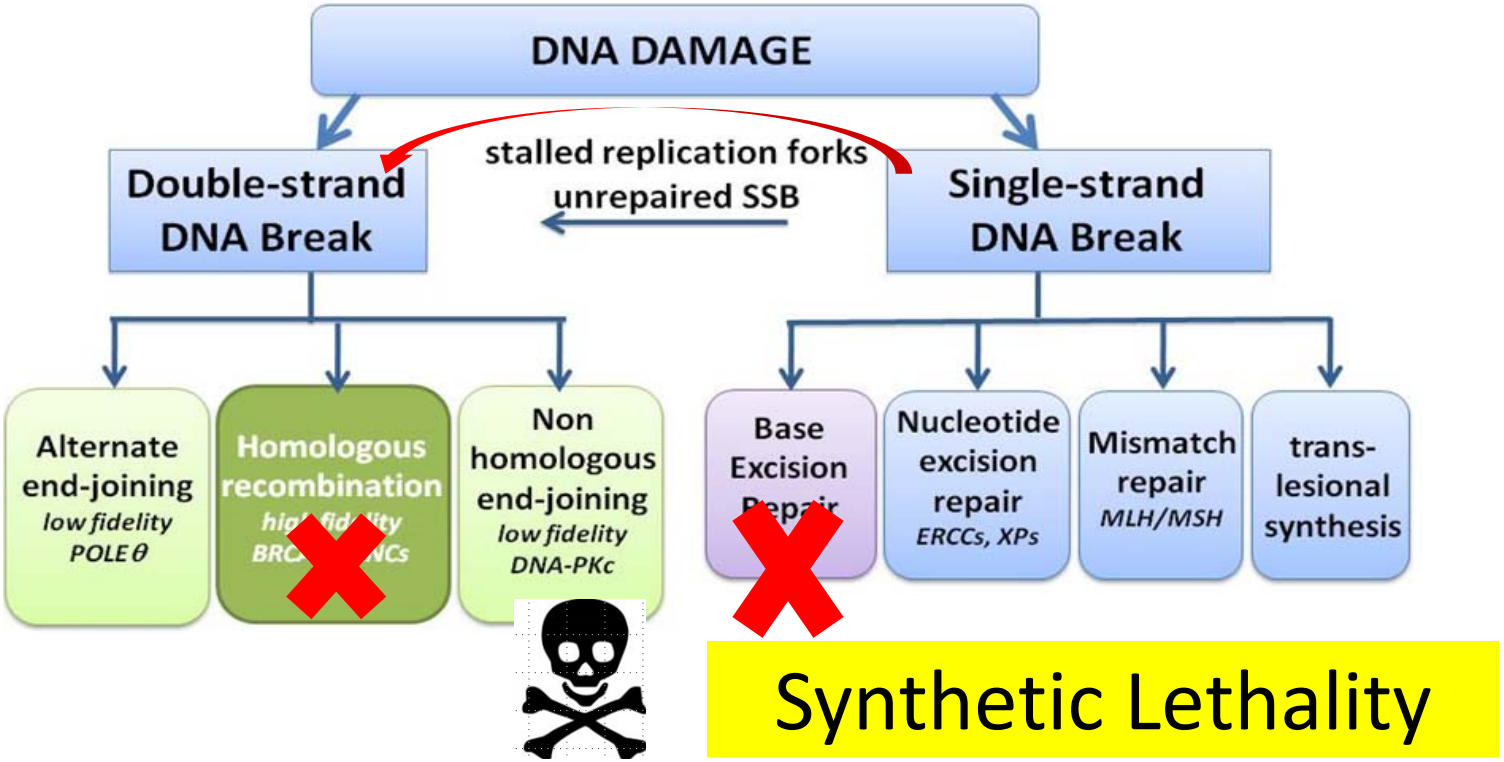
Disclosures

Consulting Agreements	Bayer HealthCare Pharmaceuticals, Bellicum Pharmaceuticals Inc, Dendreon Pharmaceuticals Inc, Exelixis Inc, Ferring Pharmaceuticals, Johnson & Johnson Pharmaceuticals, Medivation Inc, Pfizer Inc, Roche Laboratories Inc, Sanofi, Takeda Oncology, Tyme
Contracted Research	Celgene Corporation, Dendreon Pharmaceuticals Inc, ImClone Systems, a wholly owned subsidiary of Eli Lilly and Company, Johnson & Johnson Pharmaceuticals, OncoGenex Pharmaceuticals Inc, Progenics Pharmaceuticals Inc, Roche Laboratories Inc, Takeda Oncology
Stock Ownership	Bellicum Pharmaceuticals Inc, Tyme

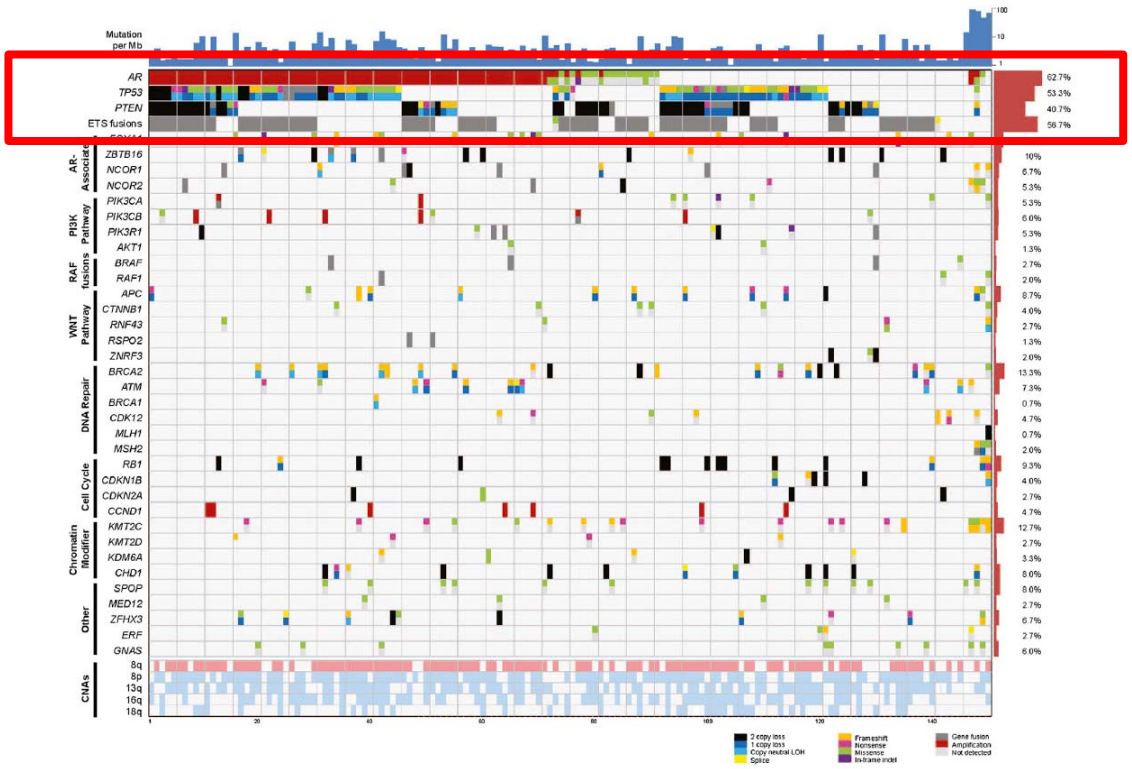


Sonnenblick. Nature Review 2015

Synthetic Lethality: PARP inhibition in HRD cancer



Genomic aberrations of mCRPC

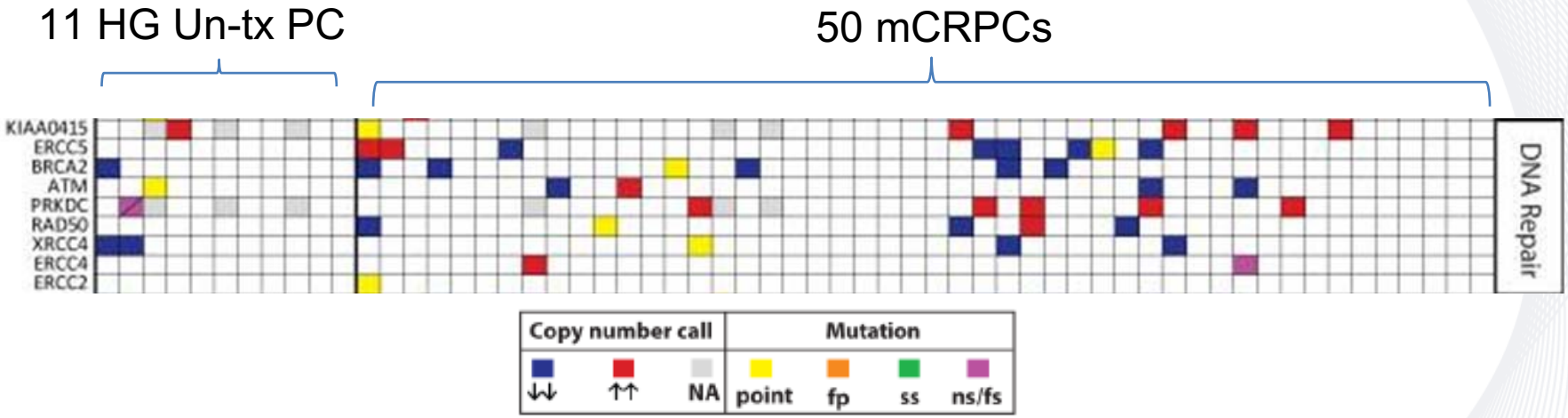


AR
TP53
PTEN
ETS fusion

>90% of mCRPCs harbor actionable mutations

~23% harbor mutations in DNA repair pathway, including bi-allelic loss of *BRCA2, ATM, BRCA1, FANCA, RAD51B, RAD51C and CDK12*

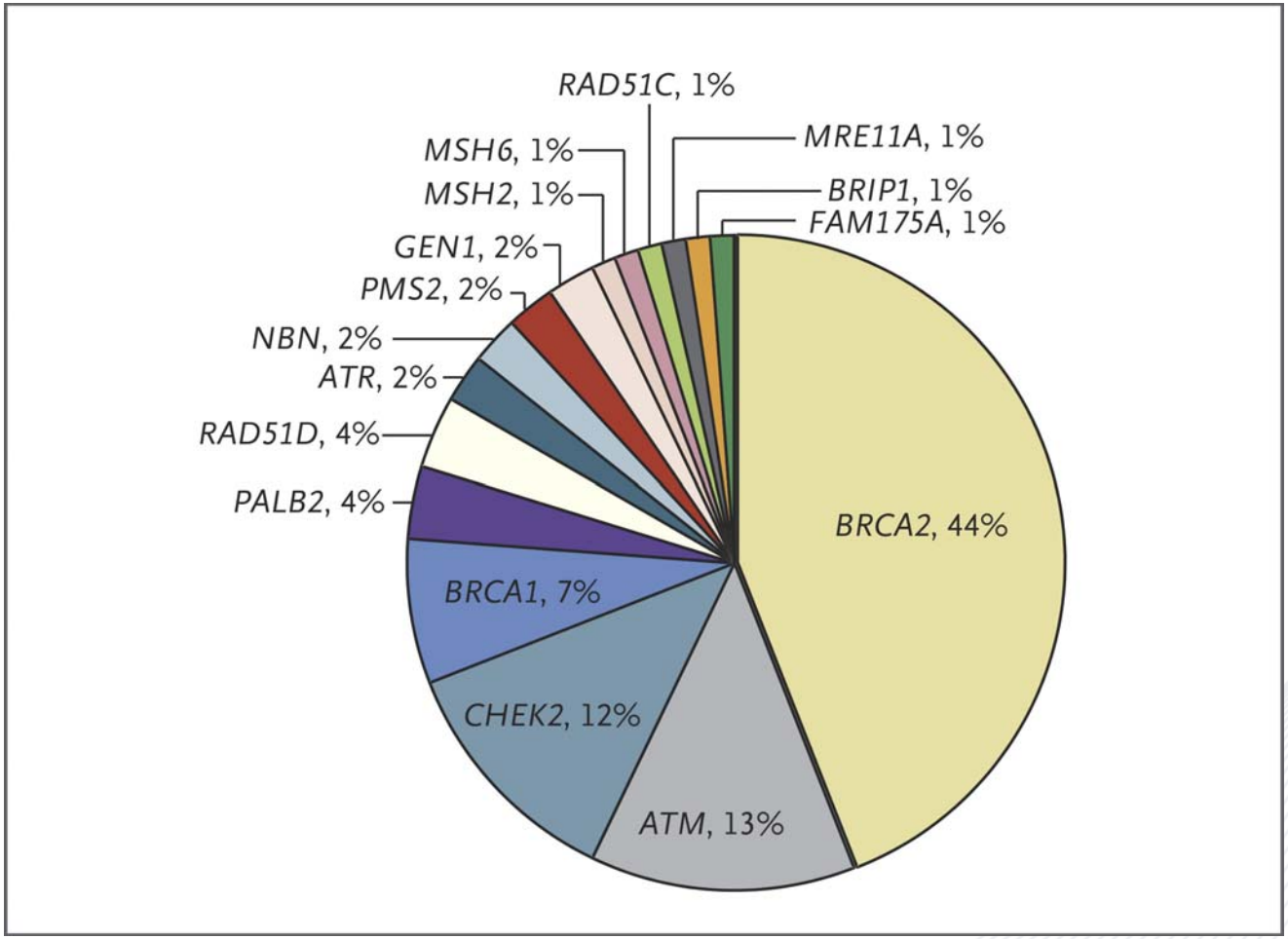
Robinson D. Cell 2015



Approximately 50% (24 cases of mCRPC) with aberration in DNA repair genes

Grosso 2012. Nature

Distribution of Presumed Pathogenic Germline Mutations



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Germline DNA-Repair Gene Mutations in Seven Metastatic Prostate Cancer Case Series

Table 3. Germline DNA-Repair Gene Mutations in Seven Metastatic Prostate Cancer Case Series.

Case Series	Description	Patients	Patients with Mutations
		no.	*no. (%)*
1	Stand Up To Cancer–Prostate Cancer Foundation discovery series	150	15 (10.0)
2	Stand Up To Cancer–Prostate Cancer Foundation validation series	84	9 (10.7)
3	Royal Marsden Hospital	131	16 (12.2)
4	University of Washington	91	8 (8.8)
5	Weill Cornell Medical College	69	7 (10.1)
6	University of Michigan	43	4 (9.3)
7	Memorial Sloan Kettering Cancer Center	124	23 (18.5)
Total		692	82 (11.8)

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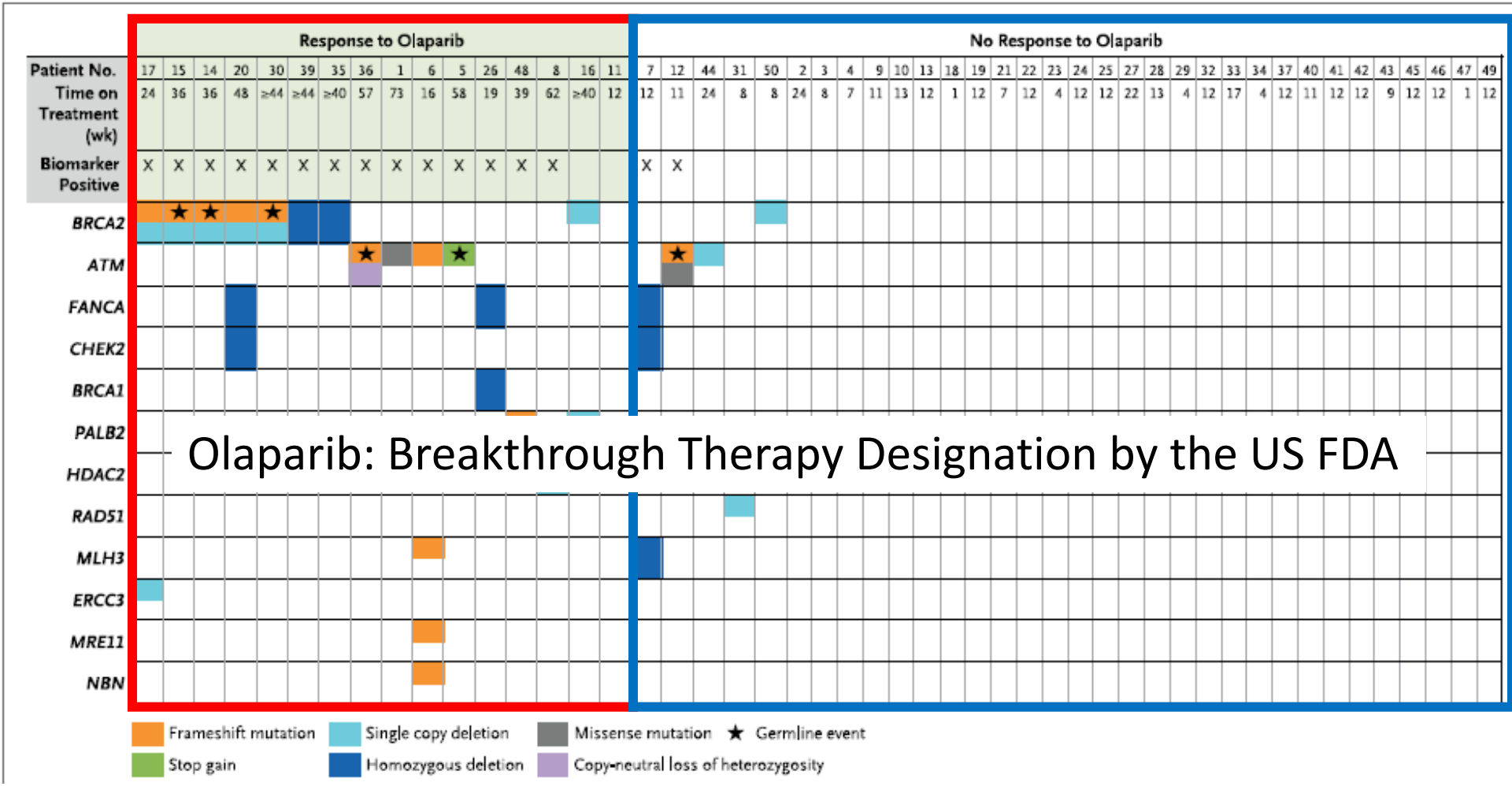
Olaparib in Prostate Cancer

- **TOPARP study: n=49 patients with mCRPC who are docetaxel-pre-treated** (Mateo et al. 2015):
  - **32.7% (16/49**) response rate in “unselected” mCRPC patients
  - Genomic analysis of their prospectively obtained tumor samples:
    - **16 (33%)** had mutations in DNA repair pathway (*ATM, BRCA2* and others*)* (biomarker positive)
      - **14 of these patient responded**
    - **33 (67%)** had no such mutations (biomarker negative)
      - **2** of these patients responded


Response to Olaparib
No Response to Olaparib
Patient No.
Time on Treatment (wk)
Biomarker Positive
17 15 14 20 30 39 35 36 1 6 5 26 48 8 16 11
24 36 36 48 ≥44 ≥44 ≥40 57 73 16 58 19 39 62 ≥40 12
X X X X X X X X X X X X X X
7 12 44 31 50 2 3 4 9 10 13 18 19 21 22 23 24 25 27 28 29 32 33 34 37 40 41 42 43 45 46 47 49
12 11 24 8 8 24 8 7 11 13 12 1 12 7 12 4 12 12 22 13 4 12 17 4 12 11 12 12 9 12 12 1 12
X X
BRCA2
ATM
FANCA
CHEK2
BRCA1
PALB2
HDAC2
RAD51
MLH3
ERCC3
MRE11
NBN
Olaparib: Breakthrough Therapy Designation by the US FDA
Frameshift mutation
Single copy deletion
Missense mutation
Germline event
Stop gain
Homozygous deletion
Copy-neutral loss of heterozygosity

Ongoing Trials of PARP Inhibitors

Ph	Agent	Setting	Tx Arms	Primary Endpoint	NCT
1	Olaparib	**Intermediate/High Risk Prostate Cancer Before Radical Prostatectomy (CaNCaP03)**	Olaparib + Degarelix vs Olaparib alone	Biomarker endpoint (PARP inhibition)	NCT02324998 (Not yet open)
2	Rucaparib	HR deficient mCRPC (deleterious mt in BRCA1/2 or ATM or other HR genes)	Rucaparib	ORR and PSA response	TRITON2 NCT02952534
3	Rucaparib	mCRPC, HR deficient (BRCA1/2 or ATM)	Rucaparib vs Investigator choice (Doc, Abi, Enz)	rPFS	TRITON3 NCT02975934 (Not yet open)
2	Niraparib	mCRPC (taxane and AR pre-treated) (Biomarker positive for HR deficient)	Niraparib	Response rate	NCT02854436 (Open)

Combination Trials

Ph	Agent	Setting	Tx Arms/Cohort	Primary Endpoint	NCT
Ib/II	Olaparib	mCRPC A: Post-Docet B: Post-Ai/Enz C: Post-Abi / naïve to Enz and chemo	A: Pembro + Olaparib B: Pembro + Docet/Pred C: Pembro + Enzalutamide	PSA response and toxcity	KEYNOTE-365
R-II	Olaparib	mCRPC (≥ 2 prior lines)	Cediranib plus Olaparib vs Olaparib	rPFS	NCT02893917
I/II	Olaparib	mCRPC, (lung, breast, Ov, CRC)	Durva + Ced Durva + Ola Durva + CO	Safety and dose finding	NCT02484404

PD-L1 Expression in Prostate Cancer

- Hormone sensitive radical prostatectomy specimens express high levels of PD-L1 in 52.2% of cases (Gevensleben et al. Clin Cancer Res 2016)
- Patients progressing on enzalutamide have significantly increased PD-L1/2 dendritic cells in blood compared to those responding to treatment (Bishop et al. Oncotarget 2016)
- Nivolumab treatment in men with CRPC demonstrated no objective responses in 17 patients; 2 patients who had tissue stained for PD-L1 demonstrated no immunoreactivity (Topalian NEJM 2012)
- 3/20 samples (15%) had focal areas of PD-L1 positivity, although in only two of the three positive samples was plasma membrane staining clearly observed on malignant epithelial cell (Martin et al. Prostate Cancer and Prostatic Disease 2015)

Responding Patients: Pembrolizumab in Prostate Cancer

Responding Patients*

Patient Number	Date of Cycle 1	PSA (ng/ml) Baseline to Nadir	Measurable Disease at Baseline	Best Radiologic Response	MSI	Prior Treatment for mCRPC
1	April 2015	70.65 → 0.08	yes	PR	present	abi, enz
7	October 2015	46.09 → 0.02	no	n/a	n/a	abi, enz
10	January 2016	2502.75 → <0.01	yes	PR	absent	enz

* All responding patients remain on study.

PR – partial response; n/a – not aplicable (i.e. no baseline biopsy done); MSI – microsatellite instability; abi – abiratore; enz – enzalutamide

Graff JN et al. Oncotarget 2016;7(33):52810-7

Programmed death-1 blockade in mismatch repair deficient cancer independent of tumor histology

- 29 patients were enrolled and treated on this study, including the following histologies: (endometrial: 9; pancreatic: 4; ampullary: 4; biliary: 3; small bowel: 3; gastric: 3; thyroid: 1; prostate: 1)
- The one prostate cancer patient demonstrated an objective response

Diaz LA et al. J Clin Oncol 34, 2016 (suppl); abstr 3003

Conclusions

- Olaparib has activity in patients who have aberrant DNA repair pathways.
- Pembrolizumab demonstrated activity in unselected CRPC patients; Activity has been also demonstrated in a prostate cancer patient who is MSI high.