Precision Medicine at AstraZeneca: A patient-focused approach

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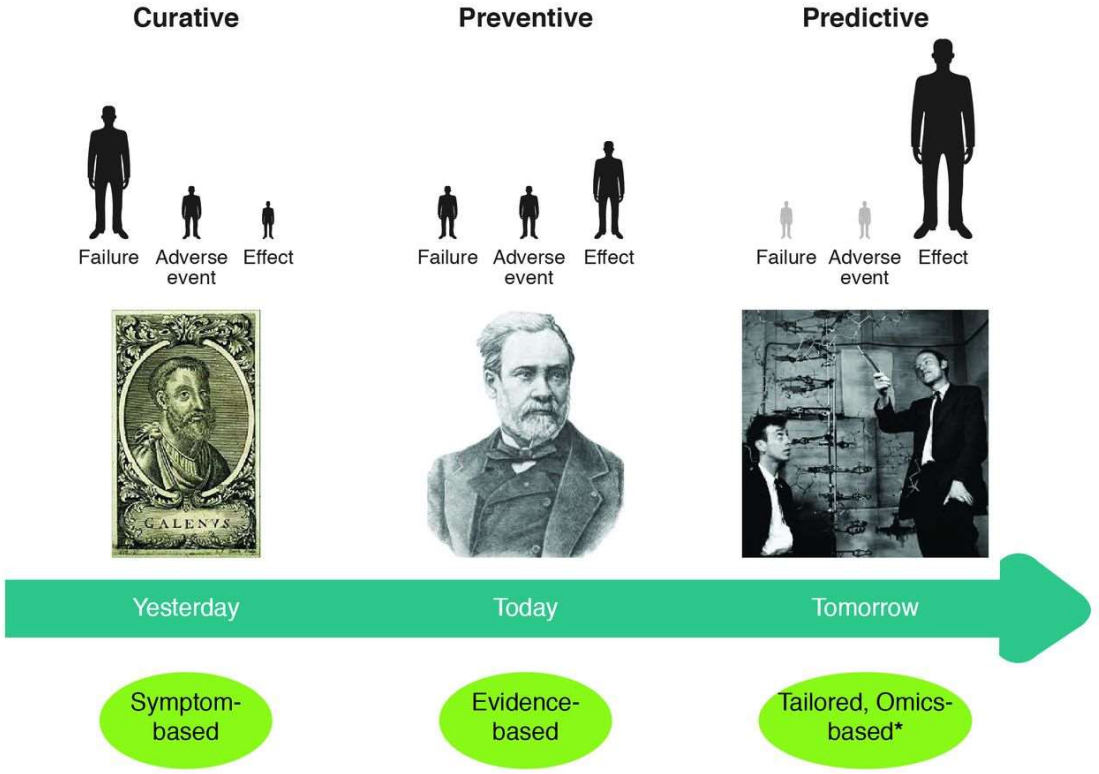
A shift in treatment paradigm

"... medicine was, in its history, first of all curative, then preventive and finally predictive ...
– whereas today the order is reversed: initially predictive, then preventive and finally, only in desperation, curative?"
2001

Jean Dausset
Joint Nobel Prize winner in Physiology or Medicine 1980

Editorial for the Journal of Biomedicine and Biotechnology:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC102137/
Awarded Nobel

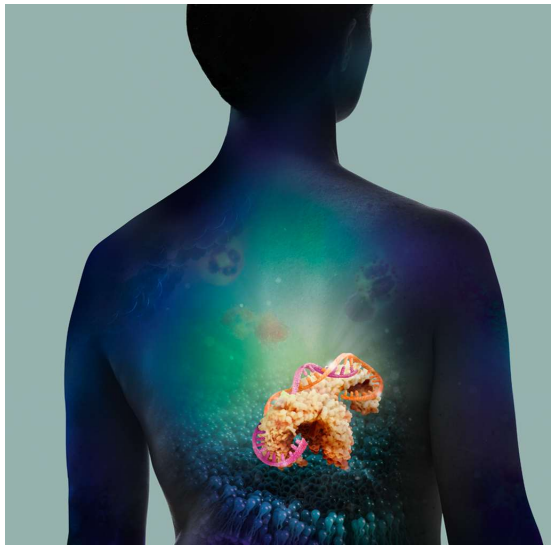


*Genetic, biomarker, imaging, phenotypic, and psycological characteristics, patient's preference

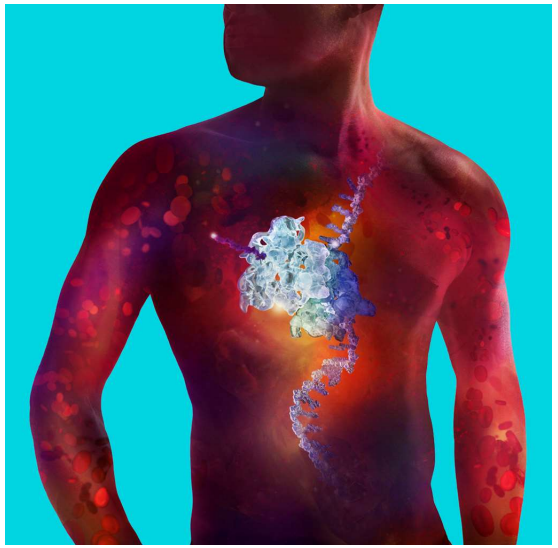
Image source: Giovanni Di Minno, and Elena Tremoli Haematologica 2017;102:411-418

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

Diagnostics linked to four AZ medicines to guide therapy

Durvalumab
PD-L1 monoclonal antibody

PD-L1 complementary Dx (for Bladder - US)

Partner: Ventana

VENTANA
A Member of the Roche Group

Gefitinib
EGFR inhibitor

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

QIAGEN

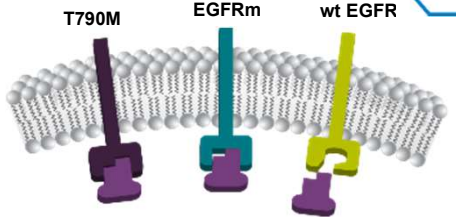
***EGFR* tissue & plasma US)** *Partner: RMS*

Roche

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

Roche



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

FOUNDATION MEDICINE

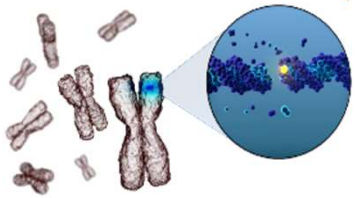
Olaparib
PARP inhibitor

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

MYRIAD

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

MYRIAD QIAGEN Multiplicom
A part of Agilent Technologies



AstraZeneca diagnostic test approvals

- AstraZeneca has achieved **25 diagnostic test approvals since 2014**, in **three major global markets** (US, EU and Japan).
- These innovative diagnostics are linked to **five therapies**, including **four AstraZeneca precision medicines.**

The 5R framework has guided scientific rigor to ask the ‘killer’ questions

Identifying the **right target**

Making sure our molecule gets to the **right tissue** where it is needed

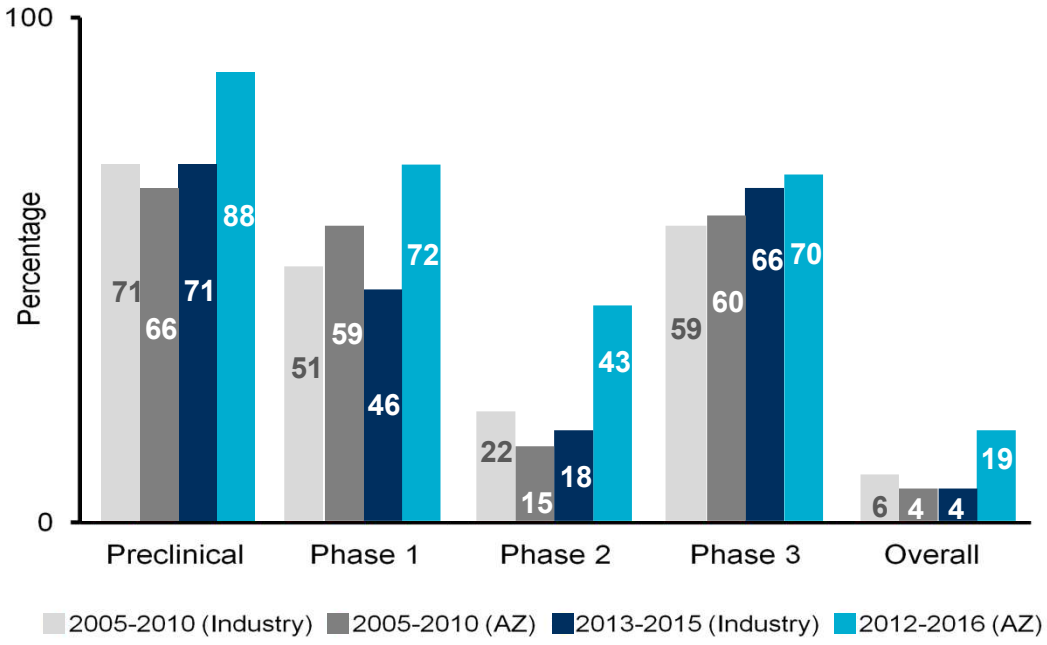
Ensuring **right safety** with minimal side effects

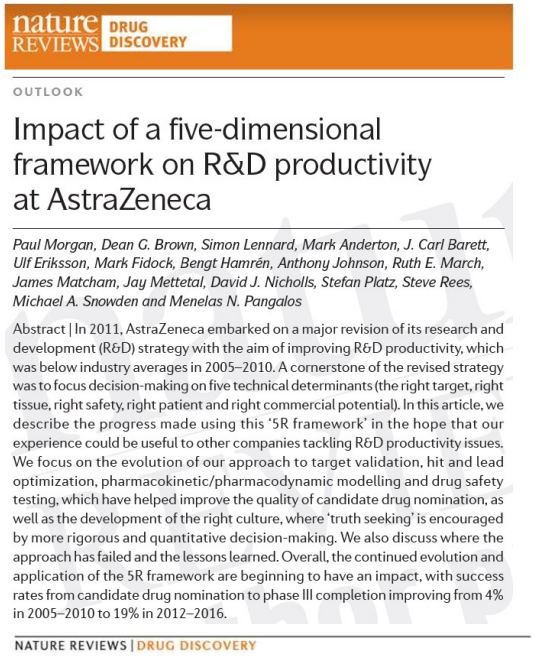
Selecting the **right patients** that will benefit

Defining the **right commercial** value and future viability

Underpinned by the **right culture** of truth-seeking behaviours and scientific rigor

As a result, we have delivered >4-fold improvement in AstraZeneca success rates from pre-clinical to Phase 3 completion since 2012





nature REVIEWS DRUG DISCOVERY

OUTLOOK

Impact of a five-dimensional framework on R&D productivity at AstraZeneca

Paul Morgan, Dean G. Brown, Simon Lennard, Mark Anderton, J. Carl Barrett, Ulf Eriksson, Mark Fidock, Bengt Hamrén, Anthony Johnson, Ruth E. March, James Matcham, Jay Mettetal, David J. Nicholls, Stefan Platz, Steve Rees, Michael A. Snowden and Menelas N. Pangalos

Abstract | In 2011, AstraZeneca embarked on a major revision of its research and development (R&D) strategy with the aim of improving R&D productivity, which was below industry averages in 2005–2010. A cornerstone of the revised strategy was to focus decision-making on five technical determinants (the right target, right tissue, right safety, right patient and right commercial potential). In this article, we describe the progress made using this '5R framework' in the hope that our experience could be useful to other companies tackling R&D productivity issues. We focus on the evolution of our approach to target validation, hit and lead optimization, pharmacokinetic/pharmacodynamic modelling and drug safety testing, which have helped improve the quality of candidate drug nomination, as well as the development of the right culture, where 'truth seeking' is encouraged by more rigorous and quantitative decision-making. We also discuss where the approach has failed and the lessons learned. Overall, the continued evolution and application of the 5R framework are beginning to have an impact, with success rates from candidate drug nomination to phase III completion improving from 4% in 2005–2010 to 19% in 2012–2016.

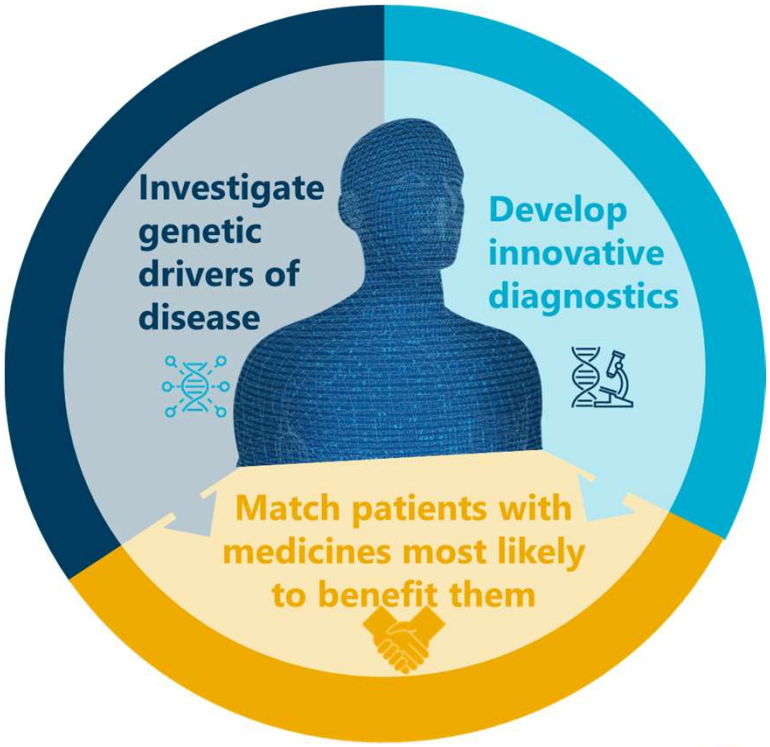
NATURE REVIEWS | DRUG DISCOVERY

Morgan et al., 2018 *Nature Reviews Drug Discovery*

Precision medicine and genomics at AstraZeneca

'The right patient'

We are driven by patient need, with a commitment to matching life-changing precision medicines to patients most likely to benefit



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

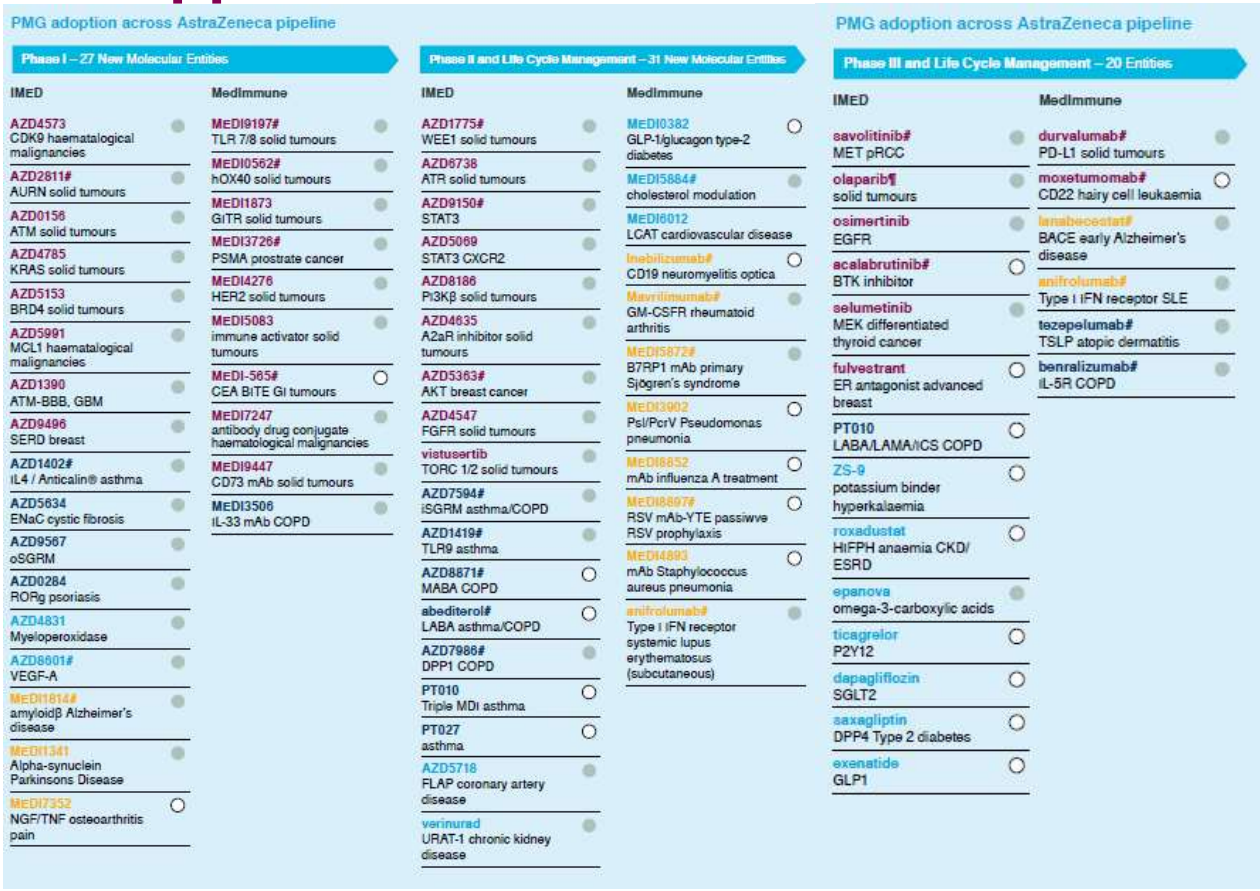
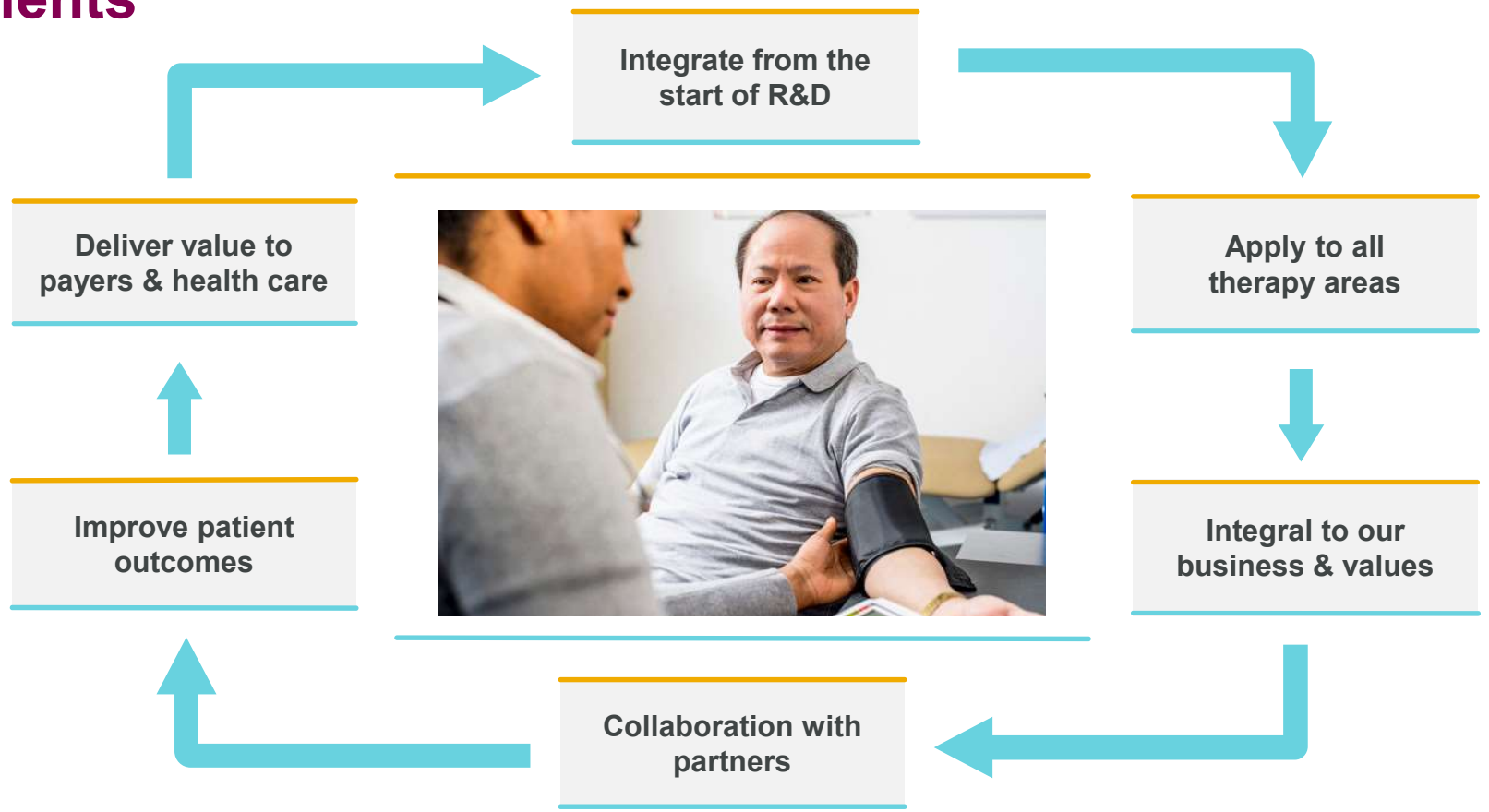
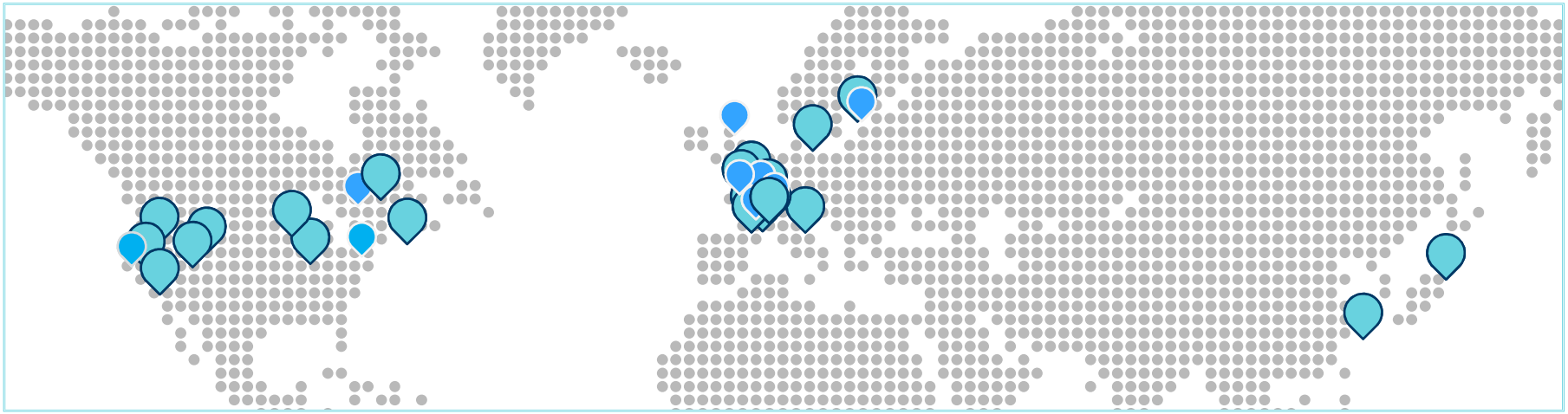


Figure from 2017 AZ IMED Annual Report

Precision medicine is based on science and centered on patients



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
wellcome trust sanger institute
CHEMBIO DIAGNOSTIC SYSTEMS, INC.
DNAnexus
GUARDANT HEALTH
illumina
MYRIAD
REGENERON GENETICS CENTER
UNIVERSITY OF CAMBRIDGE
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 and EGFR mutations

Plasma ctDNA companion diagnostic innovation

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]

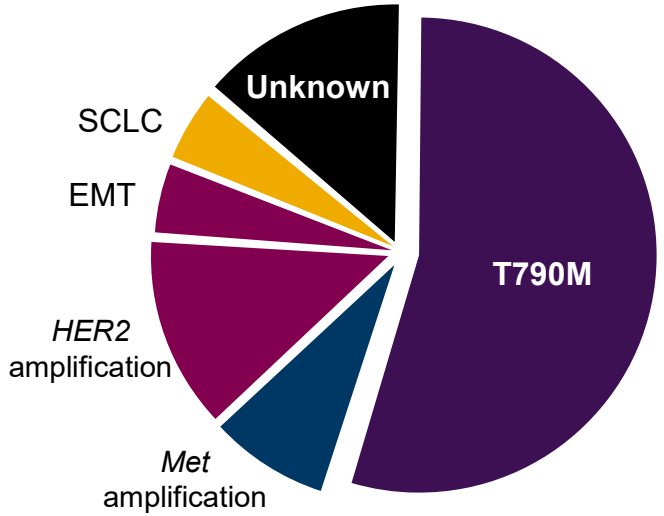
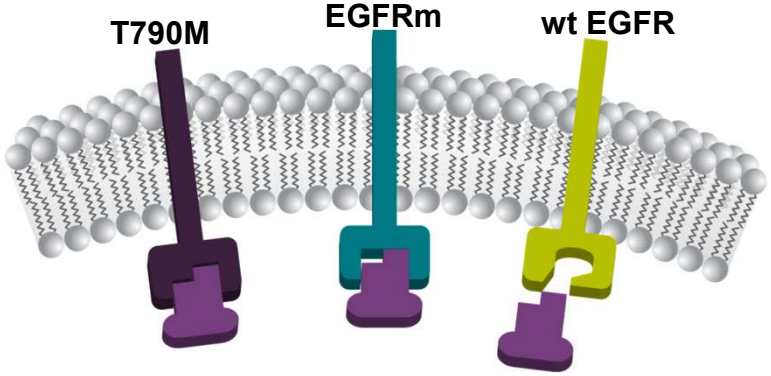


Figure adapted from Cortot A, Janne PA. Eur Resp Rev 2014



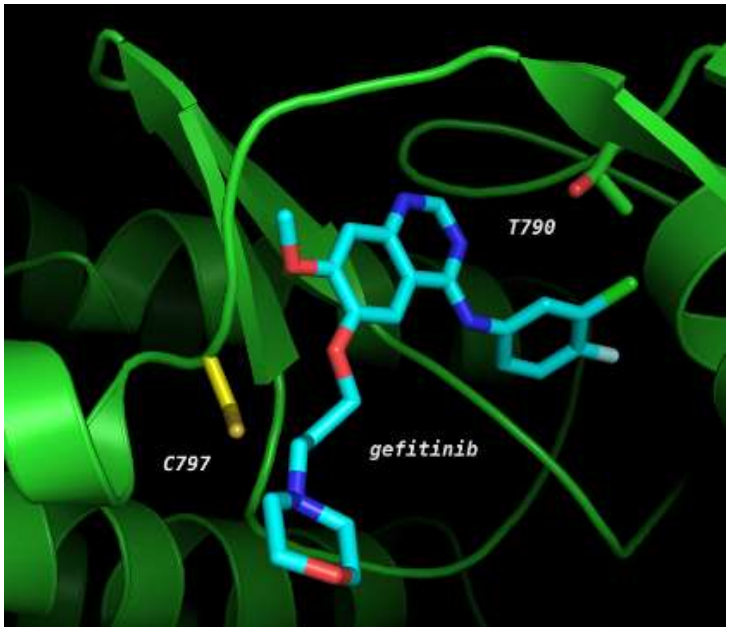
- **Inhibition of T790M[6,8]**
- **Inhibition of EGFRm (exon 19 deletion and L858R)[6,8]**
- **Lower activity for wt EGFR[6,8]**
- **Low affinity for IR / IGFR[7]**

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



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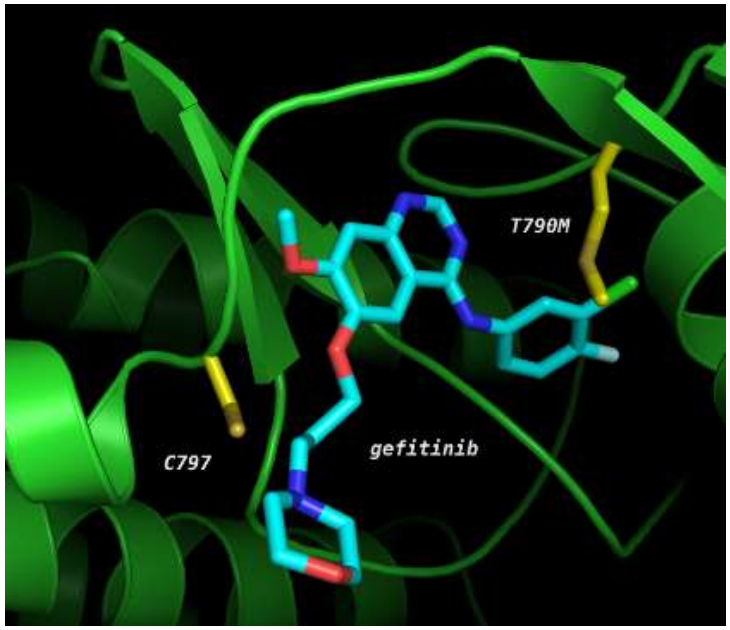

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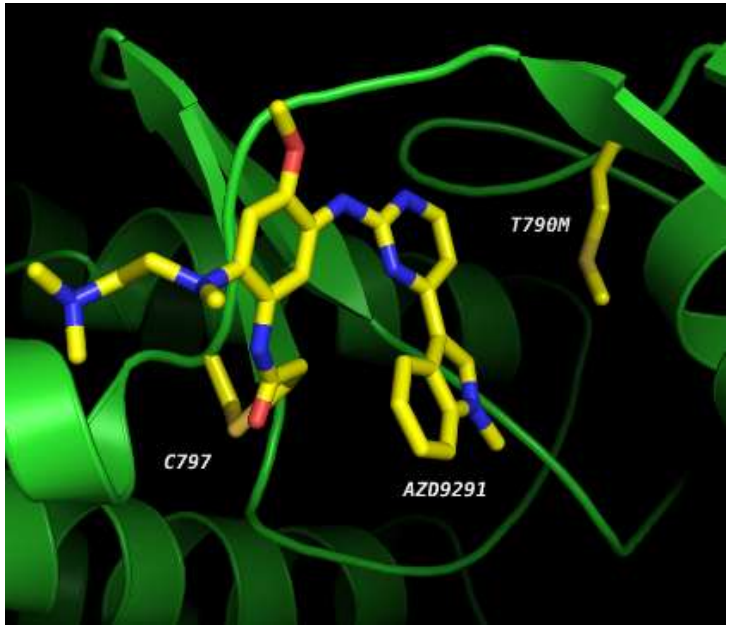
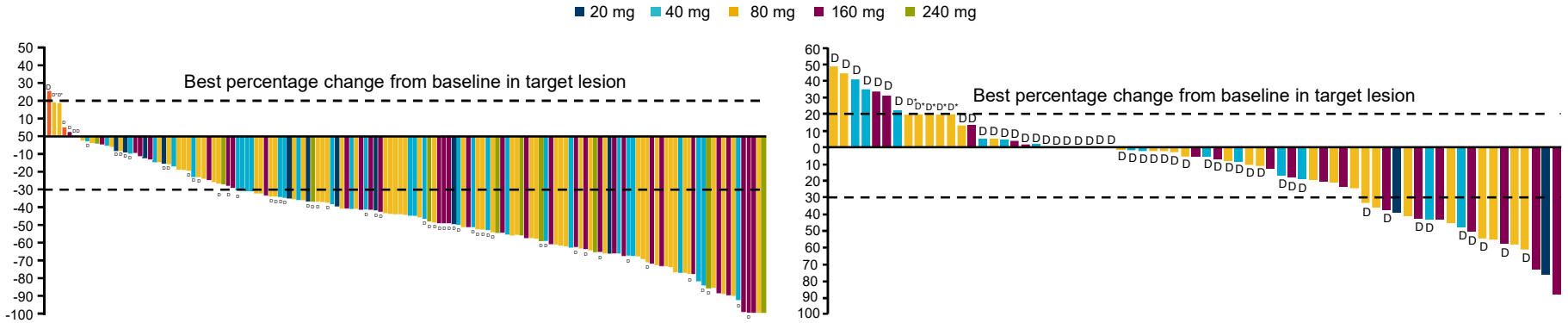


Osimertinib is highly efficacious in patients with tumours harbouring the *T790M* mutation (2L NSCLC)

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

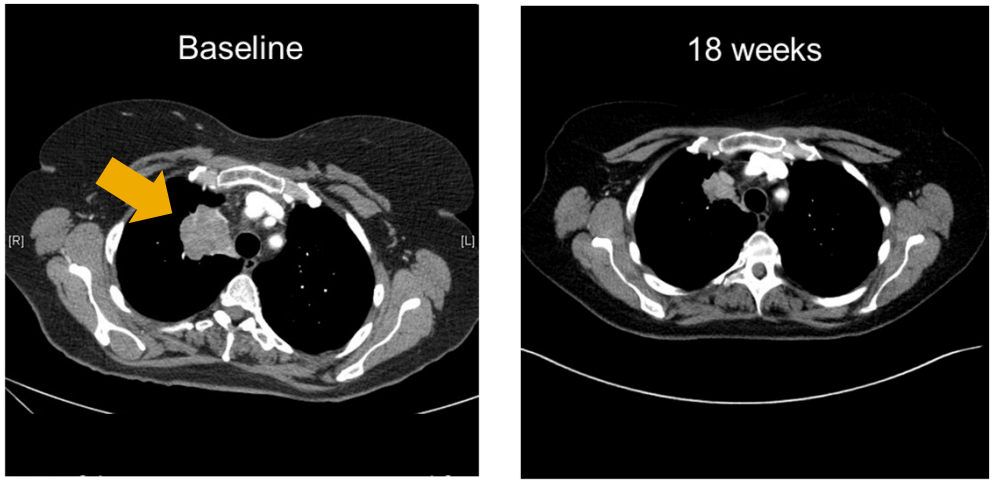
Response rate in AURA Phase I
***T790M* negative cohorts (central test)**



- 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

Osimertinib – early clinical activity at 20 mg dose

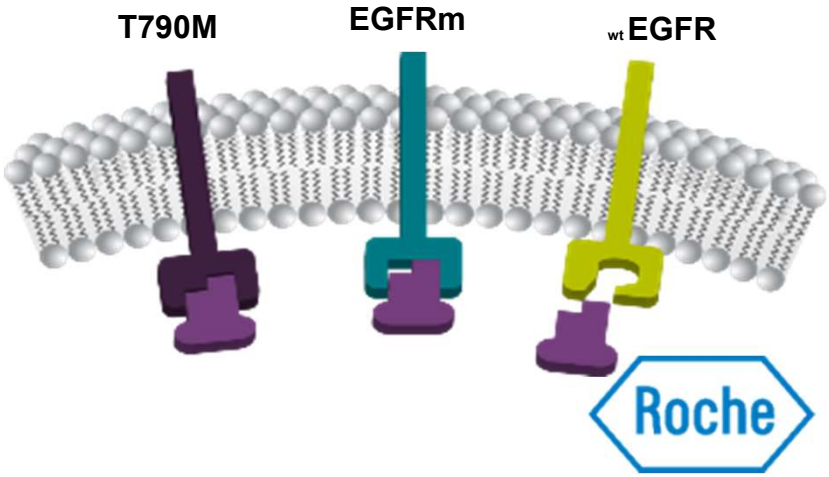


- Patient with Ex19Del and T790M+ pre-gefitinib
- Progressed on gefitinib immediately before osimertinib
- Dose escalation Cohort 1 **(20 mg/day)**

Presented by Prof M Ranson at The European Cancer Congress 2013; European Journal of Cancer Vol 49, supplement 3: LBA 33

Development of a companion diagnostic for osimertinib

- AstraZeneca partnered with Roche Molecular Systems[1] to develop **companion diagnostic tests for osimertinib**
  - **Tissue-based test** to support the US approval of osimertinib
- FDA approved the first companion diagnostic test to detect *T790M*
- The newly approved version (v2) of the test adds the *T790M* mutation to the clinically relevant mutations detected by the original cobas® EGFR Mutation Test (v1)
- Parallel development of a **less invasive plasma-based test**



The Roche cobas® EGFR Mutation Test v2 offers broad mutation coverage of EGFR exons 18, 19, 20 and 21 to help select patients with NSCLC for treatment with EGFR inhibitors[2]

1. http://www.astrazeneca.com/Media/Press-releases/Article/28072014--diagnostic-collaboration-cbrs-layout-2; 2. http://molecular.roche.com/assays/Pages/cobasEGFRMutationTest.aspx

Plasma ctDNA provides powerful complementary diagnostic approach to tissue and offers multiple assay approaches

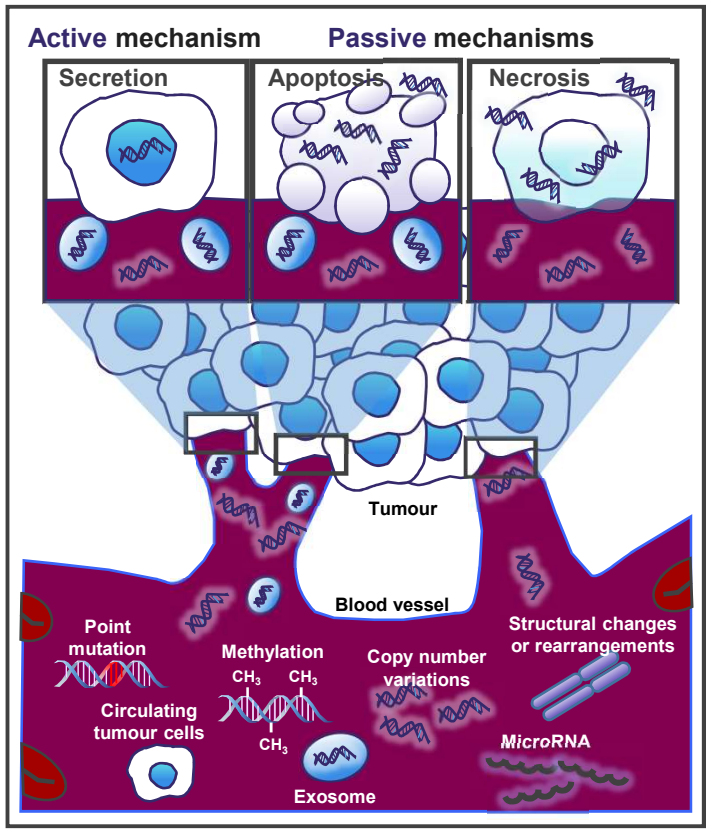
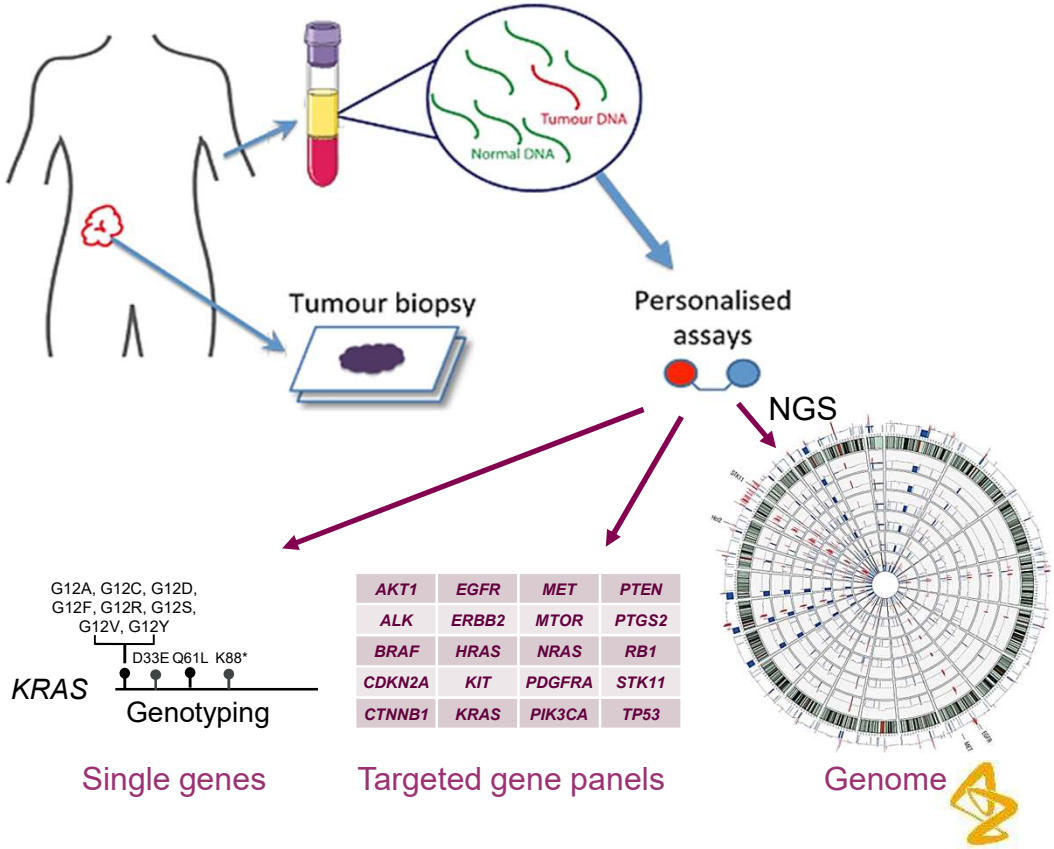


Figure adapted from Diaz L et al. JCO 2014

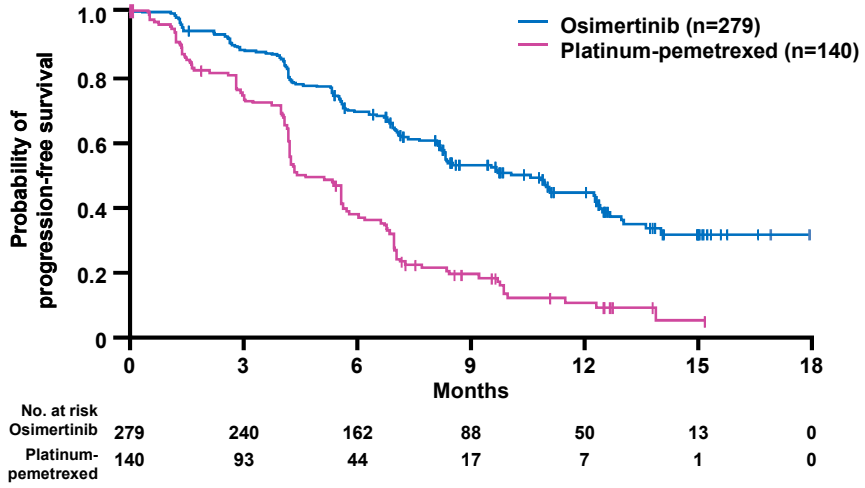


NGS, next generation sequencing

AURA3: osimertinib benefit in patients with plasma T790M-positive status is similar to patients with tissue T790M-positive status

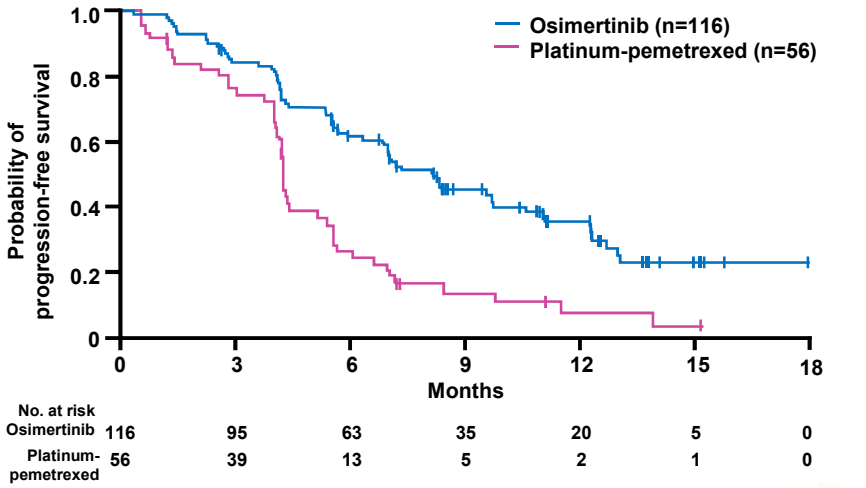
Intent-to-treat* (tumour T790M-positive†)

	Osimertinib	Platinum-pemetrexed
PFS HR (95% CI)	0.30 (0.23, 0.41)*, p<0.001	
Median PFS, months (95% CI)	10.1 (8.3, 12.3)	4.4 (4.2, 5.6)
ORR‡, % (95% CI)	71 (65, 76)	31 (24, 40)



Plasma T790M-positive status

	Osimertinib	Platinum-pemetrexed
PFS HR (95% CI)	0.42 (0.29, 0.61)	
Median PFS, months (95% CI)	8.2 (6.8, 9.7)	4.2 (4.1, 5.1)
ORR‡, % (95% CI)	77 (68, 84)	39 (27, 53)

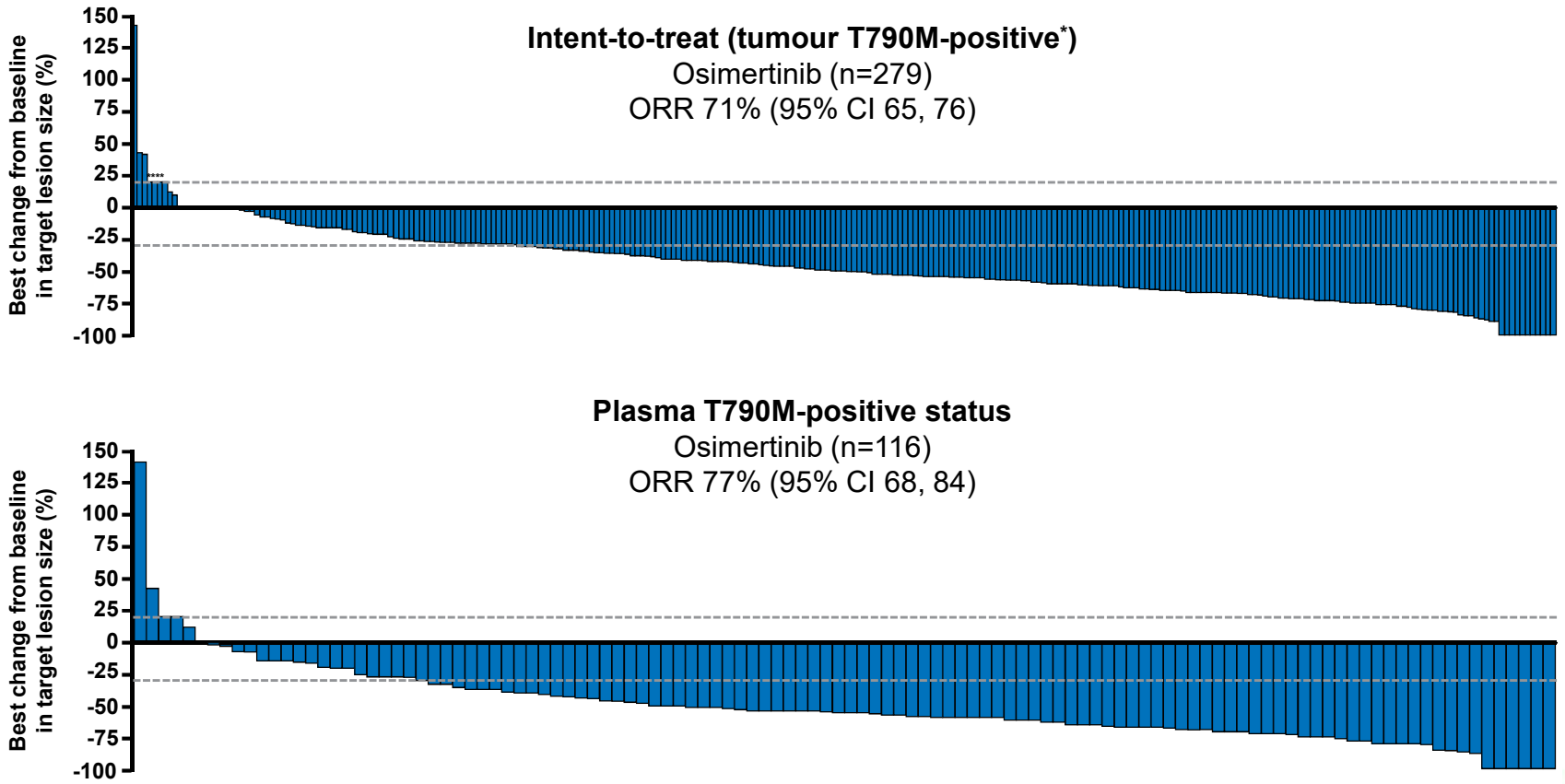


Wu et al., IASLC 17th World Conference on Lung Cancer, 2016; session MA08: Treatment Monitoring in Advanced NSCLC (abstract MA08.03)

Tick marks indicate censored data. PFS is defined as time from randomisation until date of objective disease progression or death; calculated using the Kaplan-Meier approach. Progression included deaths in the absence of RECIST progression. Osimertinib administered 80 mg orally once daily. Platinum-pemetrexed group treatment consisted of: pemetrexed 500 mg/m^2 + carboplatin AUC5 or cisplatin 75 mg/m^2 Q3W for up to 6 cycles + optional maintenance pemetrexed for patients whose disease had not progressed after 4 cycles of platinum-pemetrexed. RECIST v1.1 assessments performed every 6 weeks until objective disease progression

*PFS adjusted for ethnicity; †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; ‡Response did not require confirmation per RECIST v1.1; HR, hazard ratio; ORR, objective response rate; PFS, progression-free survival; Q3W, once every 3 weeks; RECIST, Response Evaluation Criteria In Solid Tumors

Target lesion response to osimertinib*



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

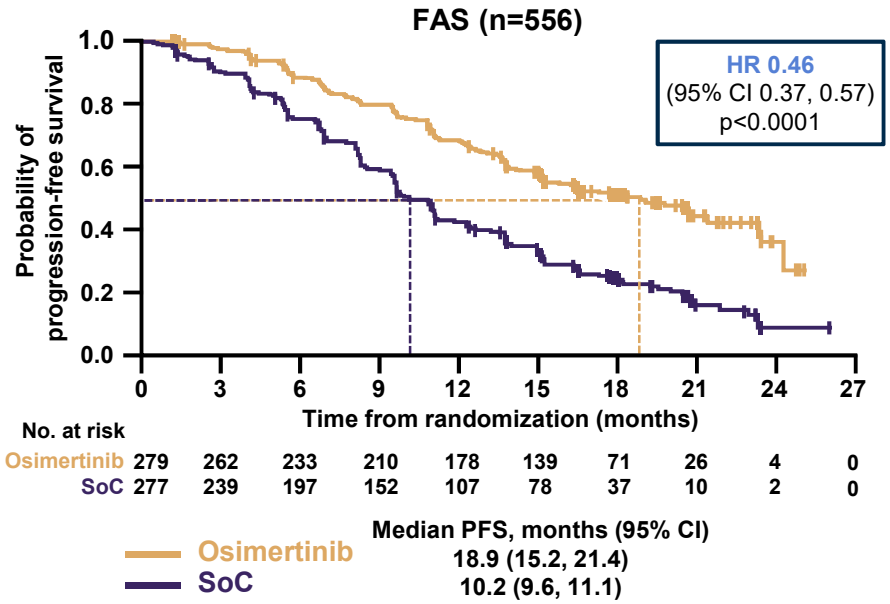
Best percentage change in target lesion size is the maximum reduction from baseline or the minimum increase.

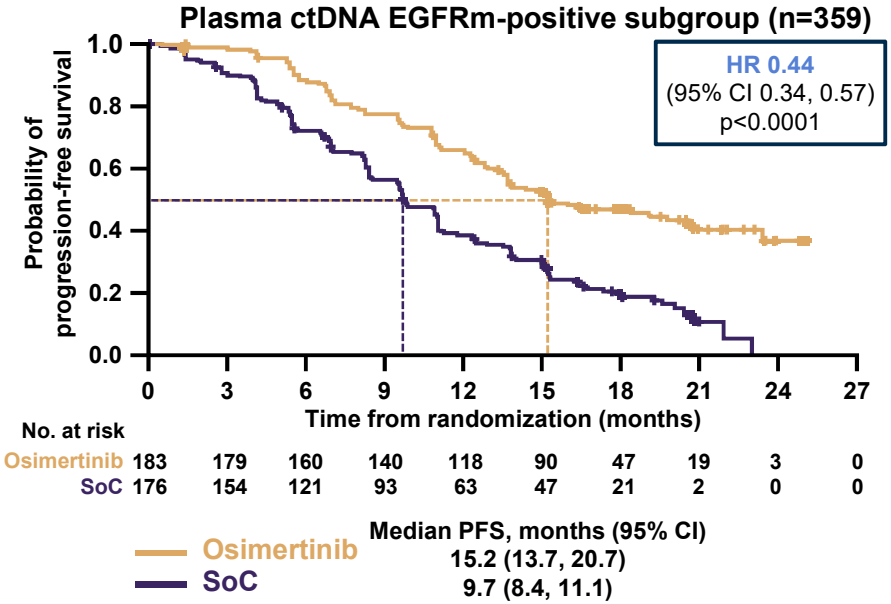
*All patients were selected using a tumour tissue test for *EGFR* T790M (by **cobas**® EGFR Mutation Test) from a biopsy after disease progression prior to study entry

*investigator assessed

FLAURA: 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.

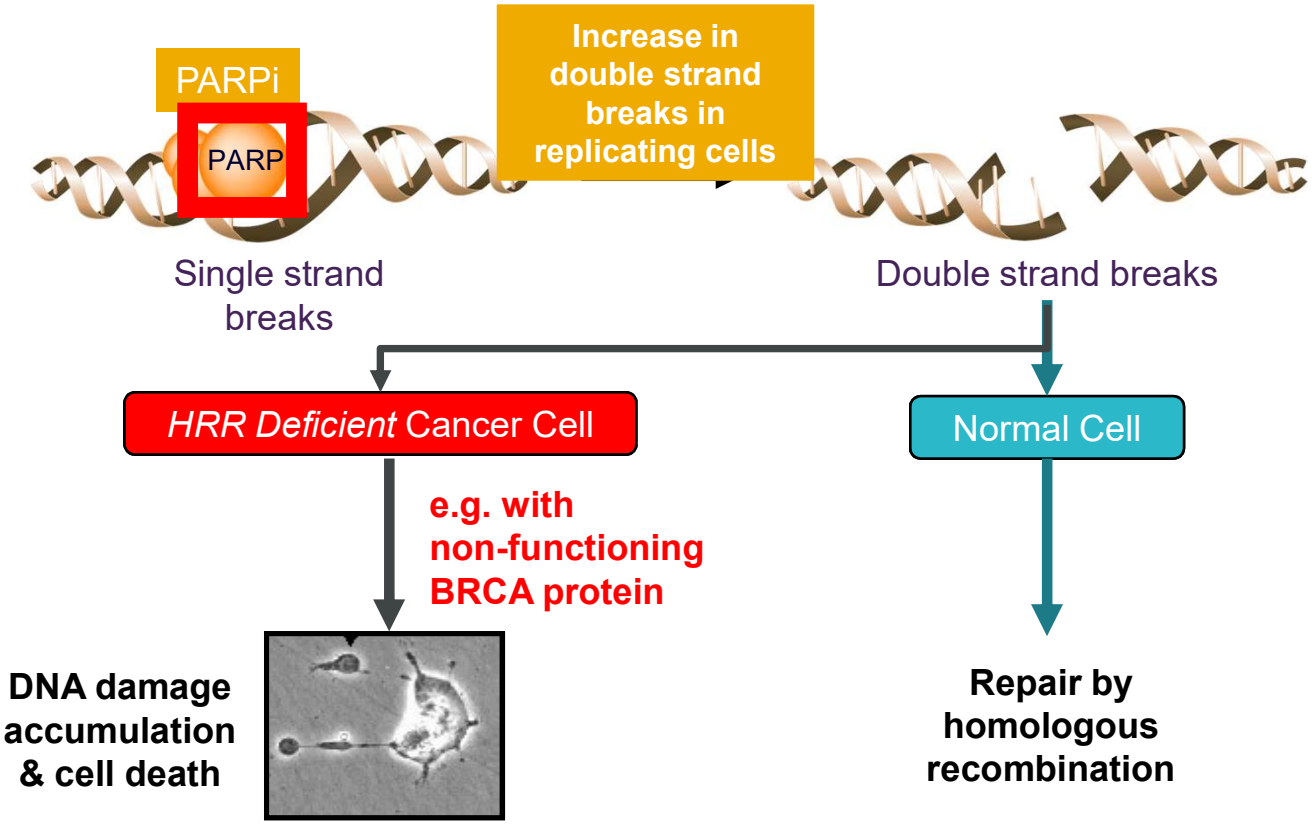
Gray et al., IASLC 18th World Congress on Lung Cancer, Japan, 2017

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

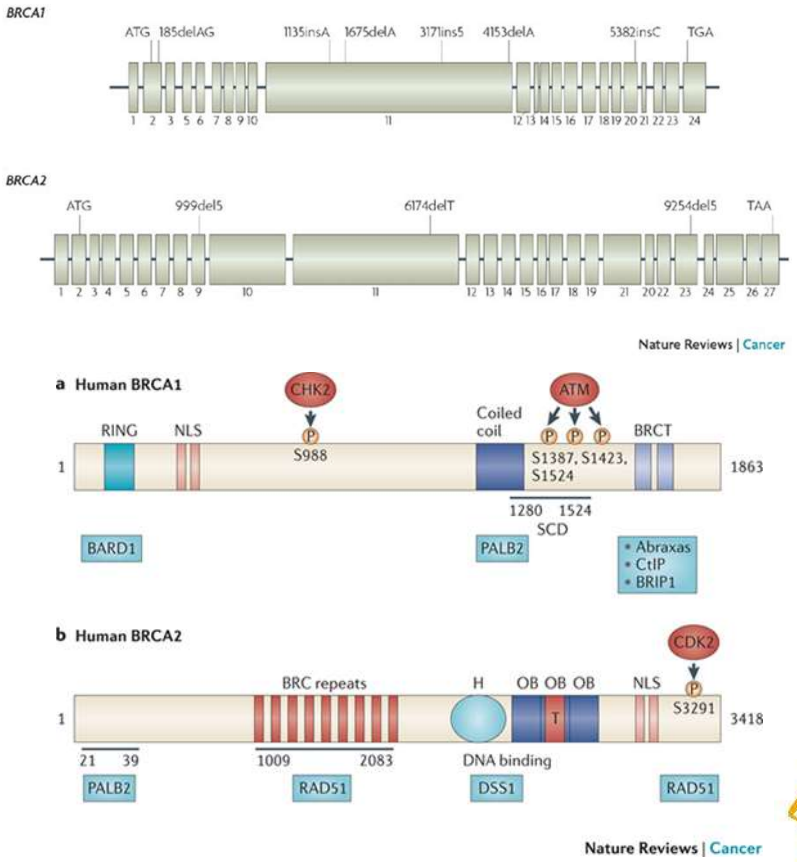
Translating evolving science into clinic

PARP inhibition and cell death in homologous recombination repair deficient tumours



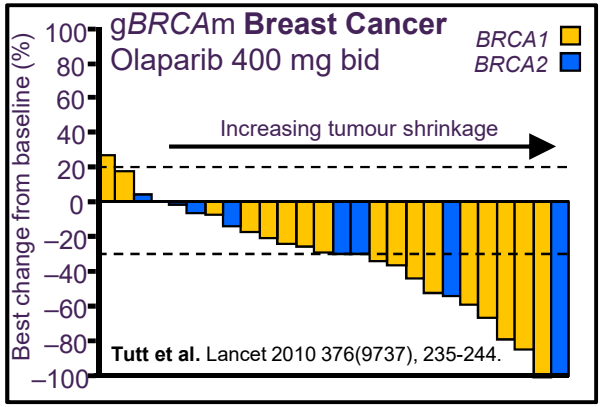
BRCA1 & BRCA2 genes

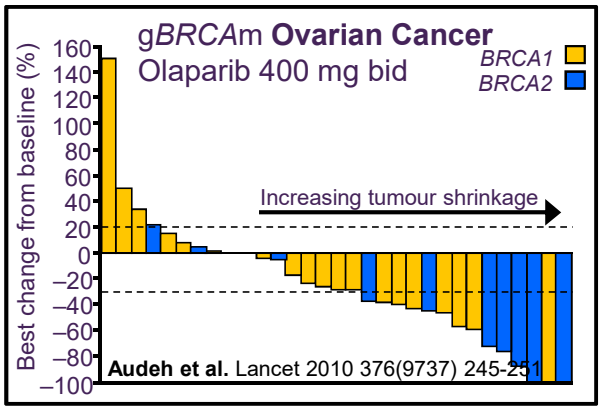
- Two large tumour suppressor genes: *BRCA1* – 81Kb, *BRCA2* – 84Kb
  - ~14,000 variants identified to date across both genes
  - ~4,000 deleterious and suspected deleterious mutations (loss of function mutations) identified by Myriad
- Laboratory-developed test (LDT) offered by Myriad for determination of hereditary breast & ovarian cancer risk
  - Offered as a CLIA/CAP certified test
  - Now approved as companion diagnostic for Lynparza in US and Japan

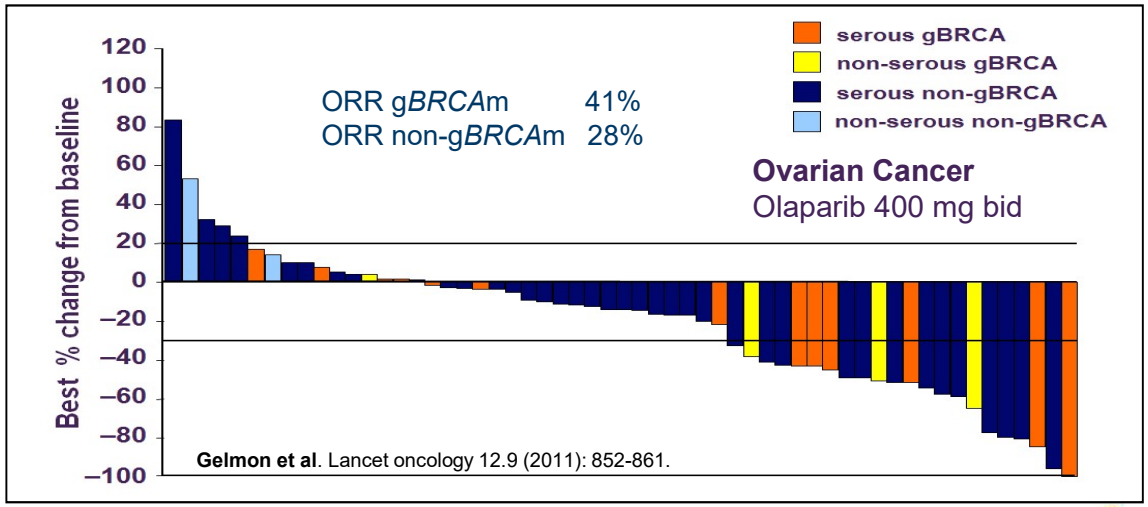


Roy R et al, Nature Reviews 2012; 12 (68-78)

Proof of Concept and Beyond

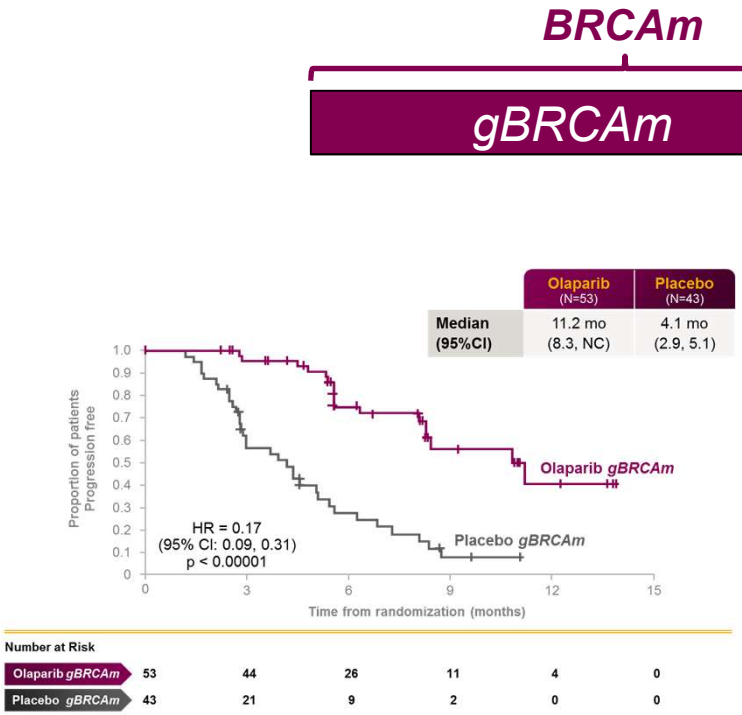




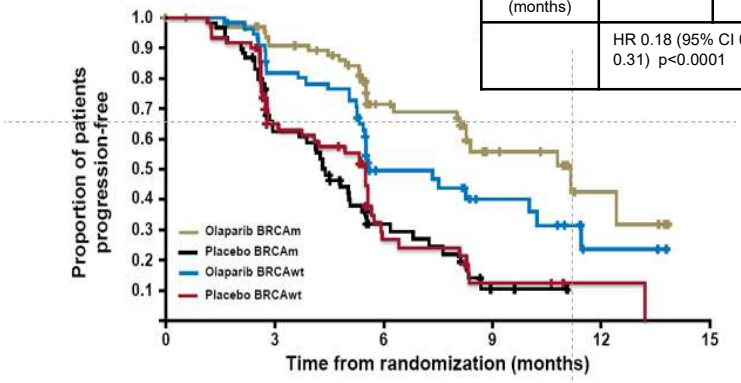


Study 19: Progression Free Survival by *BRCAm* status

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



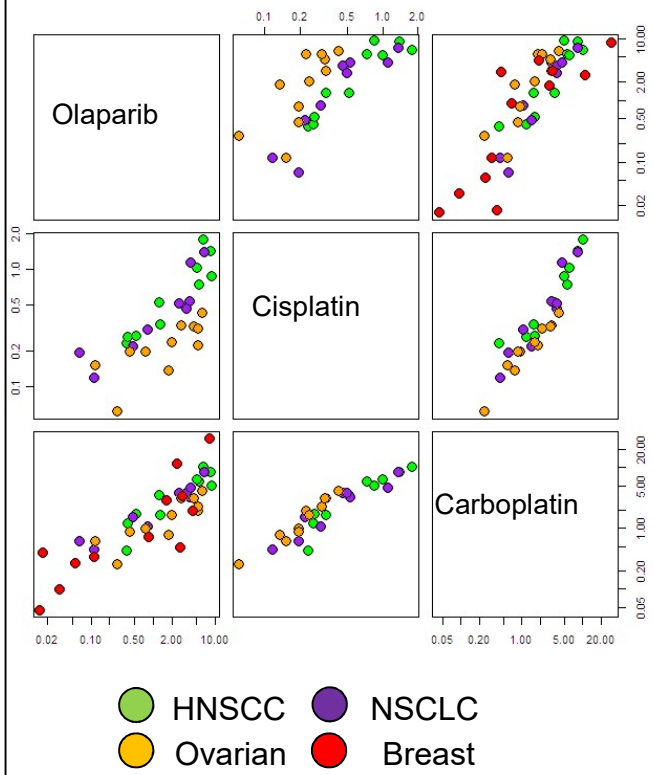
	BRCAm (n=136)		*BRCAwt* (n=118)	
	Olaparib	Placebo	Olaparib	Placebo
Median PFS (months)	11.2	4.3	7.4	5.5
	HR 0.18 (95% CI 0.10-0.31) p<0.0001		HR 0.54 (95% CI 0.34-0.85) P=0.0075	



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



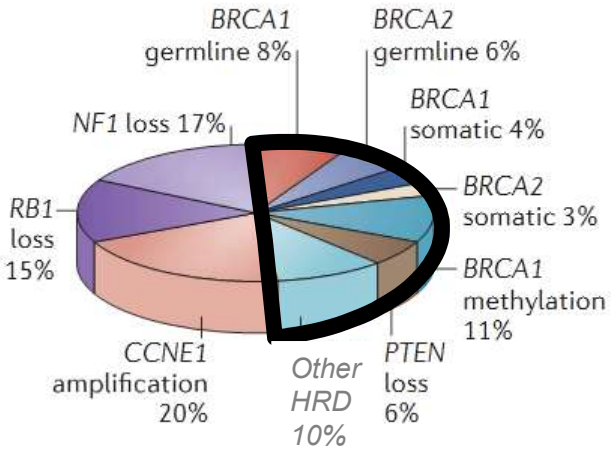
Preclinical candidates

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 Białkowska,[3] Sally Swift,[1,2] Sabrina Giavara,[2] Mark J. O'Connor,[1] Andrew N. Tutt,[2] Malgorzata Z. Zdzienicka,[3,5] Graeme C.M. Smith,[1] and Alan Ashworth[1,2]

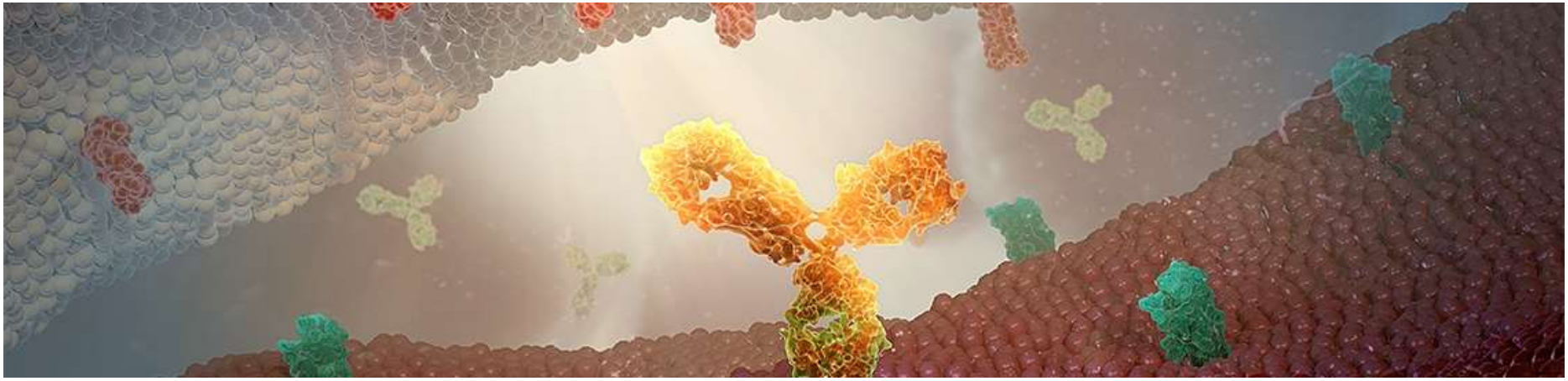
Presence of other deficiencies in DNA repair in HG serous ovarian cancer



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

Precision Medicine

How can we further improve?



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

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**

TAT, turn around time

Precision Medicine: the journey continues …

Recent

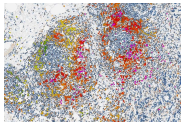
BRCA Companion Diagnostic

Circulating tumour DNA label

Single genes

Present

IO Diagnostic Solutions



Multigene DNA panels

Point-of-care Diagnostics (PoC)

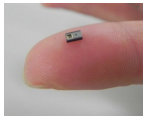
Multigene panels & PoC

Future

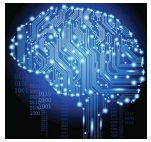
Genomics

Early diagnosis and monitoring

Sensors



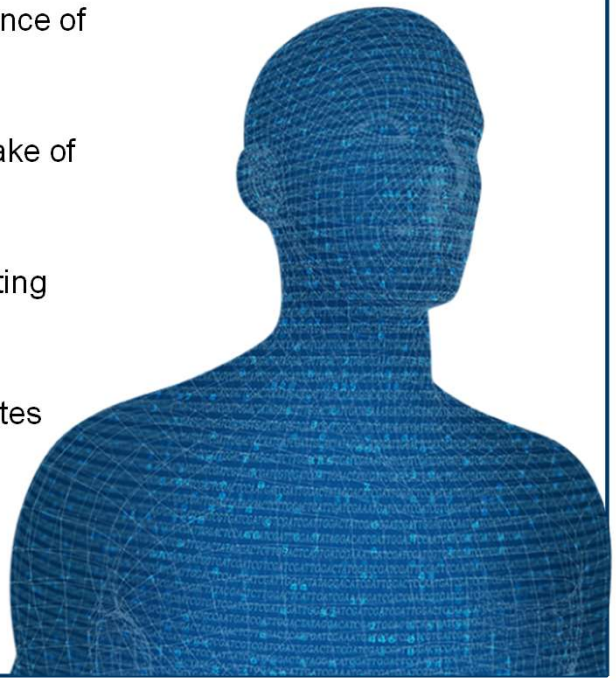
Artificial intelligence



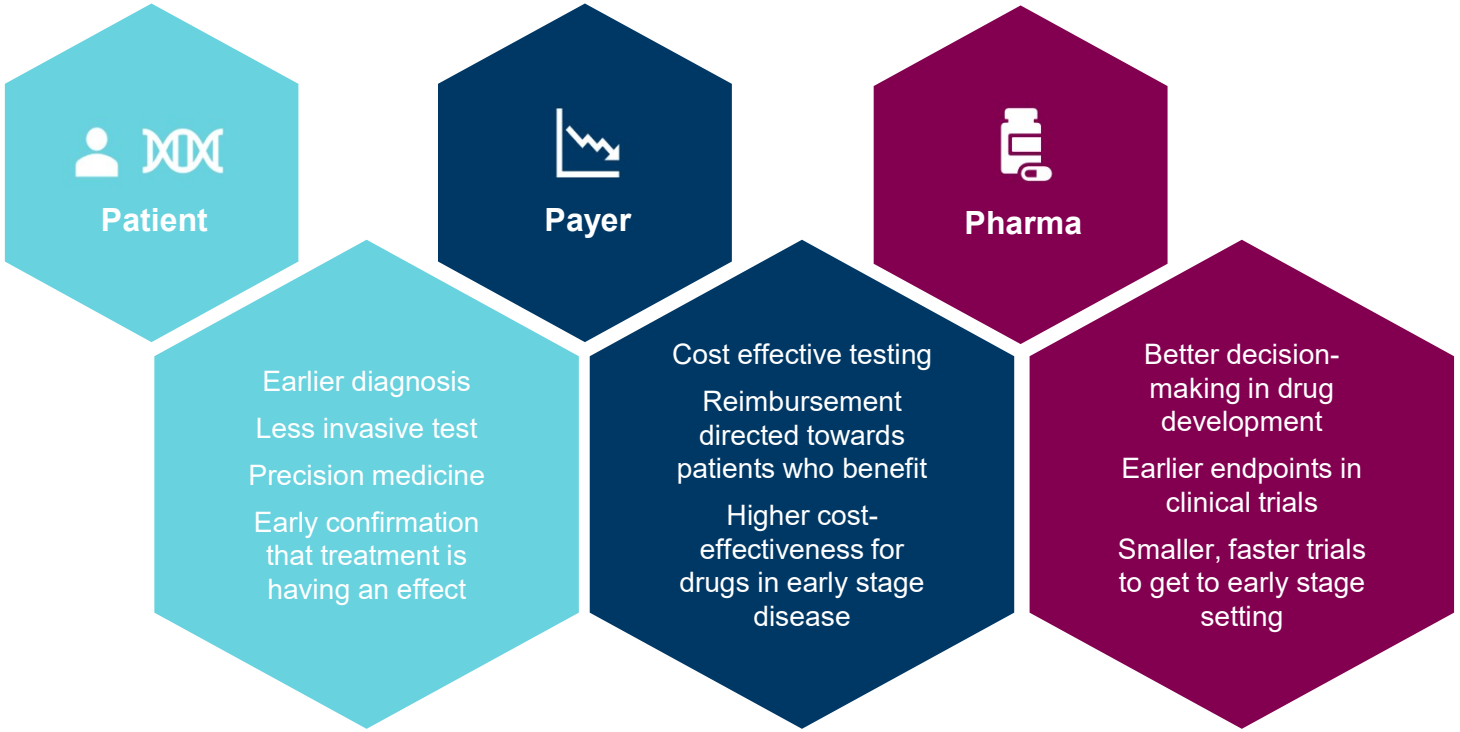
PoC Genomics & AI

Critical success factors to drive precision medicine for the benefit of patients and innovation

- **Pragmatic regulatory systems** enabling approval of emerging science of Precision Medicine
- **Supportive reimbursement environment** that accelerates the uptake of approved targeted therapies and linked diagnostics
- **Continued investment in technology** such as next-generation testing infrastructure (e.g., NGS, ctDNA) to drive diagnostic innovation
- **Coordinated health care delivery system** that continuously educates health care practitioners and empowers patients
- **Appropriate data sharing mechanisms** that harness the power of population-level genomic and clinical databases



Adoption of precision medicine represents a ‘win-win’



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