AstraZeneca
What science can do

DNA Damage Response analyst science event

Mene Pangalos, EVP, Innovative Medicines & Early Development and Business Development
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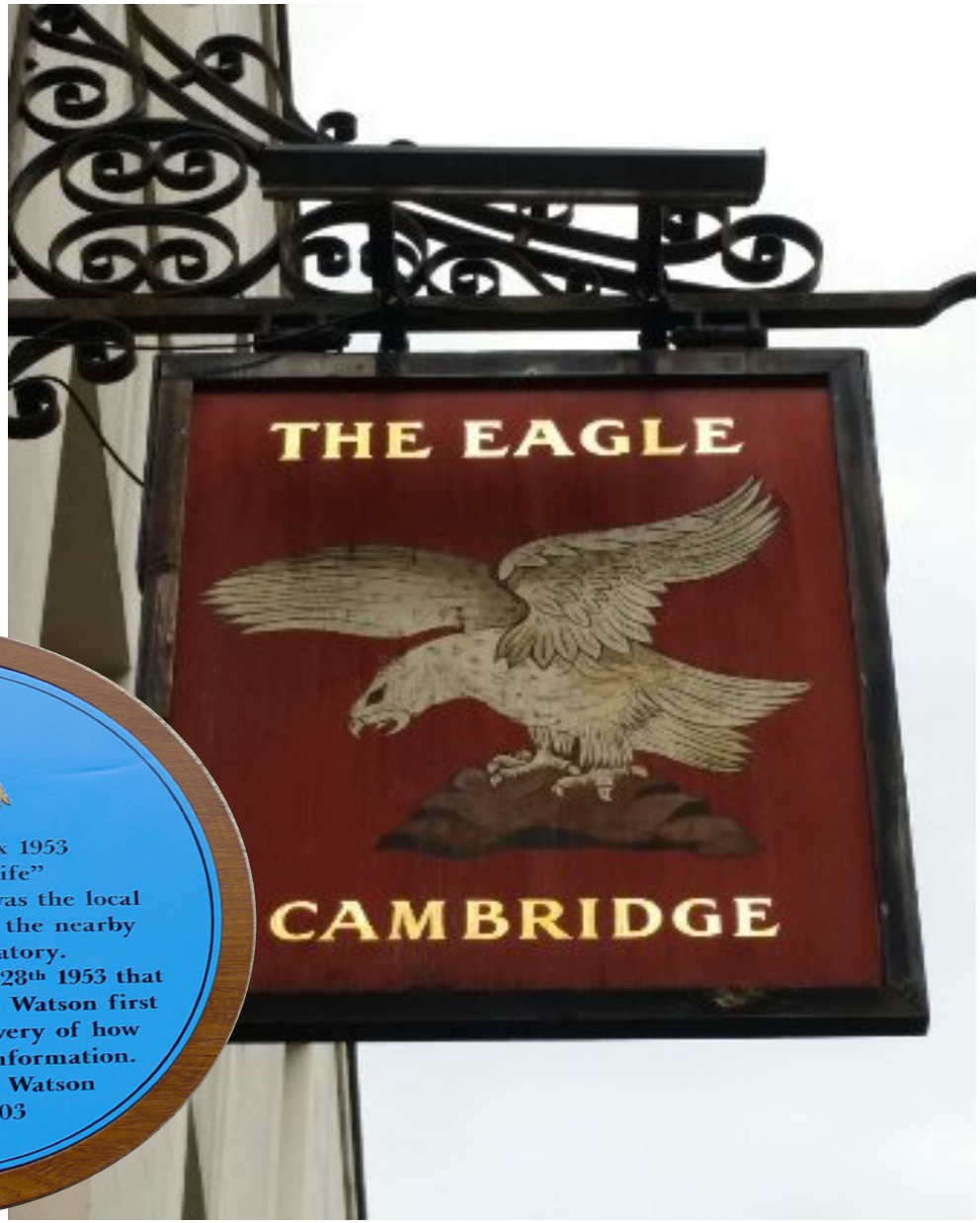
Graeme Smith, Science Director, Oncology, Innovative Medicines & Early Development
AZN IR Team

The Eagle Pub, Cambridge

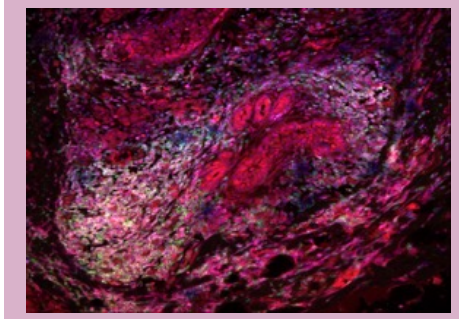
05 September 2016

Agenda

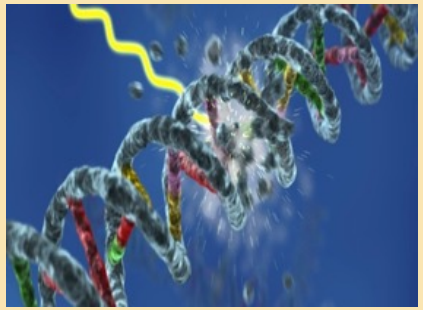
- Introduction - Mene
- Q&A - Mene, Klaus and Graeme
- Informal discussion & drinks



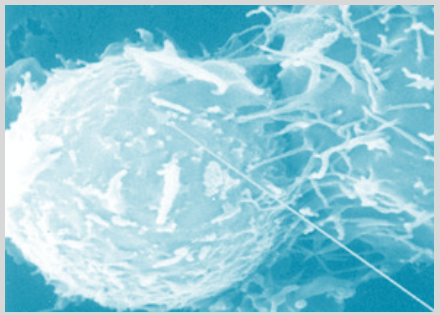
The oncology pipeline is positioned to combine medicines within and between key scientific mechanisms



Tumour drivers and resistance



DNA Damage Response (DDR)



Immuno-Oncology (IO)

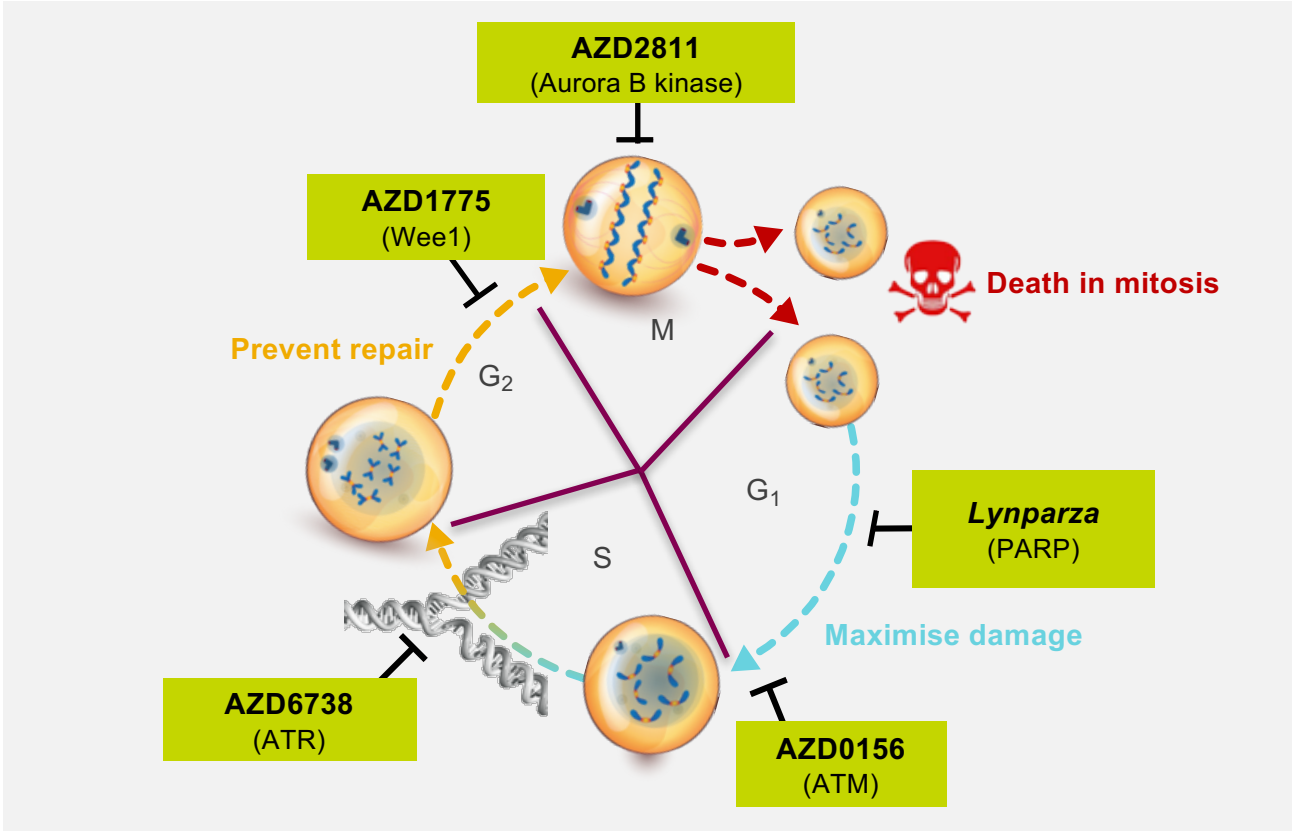
Antibody conjugates

DDR portfolio

Emergence of a new cancer-treatment paradigm

40-50% of tumours have DDR defects

- Loss of one of more DNA-repair pathways
- Increased levels of endogenous DNA damage
- DNA replication stress
- Genomic instability



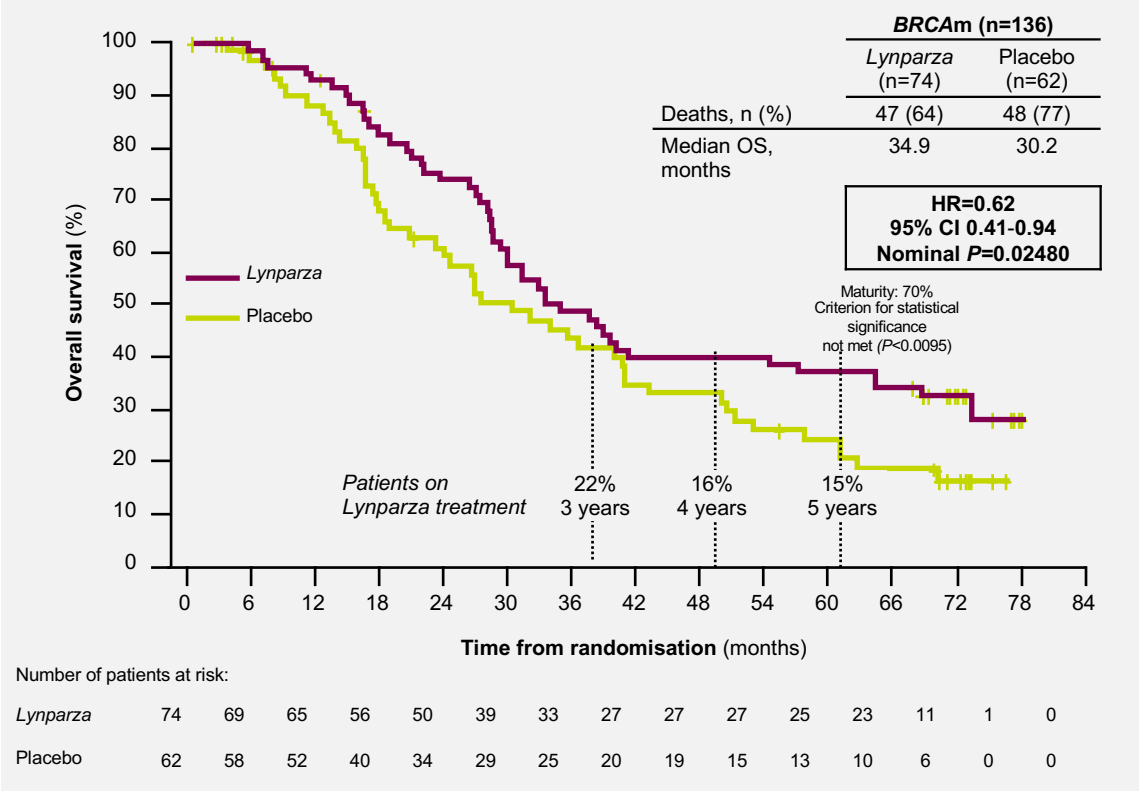
Source: AstraZeneca data on file

Our broad DDR portfolio and deep scientific understanding is driving our combination approach

Target	Company	Medicine	Pre-clinical	Phase I	Phase I/II	Phase II	Phase III	Launched
PARP	AstraZeneca	*Lynparza*						
	Clovis	rucaparib						
	Tesaro	niraparib						
	Pfizer (Medivation)	talazoparib						
	AbbVie	veliparib						
Wee1	AstraZeneca	AZD1775						
Chk 1/2	Eli Lilly	LY 2606368						
	Roche (Genentech)	GDC-0575						
	Merck	MK-8776						
	Eli Lilly	LY 2603618						
	Novartis	CHIR-214						
	Cancer Research UK	CCT241533						
ATR	AstraZeneca	AZD6738						
	Vertex	VX 970						
AKB	AstraZeneca	AZD2811						
ATM	AstraZeneca	AZD0156						
	Pfizer	CP 466722						
	AstraZeneca	AZD1390						
DNA-PK	AstraZeneca							
	Merck Serono	MSC 2490484A						
	Vertex	VX 984						

Lynparza: 1st-in-class with differentiated development

Long-term survival benefit, extensive programme underway



Source: ASCO 2016, abstract 5501

2017	2018+
	Study 8 (prostate cancer)
	[TBC] (prostate cancer)
	PAOLA bevacizumab combination (ovarian cancer)
SOLO-1 (1L BRCAm ovarian cancer)	**OlympiA** (adjuvant BC)
SOLO-2 (2L BRCAm PSR ovarian cancer)	**POLO** (pancreatic cancer)
OlympiAD (advanced breast cancer)	**SOLO-3** (3L+ gBRCAm PSR ovarian cancer)

Phase II Phase III

Timeline for key regulatory submissions

PARP inhibitors exhibit comparable efficacy

PARP inhibitor	***Lynparza*** AstraZeneca	**Rucaparib** Clovis	**Niraparib** Tesaro	**Talazoparib** Pfizer (Medivation)	**Veliparib** AbbVie
Enzyme IC_{50} PARP-1 PARP-2	 5 nM 1 nM	 2 nM -	 4 nM 2 nM	 0.6 nM -	 5 nM 3 nM
PARP trapping relative to *Lynparza*	1	1	2	100	0.1
Monotherapy dose/ schedule	300mg bd (tablet)	360mg bd up to 600mg bd	300mg od	1mg od	Not progressed as monotherapy
Response rate (RR) in BRCAm ovarian cancer as monotherapy at Phase III dose	40-50% RR Apparent differences in response rate likely due to line of treatment and platinum sensitivity				
Dose-limiting toxicities (DLT)	Thrombocytopenia, fatigue. Gr 3/4 AE's fatigue, anaemia, nausea & vomiting	Nausea at 360mg bid. Gr 3/4 AE's = nausea, vomiting and fatigue	Thrombocytopenia. Gr 3/4 AE's = anaemia, thrombocytopenia, nausea and fatigue	Thrombocytopenia. Gr 3/4 AE's = N&F, thrombocytopenia anaemia	Thrombocytopenia, nausea and vomiting and seizure. Most common other AE's = nausea & vomiting

Source: Murai et al. (2013; 2014), Fong et al. (JCO 2010)

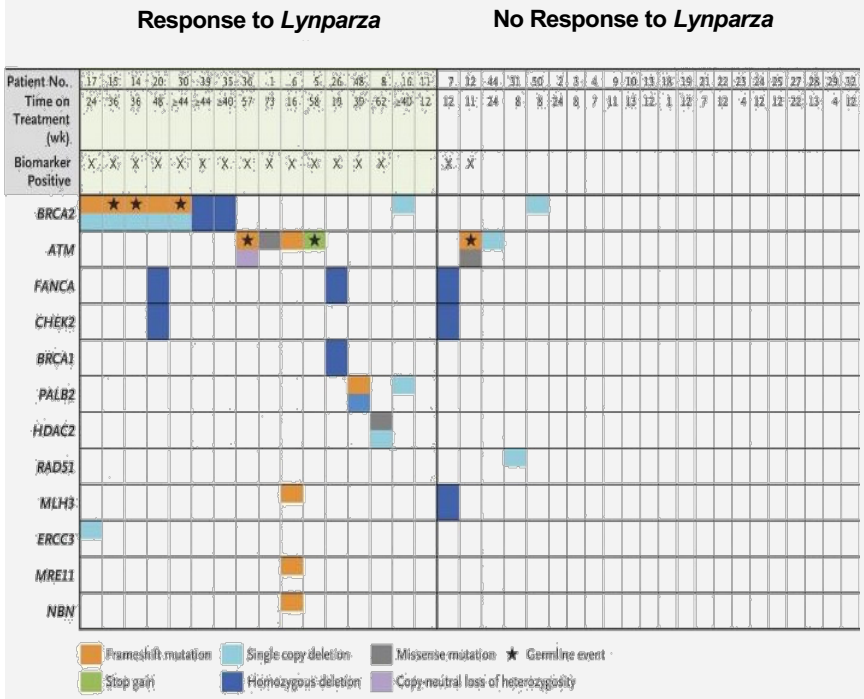
Lynparza: Key opportunity outside BRCA is HRR panel

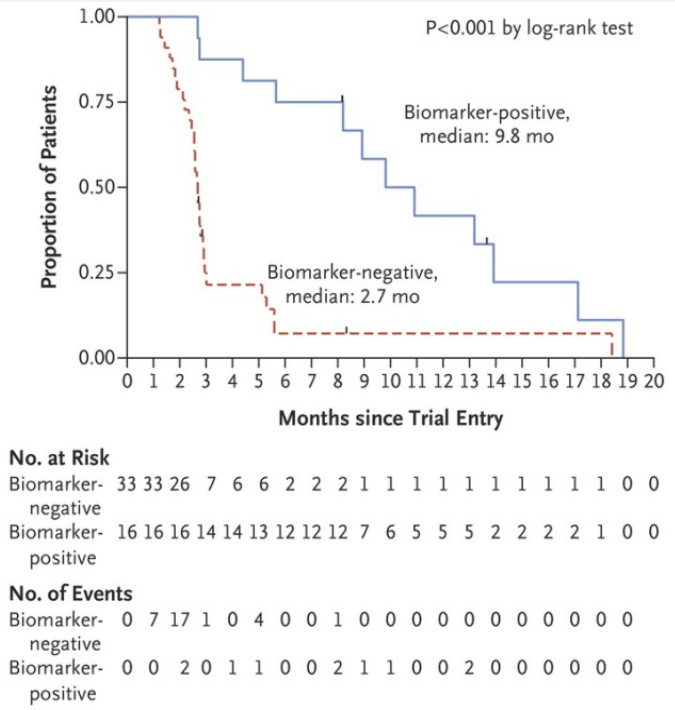
HRD scar benefit driven mainly by germline/somatic BRCA

AstraZeneca HRR 15 gene panel

BRCA1	FANCL
BRCA2	FANCN (PALB2)
ATM	BARD1
RAD51B	CHEK1
RAD51C	CHEK2
RAD54L	CDK12
RAD51D	PPP2R2A
FANCJ/BRIP1	

Genomic aberrations in DNA repair in patients with mCRPC resulted in 88% RR with *Lynparza*

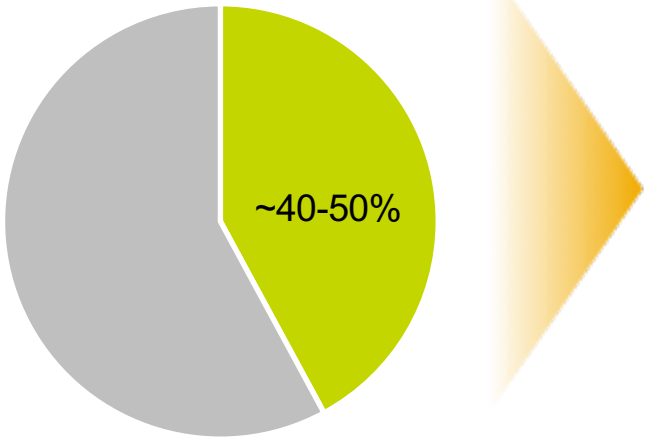


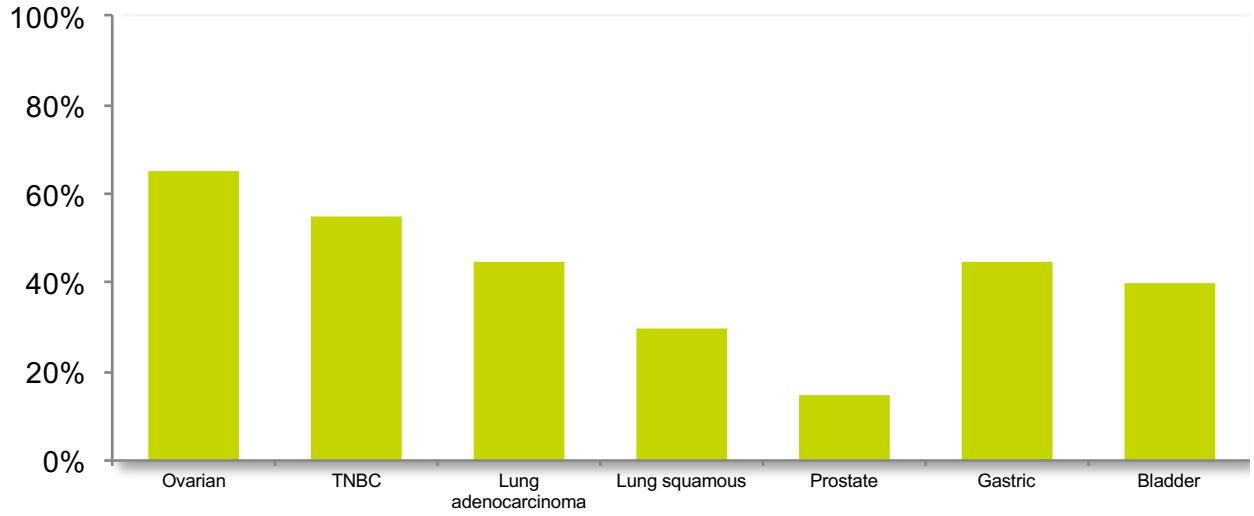


Source: Mateo J et al., N Engl J Med 2015;373:1697-1708
HRR = Homologous Recombination Repair
HRD = Homologous Repair Deficiency
RR = Response Rate
mCRPC = metastatic Castration Resistant Prostate Cancer

DDR abrogation is frequent across multiple cancer types

Cancer patients with targetable DDR defects





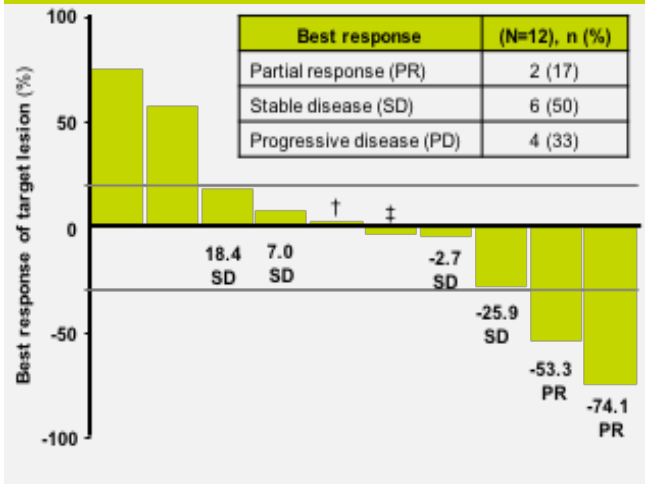
DDR abrogations include:

Cell cycle, oncogenic driver and homologous recombination repair

Source: AstraZeneca data on file

DDR emerging monotherapy and combination data

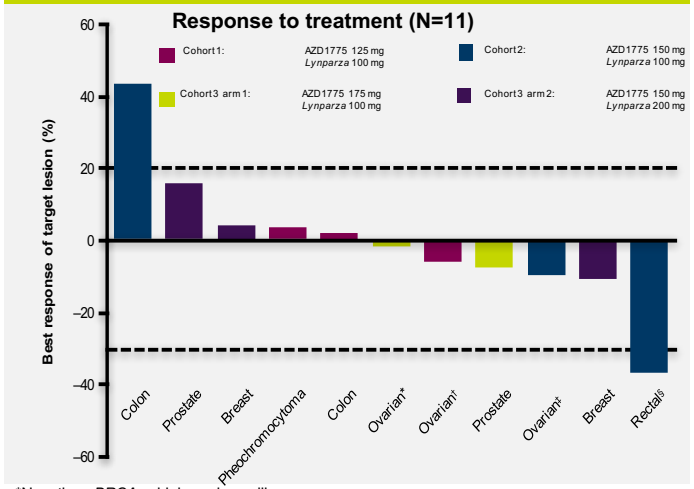
AZD1775 monotherapy clinical data



Best response	(N=12), n (%)
Partial response (PR)	2 (17)
Stable disease (SD)	6 (50)
Progressive disease (PD)	4 (33)

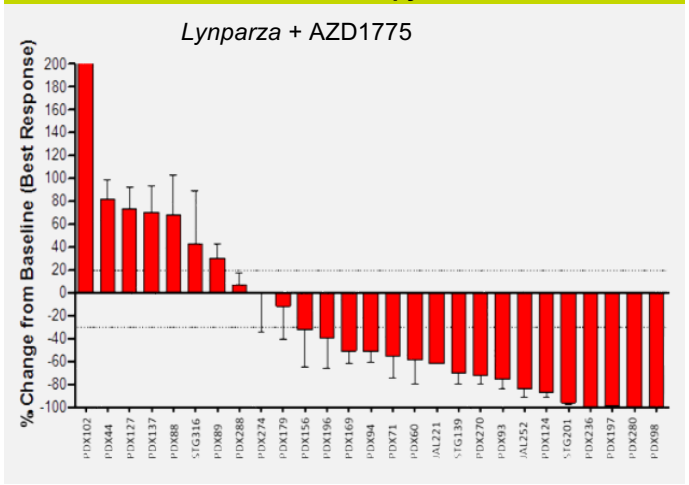
* Two additional patients with stable disease had evaluable, but not measurable, disease; †Patient had clinical progression; ‡Patient had new lesion

Lynparza + AZD1775 Phase I clinical data



*Negative g*BRCA*m; high grade papillary serous;
†Negative g*BRCA*m; high grade undifferentiated;
‡*BRCA* polymorphism R504 (1630 G>A); high grade papillary serous;
§*BRCA*m; poorly differentiated squamous cell carcinoma

Pre-clinical data *Lynparza* + AZD1775 in TNBC patient-derived tumour models show improved activity vs *Lynparza* monotherapy



Lynparza + AZD1775 combination in Phase I to identify dose/schedule

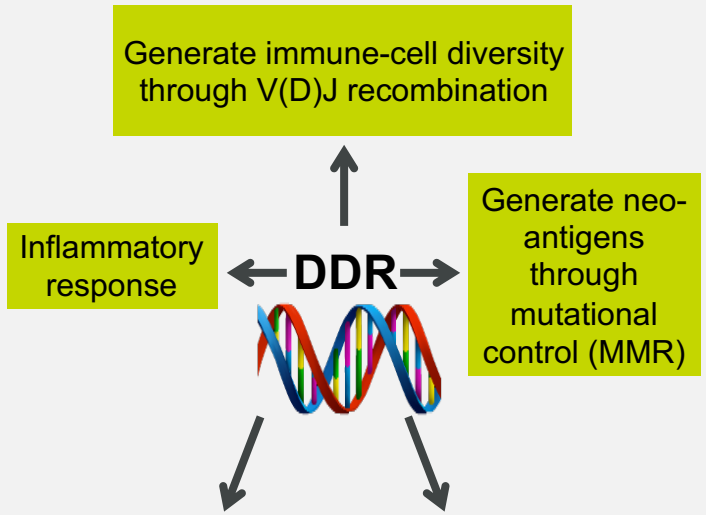
- **Ovarian (50 patients) (>15 gBRCA, PARPi failures)**
- **SCLC (50 patients) (>15 MYC/CCNE1 amplified)**
- **TNBC (50 patients) (>15 MYC/CCNE1 amplified)**

Lynparza + AZD0156 and _Lynparza_ + AZD6738 currently in clinic

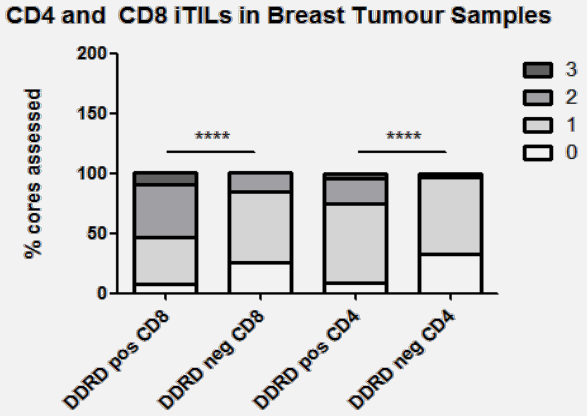
Source: AstraZeneca data on file; AACR 2016, O'Connor; ASCO 2016, abstract 5562

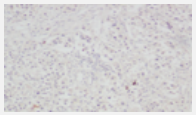
DDR engages the immune response

Mechanisms

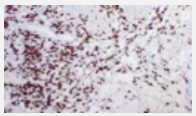


Biomarker evidence



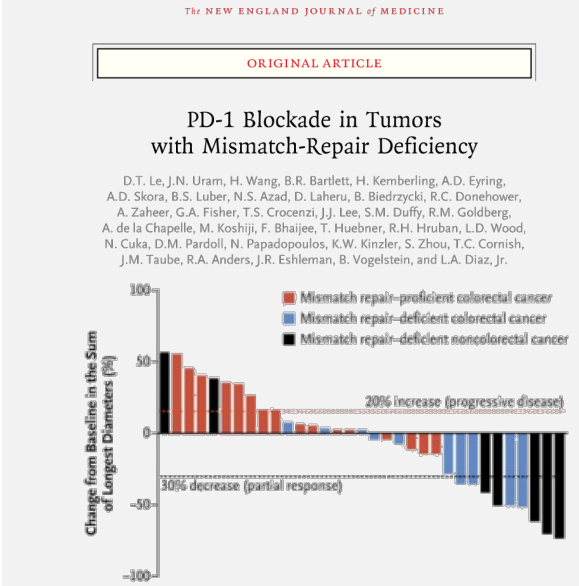


DDRD negative core
No lymphocytes



DDRD positive core
Profuse lymphocytic infiltration

Clinical evidence


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.

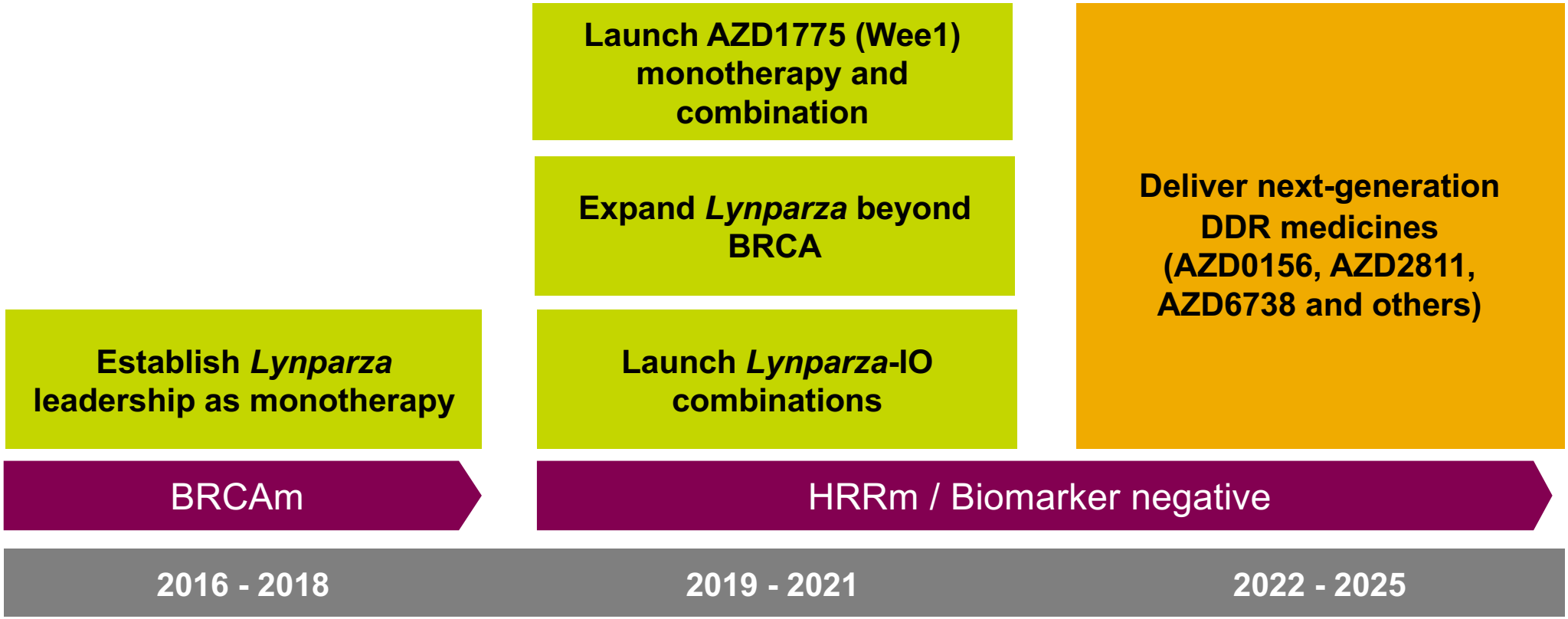
MSI-H is caused by MMR deficiency, but also impacts DNA double-strand break-repair capability due to microsatellite deletions in ATM gene

Unique advantage: Housing both DDR and IO

Source: AstraZeneca data on file; NEJM
DDRD = DNA Damage Response Deficiency

Beyond BRCA, beyond *Lynparza*: DDR

Developing chemo-free regimen, extending survival



Summary

1	AstraZeneca portfolio of DDR-targeting agents is the broadest with multiple agents in proof-of-concept studies
2	Targeting DDR deficiencies is clinically validated and a subset of patients experience long-term benefit
3	Patient selection is critical. NGS test development is underway for HRR panel for *Lynparza* and AZD1775
4	DDR deficiencies are common in multiple cancers (40-50%)
5	There is a significant scientific rationale and clinical evidence that DDR and immune responses are linked and potentially synergistic

Investor Relations

About AstraZeneca

AstraZeneca is a global, science-led biopharmaceutical company that focuses on the discovery, development and commercialisation of prescription medicines, primarily for the treatment of diseases in three therapy areas – Respiratory & Autoimmunity, Cardiovascular & Metabolic Diseases and Oncology. The Company is also active in inflammation, infection and neuroscience through numerous collaborations. AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide.

For more information please visit: www.astrazeneca.com.

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