Precision Medicine: From patient need to providing solutions in clinical practice

Thorsten S Gutjahr
VP, Global Head of Companion Diagnostics, AstraZeneca
Precision Medicine and Genomics, IMED Biotech Unit, AstraZeneca, Cambridge, UK

November 2018

ESMO 2018 Press Release

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Olaparib maintenance extends progression-free survival by estimated 3 years in advanced ovarian cancer

Date: 21 Oct 2018
Topic: Gynaecologic malignancies

MUNICH, Germany – Two-year maintenance therapy with olaparib, a PARP (poly ADP ribose polymerase) inhibitor, olaparib, led to a substantial, unprecedented improvement in progression-free survival (PFS) in newly diagnosed patients with advanced ovarian cancer and a BRCA1 or 2 mutation, results from the phase 3 SOLO-1 trial show. (1)

"The median PFS for patients who received placebo was only 13.8 months while the median PFS for those who received olaparib was not reached but looks to be approximately three years longer than the placebo group [HR was 0.30; 95% CI: 0.23, 0.41; p<0.0001]," reported Dr Kathleen Moore, Associate Professor at the Stephenson Cancer Center, University of Oklahoma, US, presenting the results at ESMO 2018 Congress.

Need for new medicines

Cancers – 42%

Respiratory – 9%

Cardiovascular – 22%

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

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

What is precision medicine?

Identify **patient**

Patient sample

+

Identification of biomarkers

+

Right **treatment**

Diagnostic test results inform treatment decision

=

Patient benefit

Improved patient outcomes

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

The benefits of Precision Medicine: classified into three main categories

Delivering better treatments for patients

- Improved efficacy i.e. patient more likely to receive a medicine delivering a clinical benefit
- Improvement in overall survival
- Reduced adverse events

Delivering benefits to healthcare systems and society

- Prevention and prediction of disease
- Improvement in patient management
- Prevention or delay of more expensive care costs and allowing scarce healthcare resources to be using most efficiently
- Reduces hospitalisation

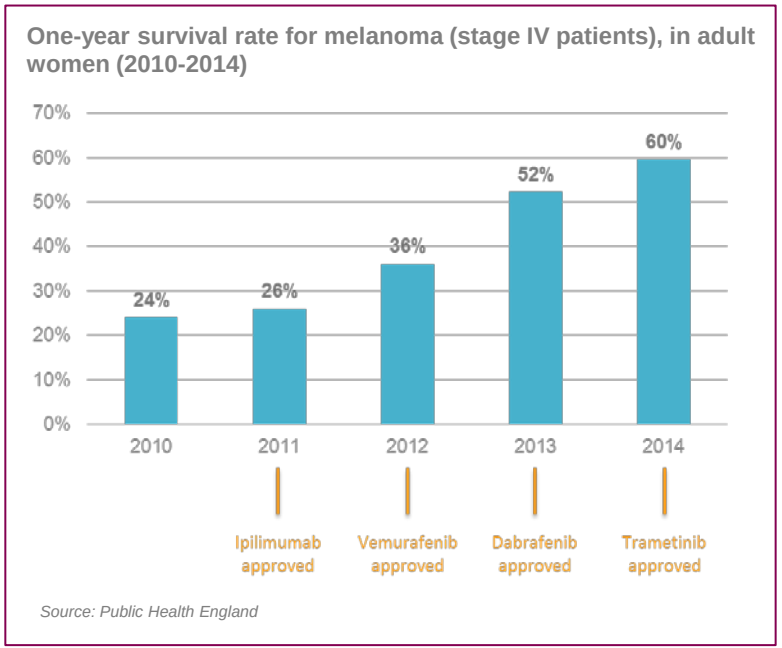
More efficient development of novel medicines

- More effective clinical trials
- Efficient clinical trials and reduction in cost

Slide adapted from CRA report for EFPIA/EBE: “An evidence-based analysis to characterise the benefits of personalised medicines to patients, society and healthcare systems” July 2018

Targeted and personalised interventions have led to better patient outcomes

- Move **away from 'trial-and-error'**
- **Progression-free survival and overall survival has increased** in many cancers
  - E.g., combination BRAF/MEK inhibitors drove major improvements in melanoma survival[1]
- **PM has targets the underlying genetic mutations** in diseases (e.g., CML and Cystic Fibrosis)
- Analysis of 570 phase II clinical trials: oncology PM therapies had **4X the response rates** compared to cytotoxic therapies[3]
- **Reduced side-effects:** anti-PD-1 treatment reduced frequency adverse events: 49.4% (chemotherapy) to 15.0%[4]



Slide adapted from CRA report for EFPIA/EBE: "An evidence-based analysis to characterise the benefits of personalised medicines to patients, society and healthcare systems" July 2018

[1] Oncologist interviews; [2] Cancer Research UK; [3] Schwaederle M et al (2015); [4] Bellmunt J et al (2017)

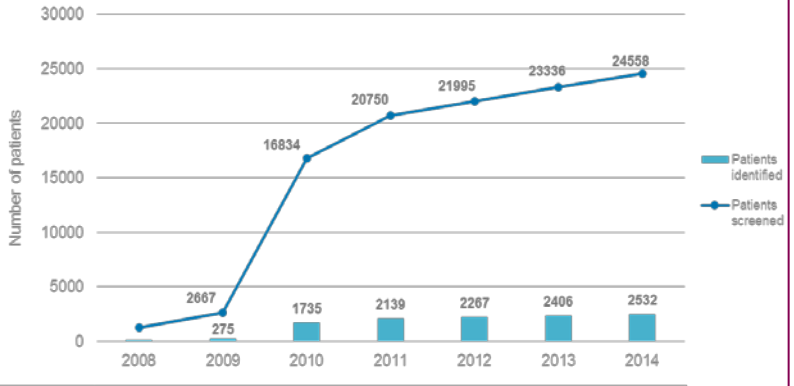
Precision Medicine enables earlier treatment or prevention and can lower healthcare costs

- **Profile disease or predict susceptibility to medicine toxicities**, to help guide treatment choices
- This can **lower overall healthcare costs** through early-detection, prevention, accurate risk assessments and efficiencies in care delivery

Example:

❖ In France, INCa allocated an additional €1.7M to EGFR testing. This resulted in substantial increase EGFR screening in patients[2]. INCa concluded that this **additional investment in EGFR testing would save €69 million to the French health insurance** by identifying patients who harboured the EGFR mutation

Number of lung cancer patients screened for EGFR mutations in France



	2008	2009	2010	2011	2012	2013	2014
Cost of screening	€ 0.1 M	€ 0.3 M	€ 1.7 M	€ 2.11 M	€ 2.1 M	€ 2.2 M	€ 2.5 M
Treatment savings *	€ 5.2 M	€ 11.0 M	€ 69.5 M	€ 85.6 M	€ 90.7 M	€ 96.3 M	€ 101.3 M

*Notes: * Treatment savings account for the spared cost of gefitinib treatment by only targeting patients more likely to respond to EGFR inhibitors*

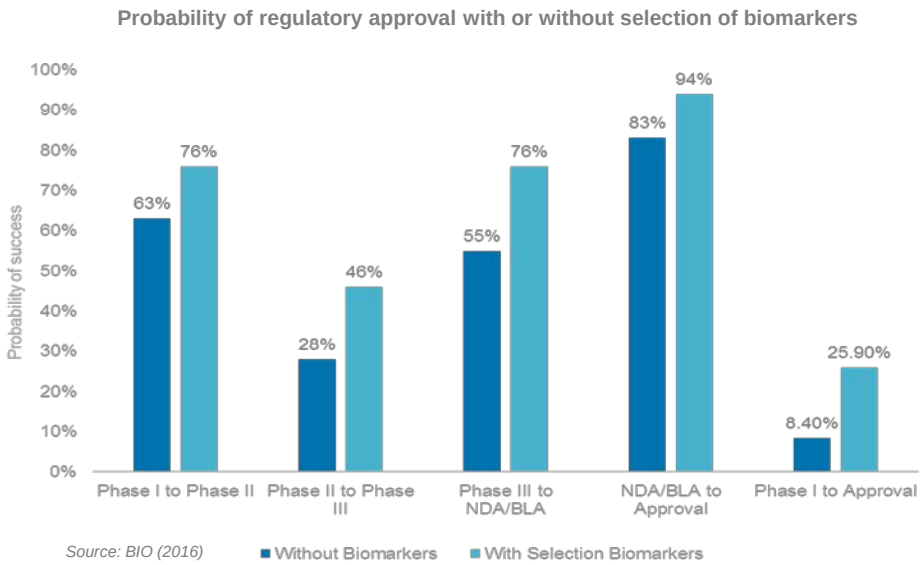
Source: CRA analysis of WIN Consortium

Slide adapted from CRA report for EFPIA/EBE: "An evidence-based analysis to characterise the benefits of personalised medicines to patients, society and healthcare systems" July 2018

[1] Marks D (2002); [2] Nowak, F. (2012)

Developments in Precision Medicine directly impacts clinical trial design, patient recruitment and probability of success

- Trials that do use selection biomarkers have a higher probability of success thus making an R&D program more cost-effective



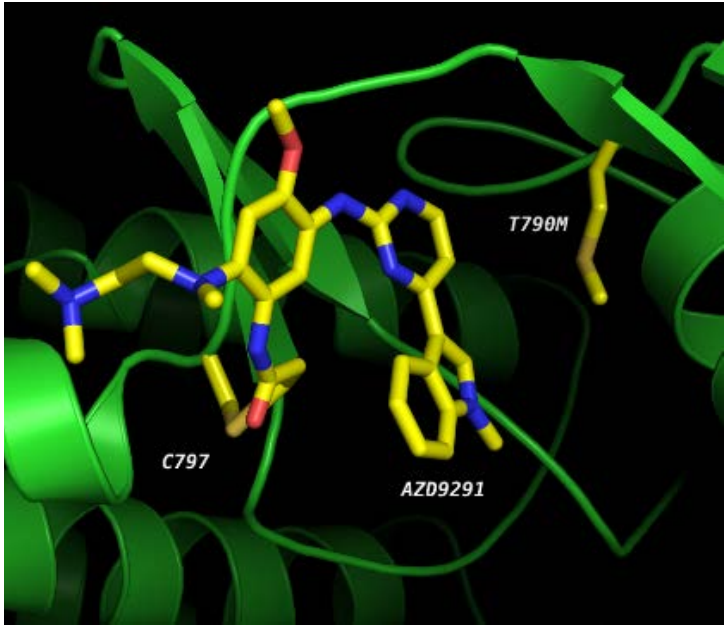
Slide adapted from CRA report for EFPIA/EBE: “An evidence-based analysis to characterise the benefits of personalised medicines to patients, society and healthcare systems” July 2018

Case Study 1

Osimertinib for patients with EGFR mutation-positive NSCLC

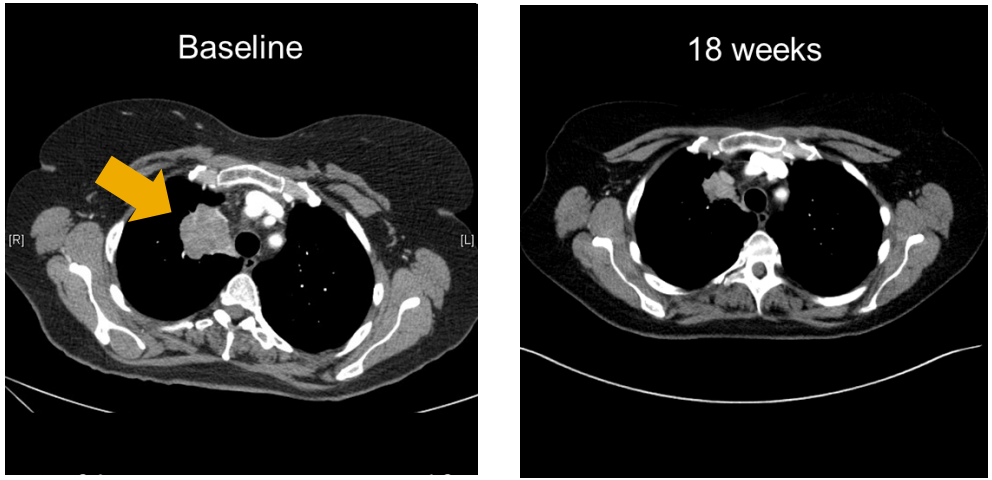
Osimertinib is an irreversible EGFR-TKI, selective for EGFR-TKI-sensitizing and T790M mutations[1,2]

- 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



1. TAGRISSO Prescribing Information;
2. Yun CH, et al. Proc Natl Acad Sci USA 2008;105:2070-5; 8. Cross DA, et al. Cancer Discov 2014;4:1046-61

Osimertinib – early clinical activity at 20 mg dose

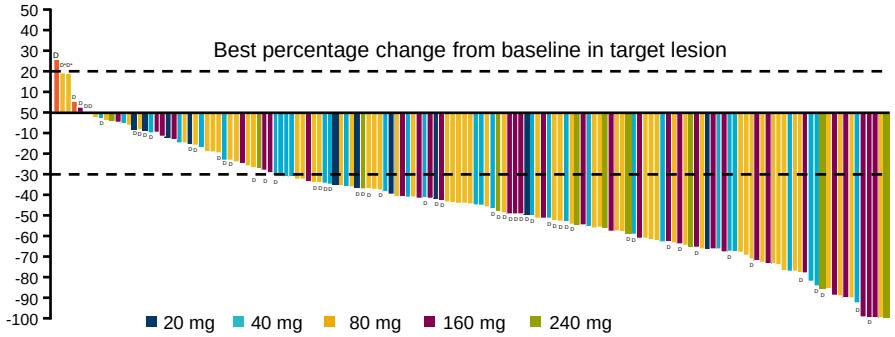


- Patient with Ex19Del and T790M+ pre-gefitinib
- Progressed on gefitinib immediately before osimertinib
- Dose escalation Cohort 1 **(20 mg/day)**

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

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)**



- 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

Plasma ctDNA is a powerful solution to patient testing

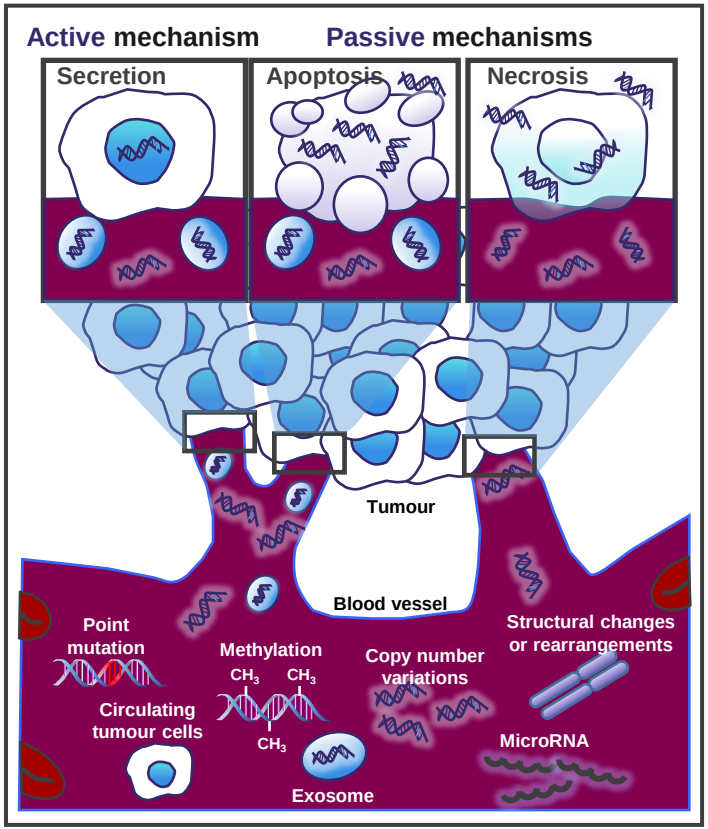
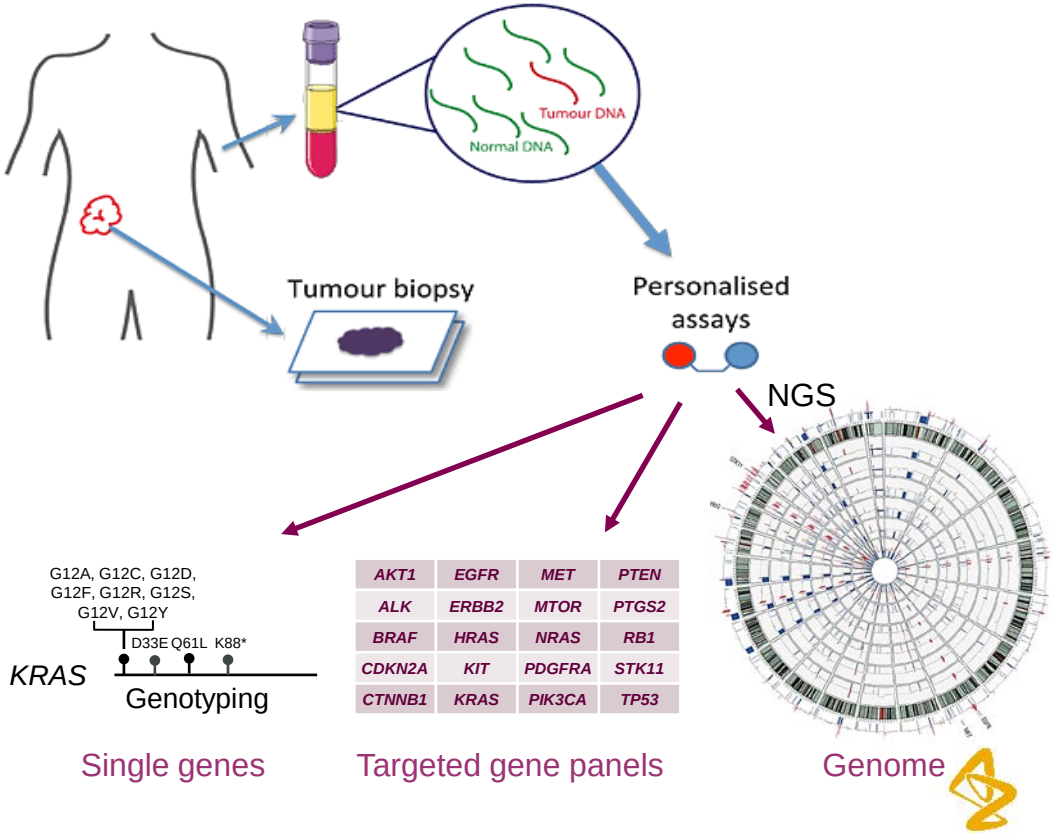


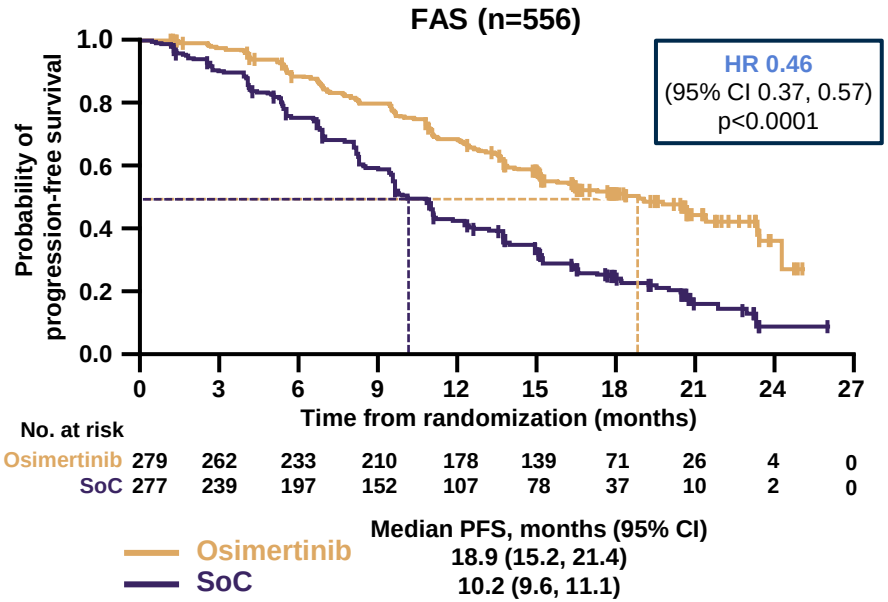
Figure adapted from Diaz L et al. JCO 2014

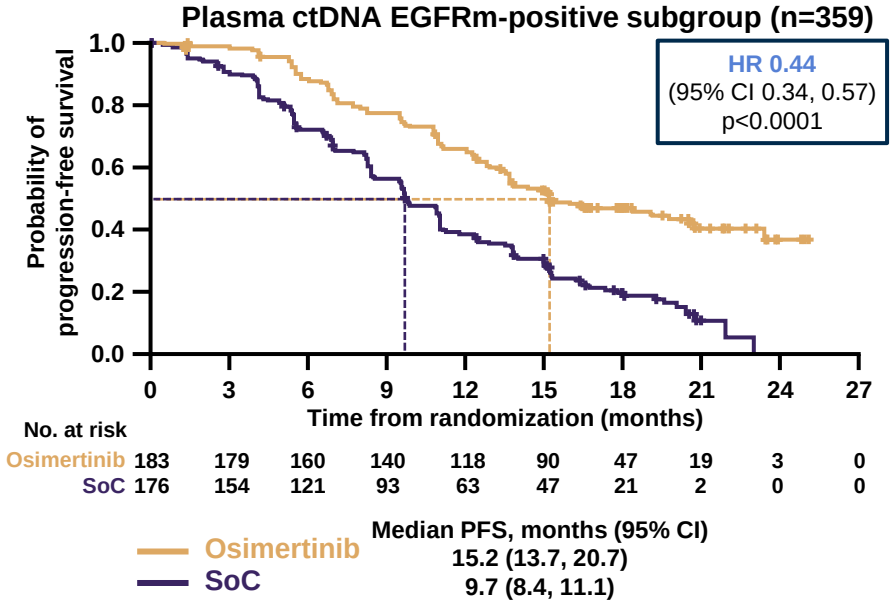


NGS, next generation sequencing

Osimertinib in 1L NSCLC vs SoC (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.

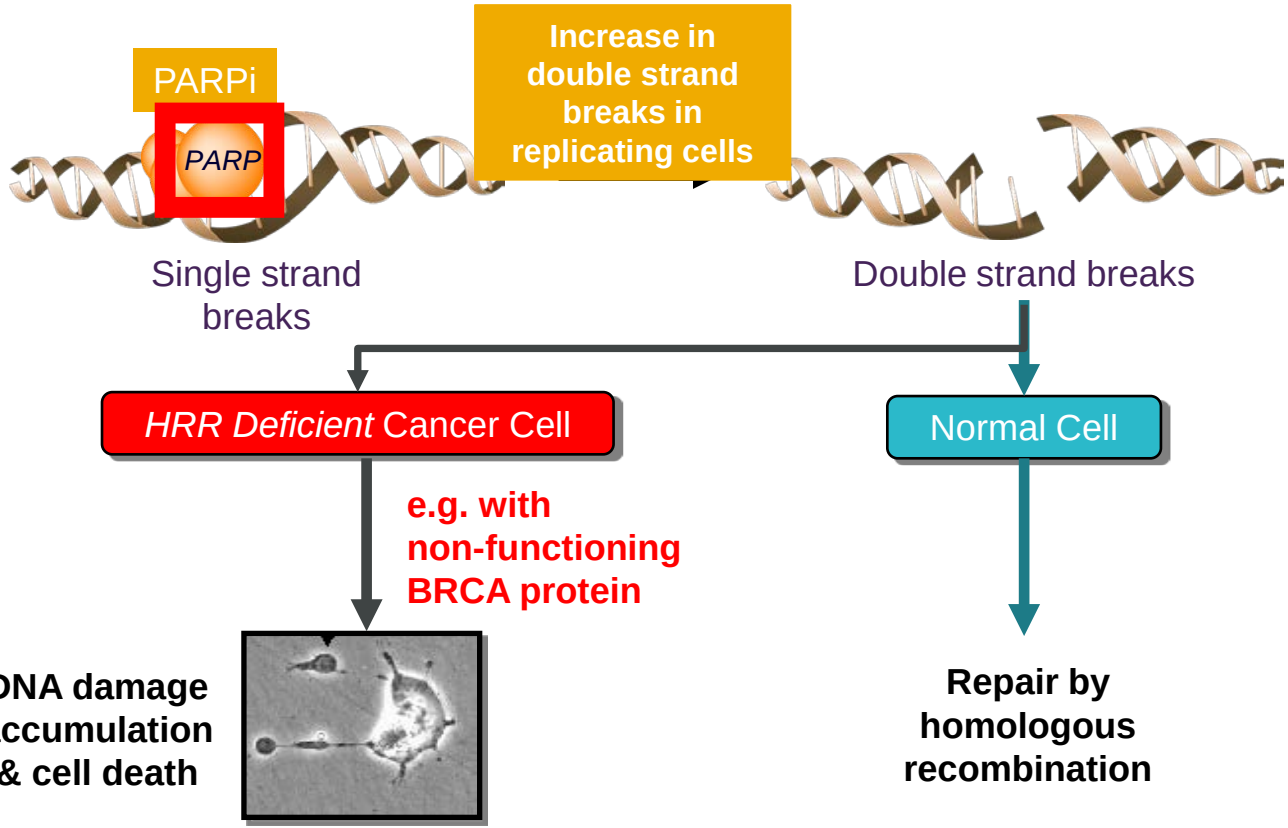
Gray et al., IASLC 18th World Congress on Lung Cancer, Japan, 2017

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

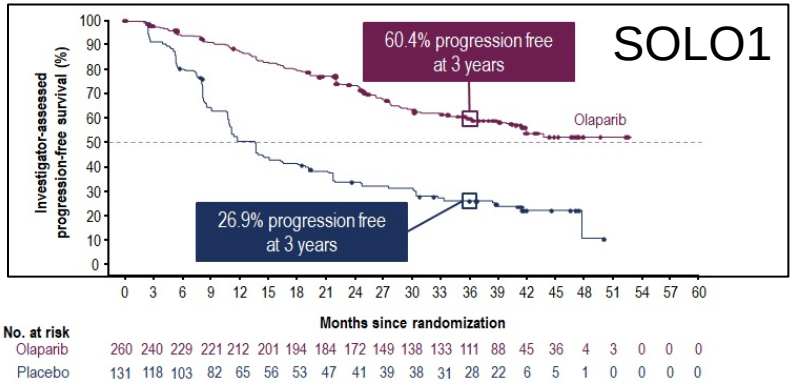
Case Study 2

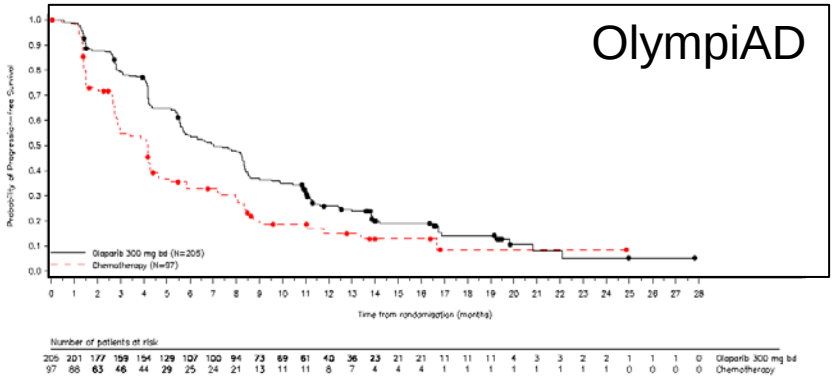
PARP-inhibitor olaparib in patients with homologous recombination repair deficient tumours

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



Significant and clinically meaningful PFS improvement for olaparib in *BRCA1/2*-mutated ovarian (SOLO1) and breast cancer (OlympiAD)





	Olaparib (N=260)	Placebo (N=131)
Events (%) [50.6% maturity]	102 (39.2)	96 (73.3)
Median PFS, months	NR	13.8
	HR 0.30	
	95% CI 0.23, 0.41; *P*<0.0001	

	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**	

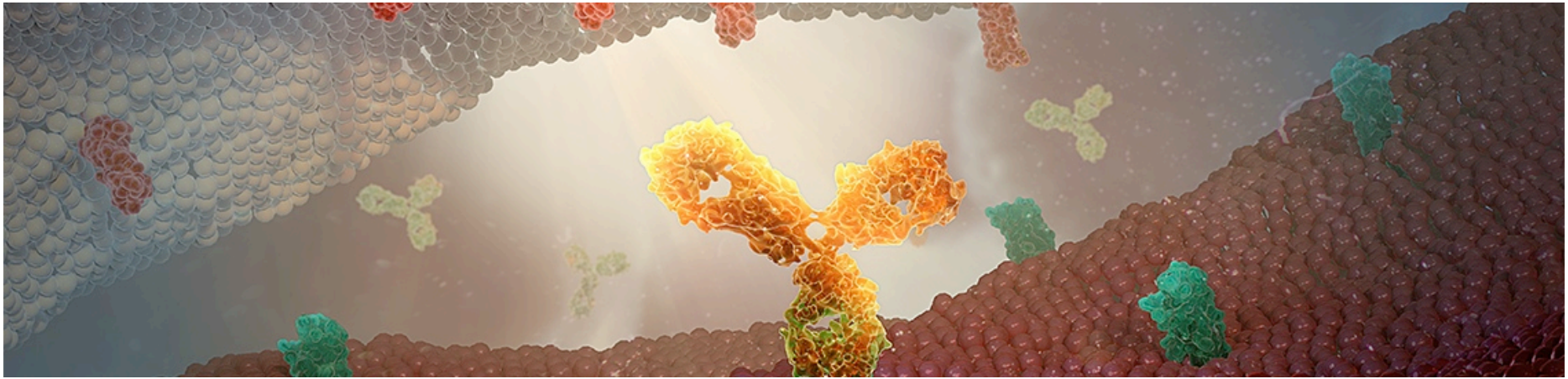
Maturity rate: 234/302=77%

Moore K et.al., Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer N. Engl.J. Med 2018;379 :1-11

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

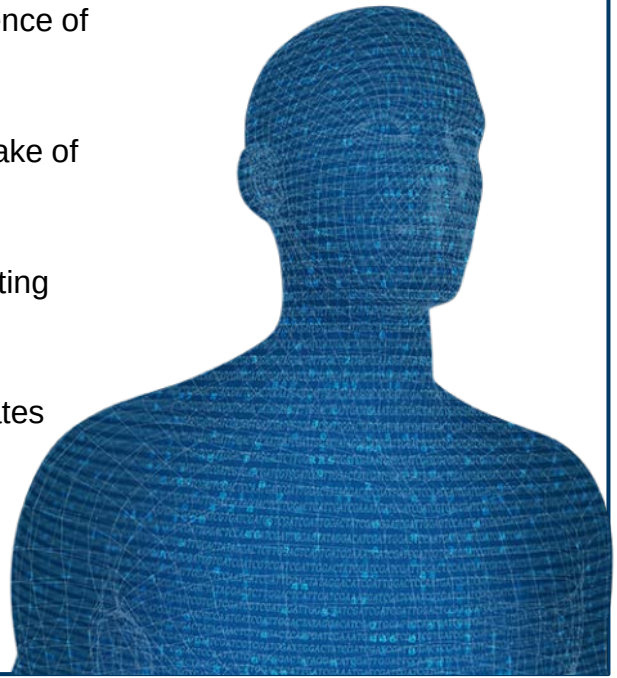
Precision Medicine

How can we further improve?



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



EFPIA/EBE have identified 5 priorities to improve access to Precision Medicines in Europe

- **Policy:** National Policy Prioritisation of Precision Medicine
- **Care Management:** Consolidated / streamlined care management and resources → drive consistency
- **Dx Investment / Funding:** Investment in next-generation testing infrastructure and dedicated funding pathways for diagnostics
- **Data & Quality:** Collect diagnostic testing data and perform EQAs of labs to drive consistent quality
- **Rx Access:** Tackle delays to reimbursement of new treatments by aligning data requirements and HTA methodologies

Slide adapted from CRA report for EFPIA/EBE: “An evidence-based analysis to characterise the benefits of personalised medicines to patients, society and healthcare systems” July 2018

The report also identified a number of key barriers and enablers for Precision Medicine

Barriers

- Insufficient diagnostic **testing capacity** or poor quality labs
- **Delays / restricted reimbursement /** access for novel PM
- **Delays to updating treatment guidelines** with testing recommendations
- **Limited physician awareness** to current research / treatment trends
- **Insufficient funding of testing services**

Enablers

- Development of specific PM plans with **dedicated investments**
- Coordinated management of care (incl **testing infrastructure and expertise**)
- Inclusion of **PM in treatment guidelines**
- **Early access schemes** that favour PM
- Funding and value assessment mechanisms for **Dx as part of HTA**
- Monitoring outcomes through **population-based registries** to facilitate managed entry agreements

Slide adapted from CRA report for EFPIA/EBE: “An evidence-based analysis to characterise the benefits of personalised medicines to patients, society and healthcare systems” July 2018

Precision Medicine: get ready for future innovation

Recent

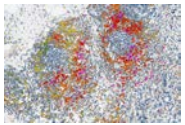
BRCA Companion Diagnostic

Circulating tumour DNA

Single genes

Present

IO Diagnostic Solutions



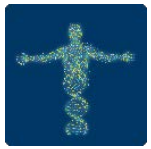
Multigene DNA panels

Point-of-care Diagnostics (PoC)

Multigene panels & PoC

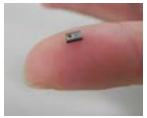
Future

Genomics



Early diagnosis and monitoring

Sensors



Artificial intelligence

PoC Genomics & AI

Confidentiality Notice