Precision Medicine and Genomics: A Pharma perspective

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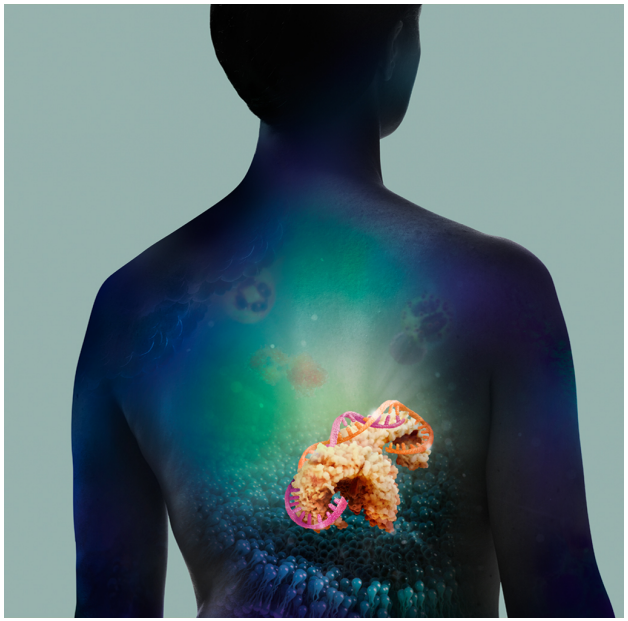
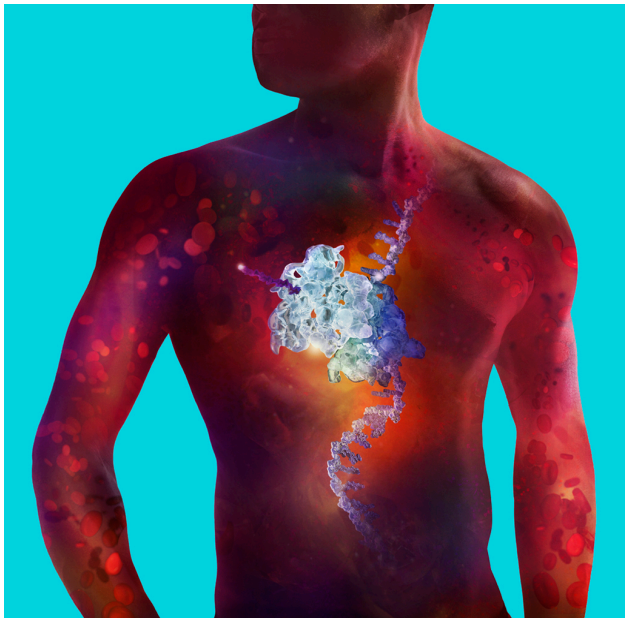
Need for new medicines

Cancers – 42%



Respiratory – 9%



Cardiovascular – 22%

%-ages refer to the premature death toll by each of those conditions

From: http://www.nhs.uk/Livewell/over60s/Pages/The-top-five-causes-of-premature-death.aspx

More precision medicine products are available for patients than ever before

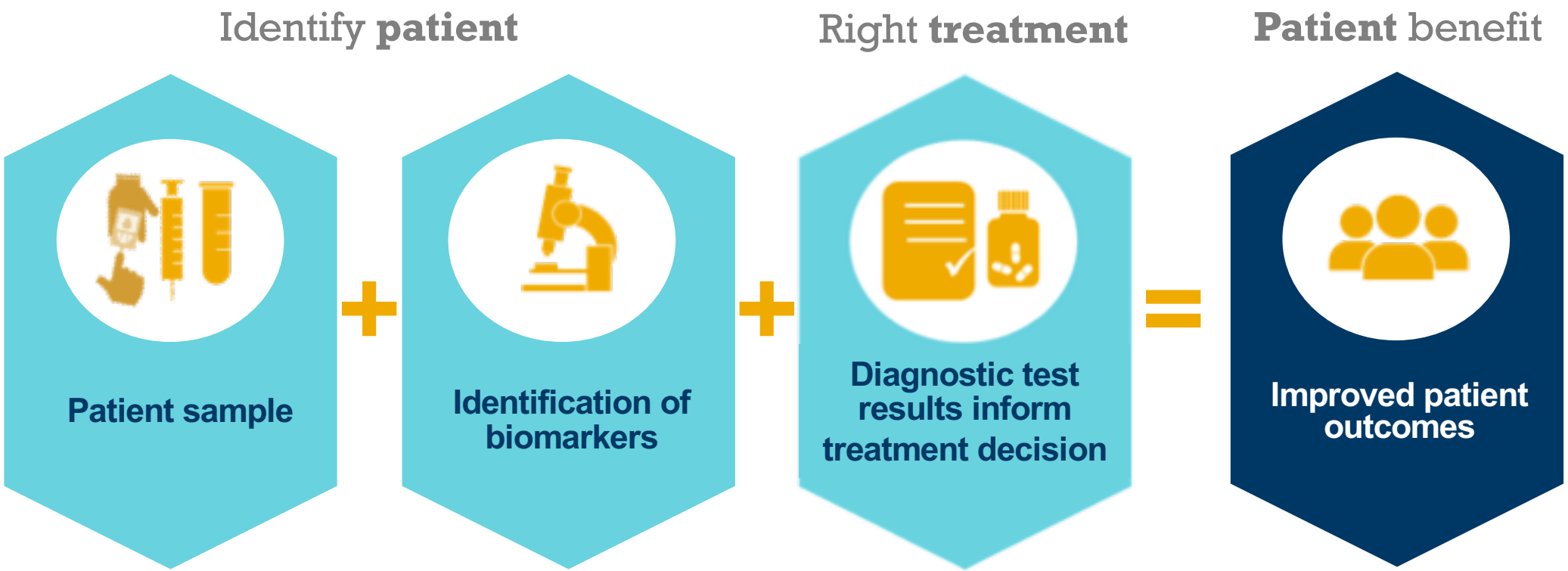
Total number of FDA-approved drugs with companion diagnostics included on their drug label*

as of October 2017

More than 1 in 5 FDA approvals 2014 - 2016 were for targeted therapies**

* https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm
** therapeutic products for which the label includes reference to specific biological markers, identified by diagnostic tools, that help guide decisions and/or procedures for the product's use in individual patients

What is precision medicine?

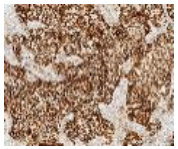


Precision medicine: based on science and centered on patient needs

Diagnostics linked to four AZ medicines to guide therapy

Durvalumab
PD-L1 monoclonal antibody

PD-L1 complementary Dx (for Bladder - US)



Partner: Ventana

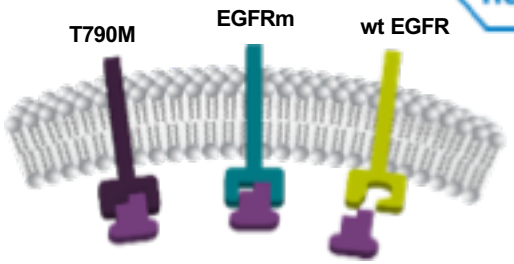
Gefitinib
EGFR inhibitor

***EGFR* tissue (US) & plasma (EU)**
1st plasma CDx CE-IVD for solid tumour
Partner: Qiagen

***EGFR* tissue & plasma US)** *Partner: RMS*

Osimertinib
Mutant-selective EGFR inhibitor

***EGFR T790M* tissue & plasma (US, EU, JPN)**
AZ's first FDA approved ctDNA test
***EGFRm* tissue & plasma (US, JPN)**
1st concurrent CDx tissue & plasma
Partner: RMS

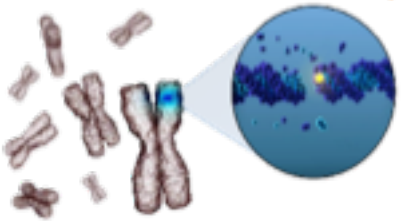


***EGFR T790M* tissue NGS panel (US)**
Partner: FMI

Olaparib
PARP inhibitor

Germline *BRCA* (US, EU, JPN)
Partner: Myriad
1st BRCA LTD CDx

Tumour *BRCA* CE IVD (EU)
Partners: Myriad, Multiplicom, Qiagen



Approximately 90% of our NME clinical pipeline follows a Precision Medicine approach

~ 90% of our clinical pipeline follows a Precision Medicine approach, compared with 10% in 2009

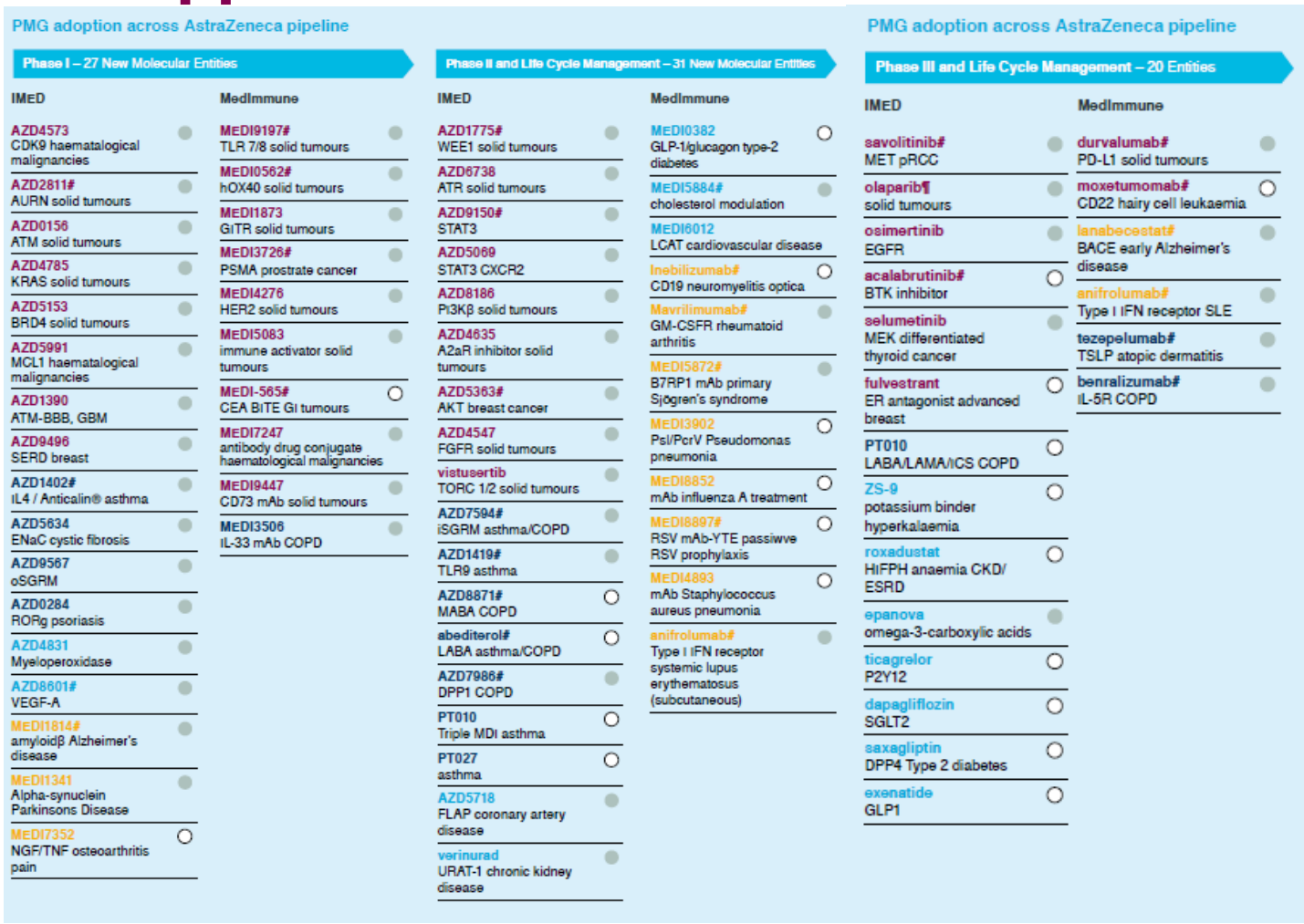
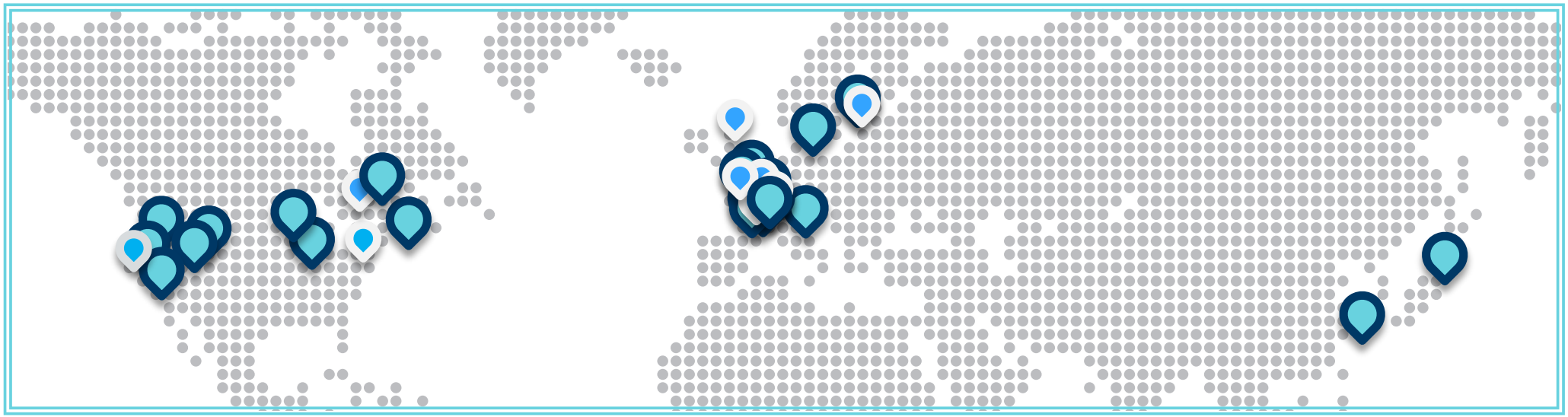


Figure from 2017 AZ IMED Annual Report

Precision Medicine needs an open and collaborative culture – AZ's partners with world-leading institutions



Abbott Diagnostics
DEFINIENS the tissue phenomics company
Genomics england
IGM Institute for Genomic Medicine
Multiplicom
Roche
welcome trust sanger institute
CHEMBIO DIAGNOSTIC SYSTEMS, INC.
DNAnexus
GUARDANT HEALTH
illumina
MYRIAD
REGENERON GENETICS CENTER
UNIVERSITY OF CAMBRIDGE
COLUMBIA UNIVERSITY
FINNGEN
HematoGenix Laboratory Services
INSTITUT DE CARDIOLOGIE DE MONTRÉAL
nova biomedical
SMS
QIAGEN
Dako
FOUNDATION MEDICINE
HUMAN LONGEVITY, INC.
Karolinska Institutet
rHEALTH
VENTANA a member of the Roche Group

Osimertinib in NSCLC patients with EGFR mutations

Osimertinib is an irreversible EGFR-TKI, selective for EGFR-TKI-sensitizing and T790M mutations[6,7]

Key mechanisms of acquired resistance to first-generation EGFR-TKIs[1-5]

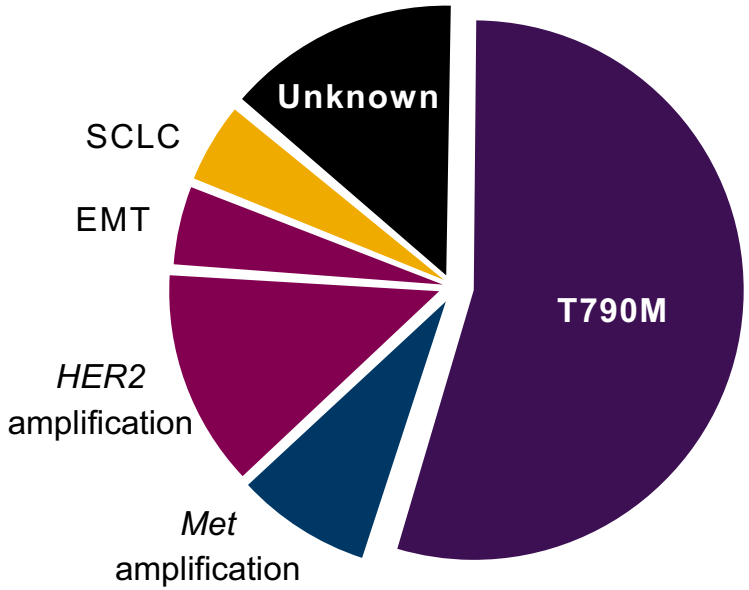
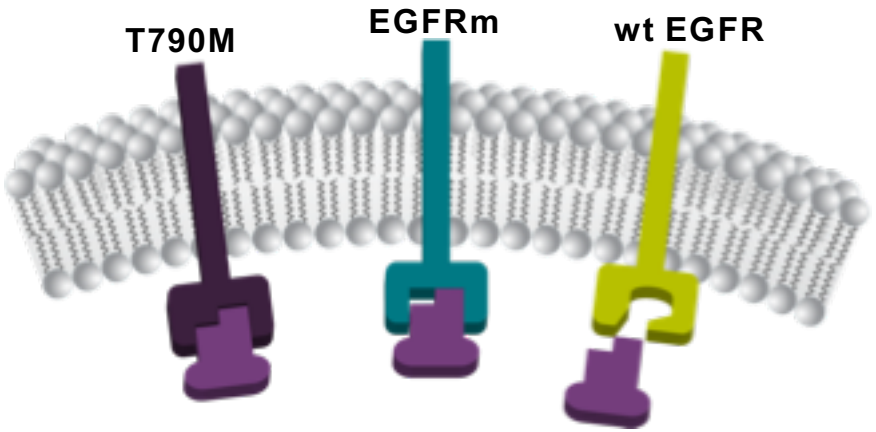


Figure adapted from Cortot A, Janne PA. Eur Resp Rev 2014

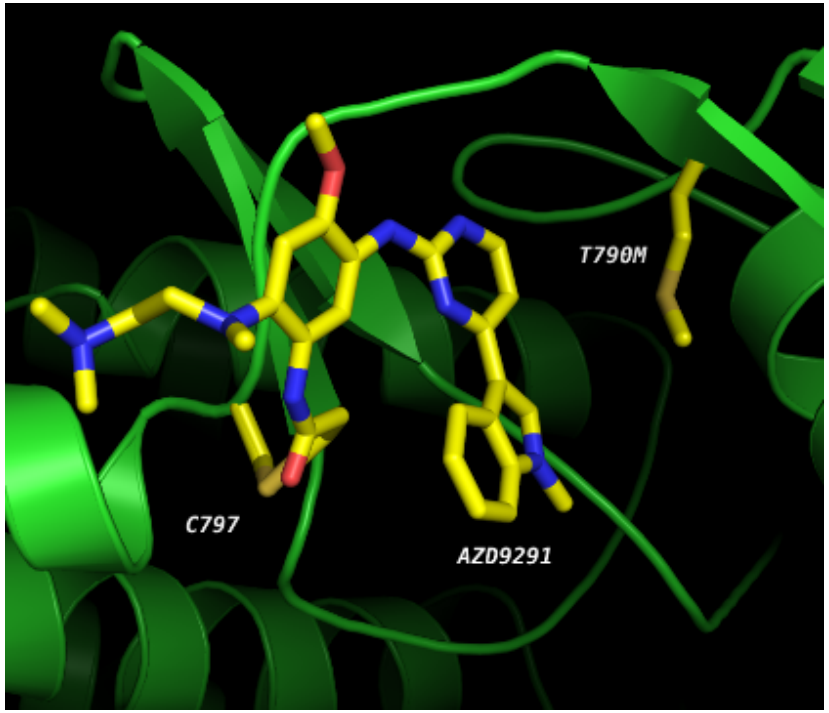


EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; *HER2*, human epidermal growth factor; IGFR; insulin-like growth factor receptor; IR, insulin receptor; NSCLC, non-small cell lung cancer; SCLC, small-cell lung cancer; TKI, tyrosine kinase inhibitor; wt, wild type

1. Cortot AB, Janne PA. Eur Respir Rev 2014;23:356-66; 2. Yu HA, et al. Clin Cancer Res 2013;19:2240-7; 3. Oxnard GR, et al. Clin Cancer Res 2011;17:1616-22; 4. Sun JM, et al. Lung Cancer 2013;82:294-8; 5. Arcila ME, et al. Clin Cancer Res 2011;17:1169-80; 6. TAGRISSO Prescribing Information; 7. Yun CH, et al. Proc Natl Acad Sci USA 2008;105:2070-5; 8. Cross DA, et al. Cancer Discov 2014;4:1046-61

Structure-based design underpins the accelerated clinical development of osimertinib

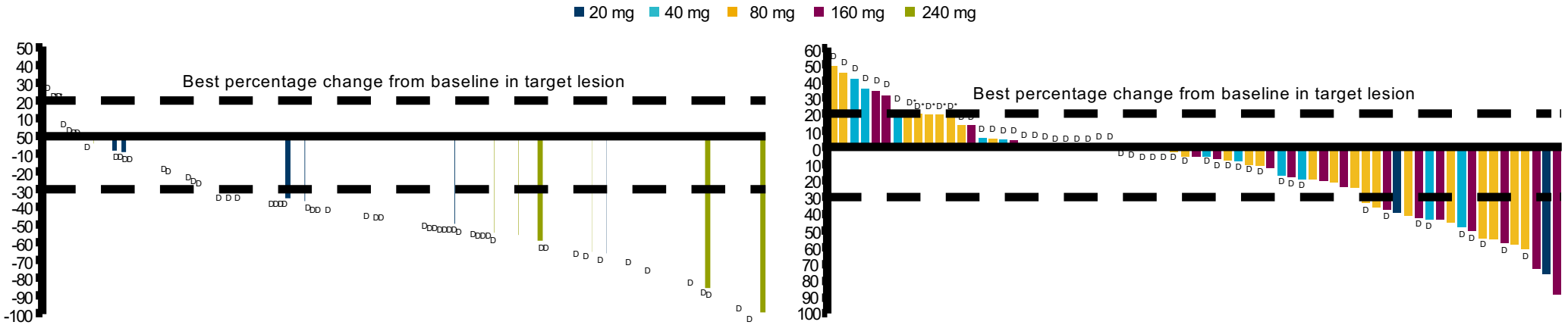
- Mutations in EGFR lead to an oncogenic phenotype & acquired resistance
- Drugs like gefitinib & erlotinib face resistance with new mutations in EGFR
- 50%-60% of acquired resistance due to T790M in exon 20 of EGFR (gatekeeper mutation)
- Osimertinib designed to target both EGFR sensitizing mutations and T790M



Osimertinib is highly efficacious in patients with tumours harbouring the *T790M* mutation (2L NSCLC)

Response rate in AURA Phase I
***T790M* positive cohorts (central test)**

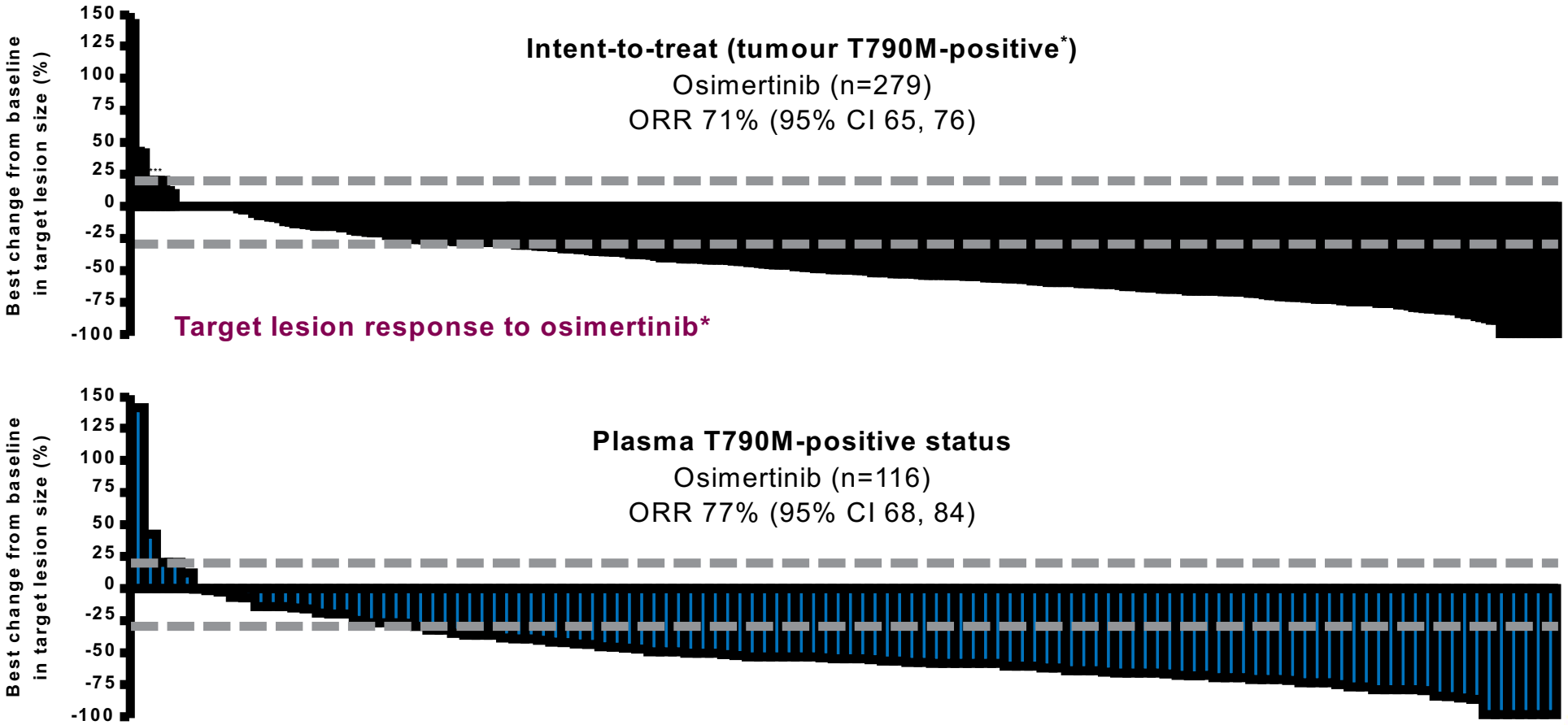
Response rate in AURA Phase I
***T790M* negative cohorts (central test)**



- Osimertinib 80mg: ORR **66%** versus **21%** in *T790M* positive versus *T790M* negative cohorts
  - Response rate consistent with osimertinib design as a selective inhibitor of *EGFR* and *T790M* mutations
- Biology of tumour TKI-resistant disease together with osimertinib profile requires selection of patients harbouring *T790M*
- Molecular diagnostics is essential in both TKI-naïve and post-TKI *EGFR*m settings

ORR, objective response rate
1. Jänne P et al. NEJM 2015

AURA3 (2L NSCLC): osimertinib benefit in patients with plasma T790M-positive status is similar to patients with tissue T790M-positive status



Wu et al., IASLC 17th World Conference on Lung Cancer, 2016; session MA08: Treatment Monitoring in Advanced NSCLC (abstract MA08.03)

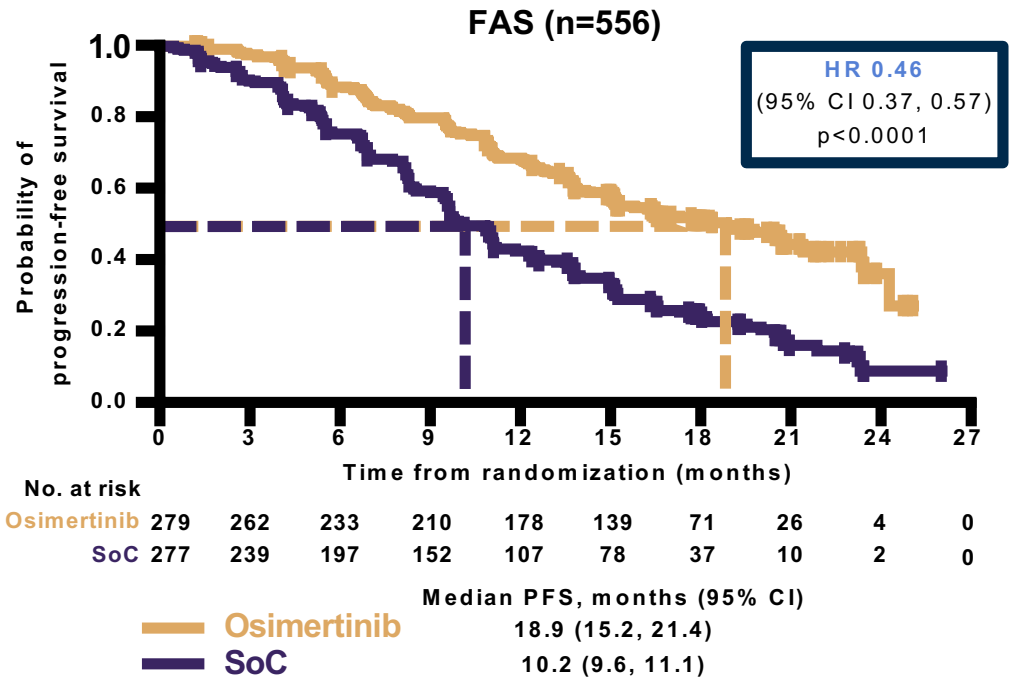
Best percentage change in target lesion size is the maximum reduction from baseline or the minimum increase.

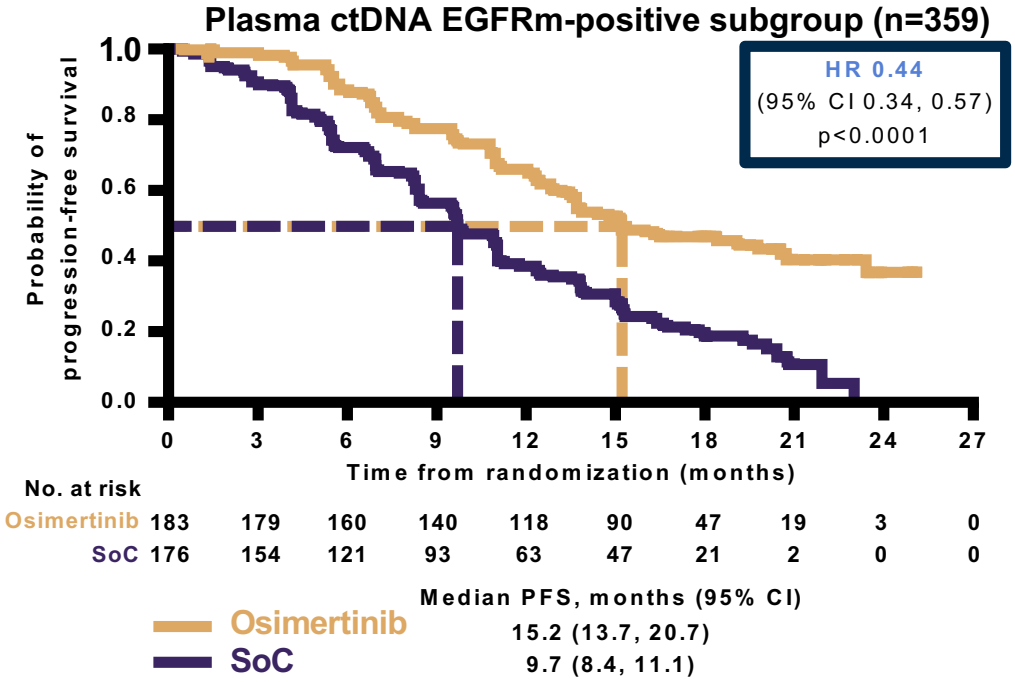
*All patients were selected using a tumour tissue test for *EGFR* T790M (by **cobas**® EGFR Mutation Test) from a biopsy after disease progression prior to study entry

*investigator assessed

FLAURA (1L NSCLC): investigator-assessed PFS in the FAS and plasma EGFRm positive subgroup

In the plasma ctDNA EGFRm-positive subgroup, risk of progression or death was reduced by 56% with osimertinib compared with SoC; PFS benefit in this subgroup is similar to the FAS





Median PFS with 95% confidence intervals calculated from Kaplan Meier method.

All patients had tumor tissue EGFRm-positive status by local or central testing.

CI, confidence interval; ctDNA, circulating tumor DNA; EGFR, epidermal growth factor receptor; EGFRm, EGFR-TKI sensitizing mutation; FAS, full analysis set; HR, hazard ratio; PFS, progression-free survival; SoC, standard of care; TKI, tyrosine kinase inhibitor.

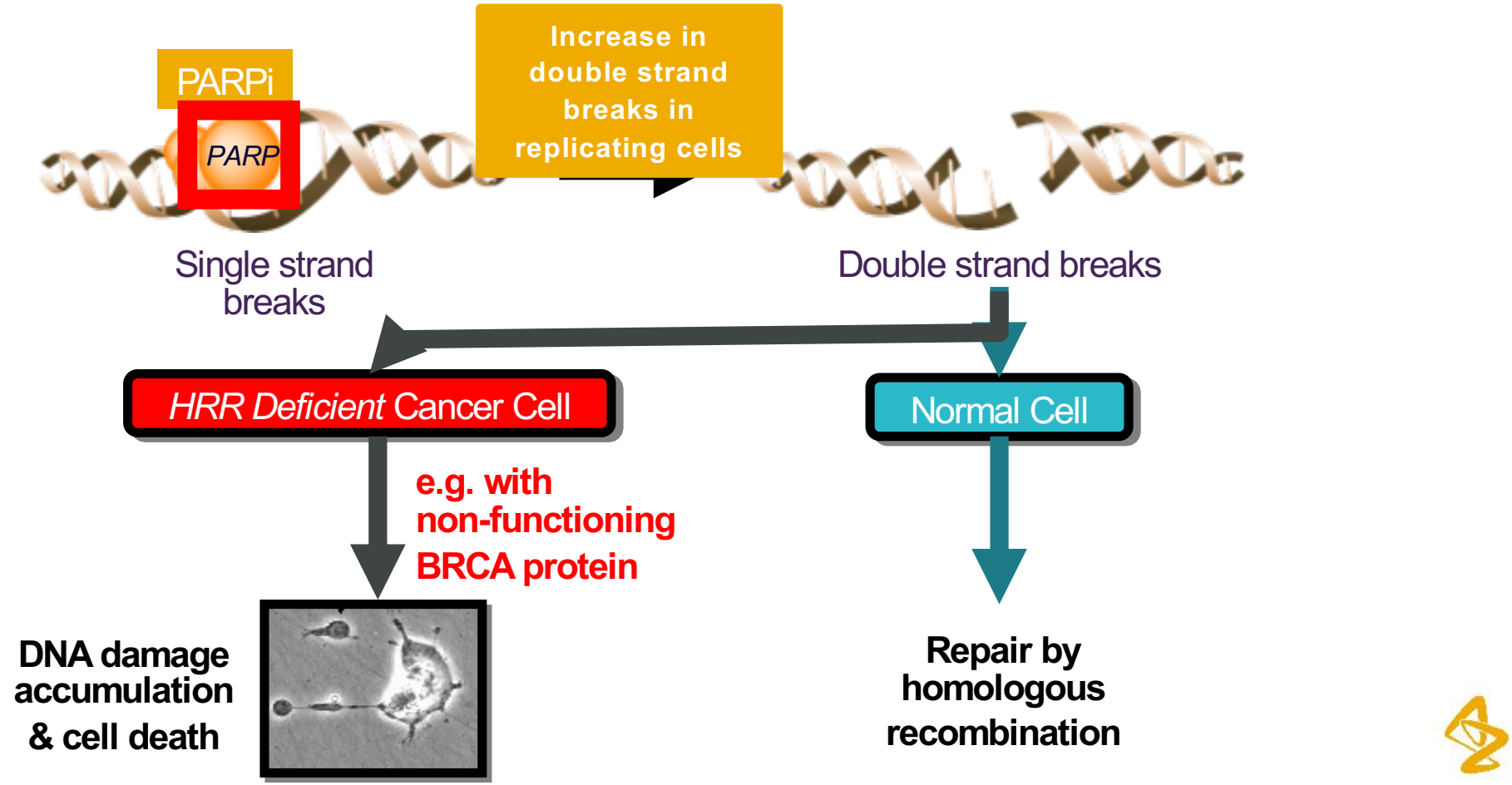
Gray et al., IASLC 18th World Congress on Lung Cancer, Japan, 2017

FLAURA (NCT02296125): PhIII, double-blind, randomised study, 1st L treatment for patients with tumor tissue-positive EGFRm advanced NSCLC

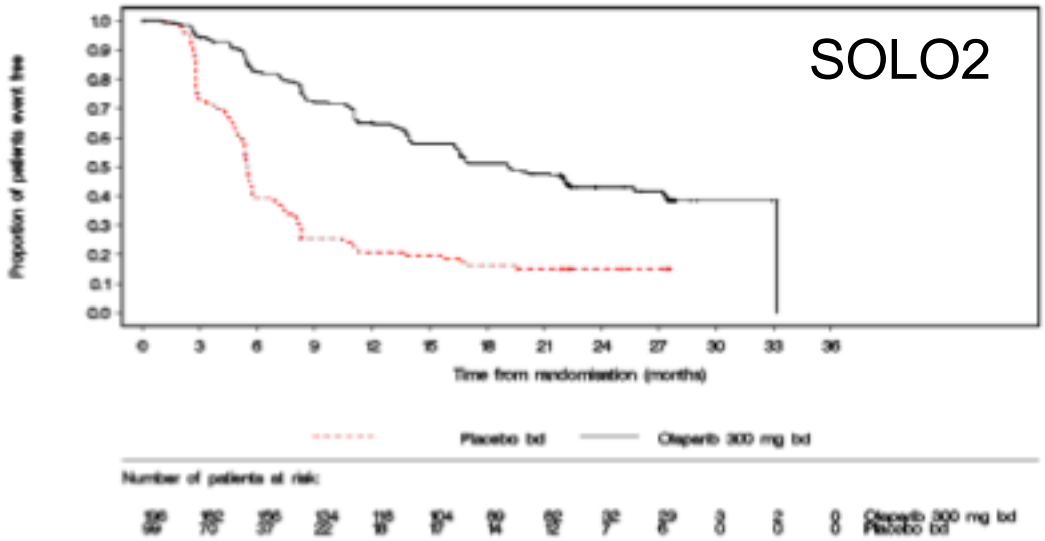
Olaparib and homologous recombination repair deficiency

Translating evolving science into clinic

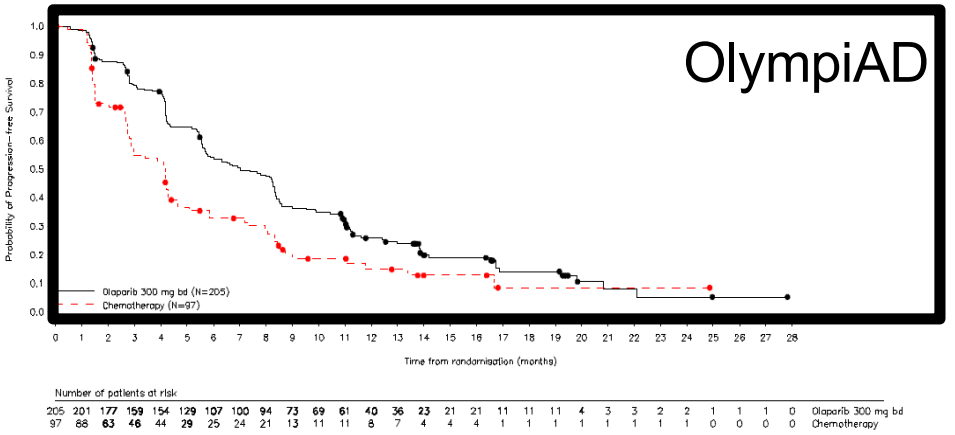
PARP inhibition/trapping and cell death in homologous recombination repair deficient tumours



SOLO2 (ovarian) and OlympiAD (breast): significant and clinically meaningful improvement in PFS primary endpoint for olaparib arms



	Olaparib	Placebo
Events	107/196 (55%)	80/99 (81%)
Median	19.1 m	5.5 m
HR	0.30 [95% CI (0.22,0.41)]; p<0.0001	
Median follow up	22.1 m	22.2 m



	olaparib	chemotherapy[a]
n	**205**	**97**
Events (%)	**163 (80%)**	**71 (73%)**
Median (m)	**7.0**	**4.2**
HR (95% CI)	**0.58 (0.43, 0.80)**	
p-value (2-sided)	**0.0009**	

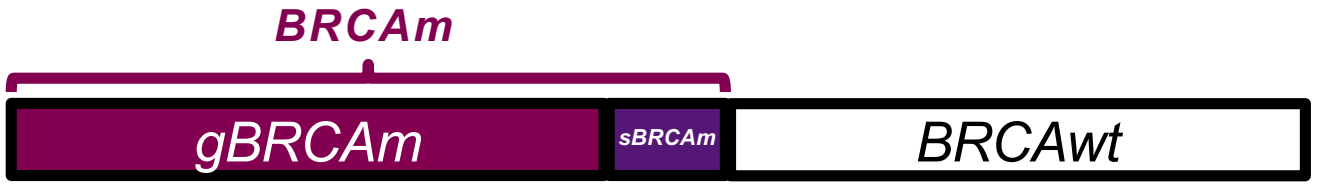
Maturity rate: 234/302=77%

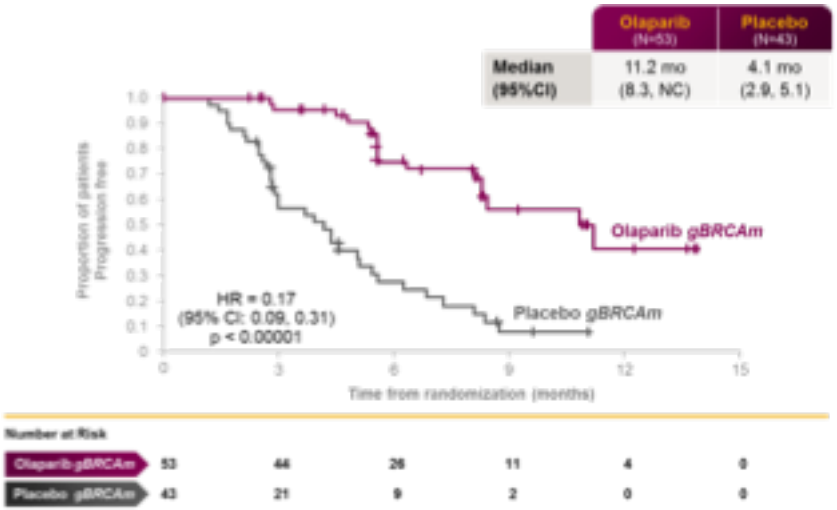
Pujade-Lauraine E et.al., Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation The Lancet Oncology 2017;18(9):1274-1284

Robson M et.al., Olaprib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation N. Engl.J. Med 2017;377:523-533

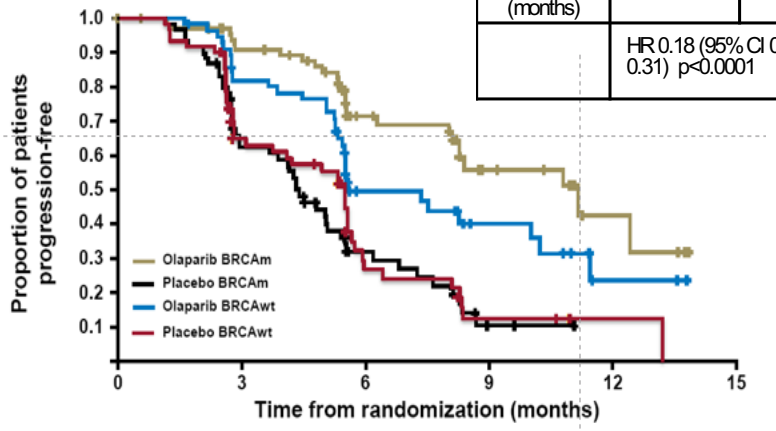
Study 19: Progression Free Survival by *BRCAm* status

Study was positive for all patients PFS HR 0.35 (95%CI 0.25-0.49) p<0.001*





	BRCAm (n=136)		*BRCAwt* (n=118)	
	Olaparib	Placebo	Olaparib	Placebo
Median PFS (months)	11.2	4.3	7.4	5.5
	HR 0.18 (95% CI 0.10-0.31) p<0.0001		HR 0.54 (95% CI 0.34-0.85) P=0.0075	

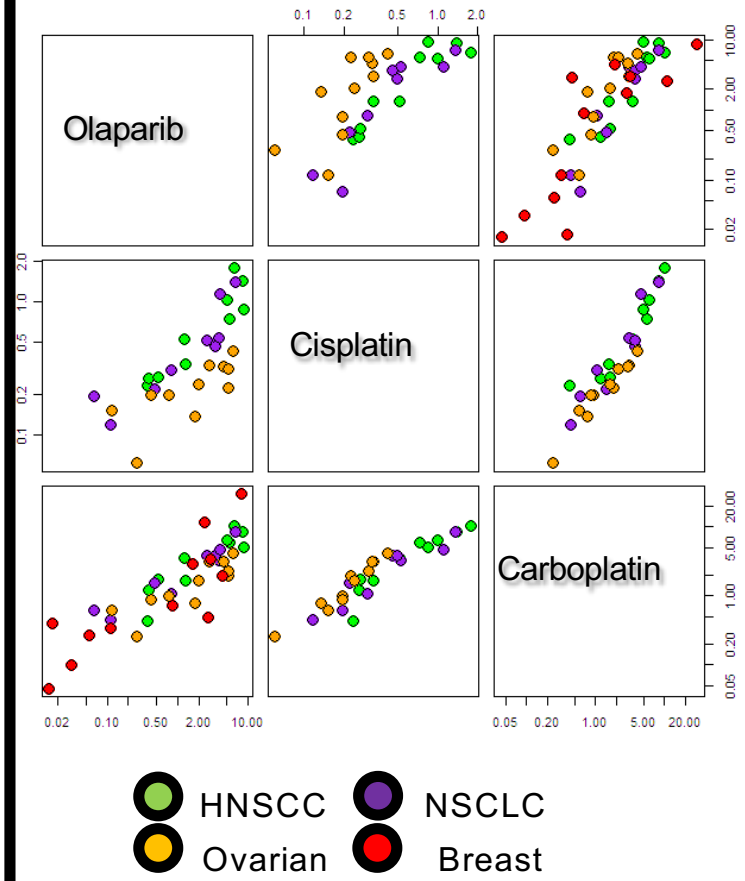


Ledermann et al. *Lancet Oncol* 2014;15:852–61

*Ledermann et al *NEJM* 2012;366:1382–1392

Clues to PARPi sensitivity beyond gBRCAm: other HRR deficiencies?

Broad correlation with platinum sensitivity in cell lines



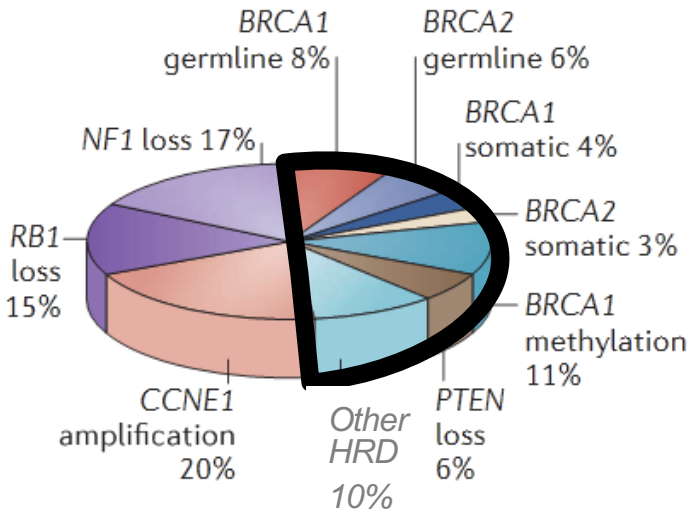
Preclinical candidates

Cancer Research 2006 66:8109-15 Research Article

Deficiency in the Repair of DNA Damage by Homologous Recombination and Sensitivity to Poly(ADP-Ribose) Polymerase Inhibition

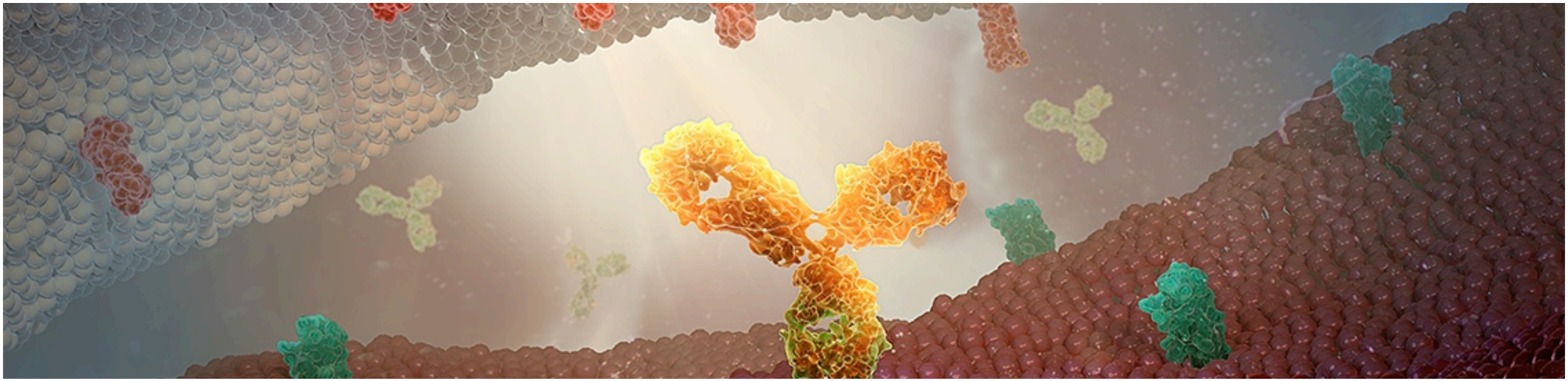
Nuala McCabe,[1,2] Nicholas C. Turner,[2] Christopher J. Lord,[2] Katarzyna Kluzek,[3] Aneta Bialkowska,[3] Sally Swift,[1,2] Sabrina Giavara,[4] Mark J. O'Connor,[4] Andrew N. Tutt,[2] Malgorzata Z. Zdzienicka,[3,5] Graeme C.M. Smith,[4] and Alan Ashworth[1,2]

Presence of other deficiencies in DNA repair in HG serous ovarian cancer



Adapted from Bowtell et al Nature Reviews Cancer 15.11 (2015): 668-679.

Precision Medicine:
How can we further improve?



Successful precision medicine requires a diverse set of skills and collaboration – to benefit patients best

Understand **patients** and physicians needs

Availability of suitable **sample**

Develop **companion diagnostic** and approval

Continuous **biomarker science;** translation to clinic

Diversity of testing methods

Access to testing and TAT

Test **reimbursement**

Create ‘win-win’ for all stakeholders
PATIENTS, payers, providers, regulators, industry, academia

TAT, turn around time

Precision Medicine: driven by innovation

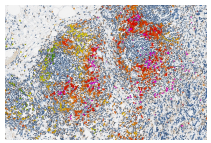
Recent

BRCA Companion Diagnostic

Circulating tumour DNA label

Present

IO Diagnostic Solutions



Multigene DNA panels

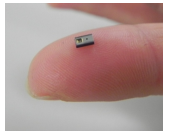
Point-of-care Diagnostics (PoC)

Future

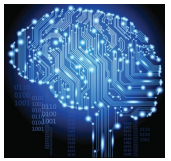
Genomics

Early diagnosis and monitoring

Sensors



Artificial intelligence



Single genes

Multigene panels & PoC

PoC Genomics & AI

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