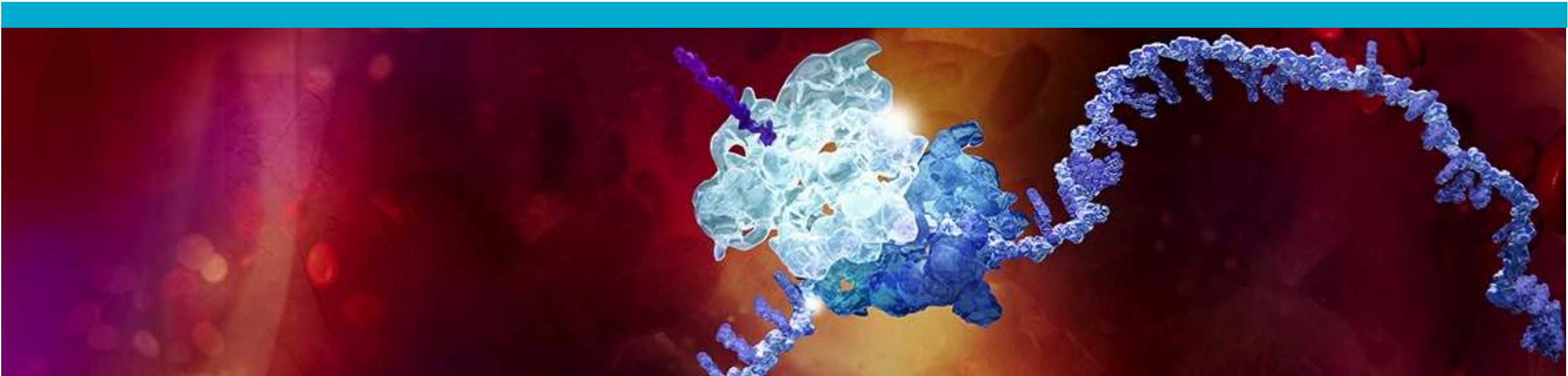


The challenge and excitement of discovering and developing new medicines

Mene Pangalos

CSAR Lecture, Churchill College

January 2016



Outline



Introduction to our industry



Reshaping our pipeline



Following the science



Future of healthcare



Outline



Introduction to our industry



Reshaping our pipeline



Following the science



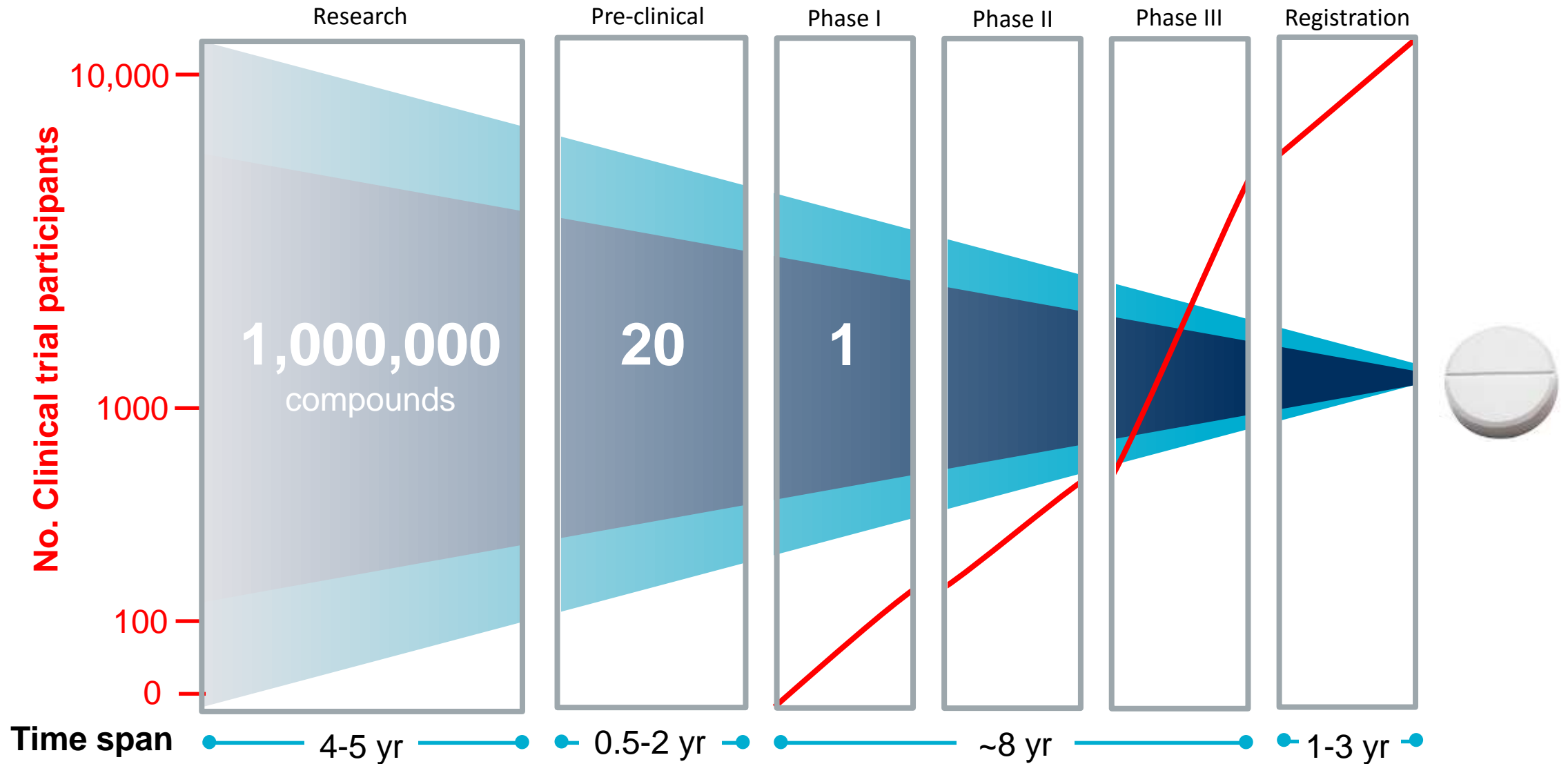
Future of healthcare



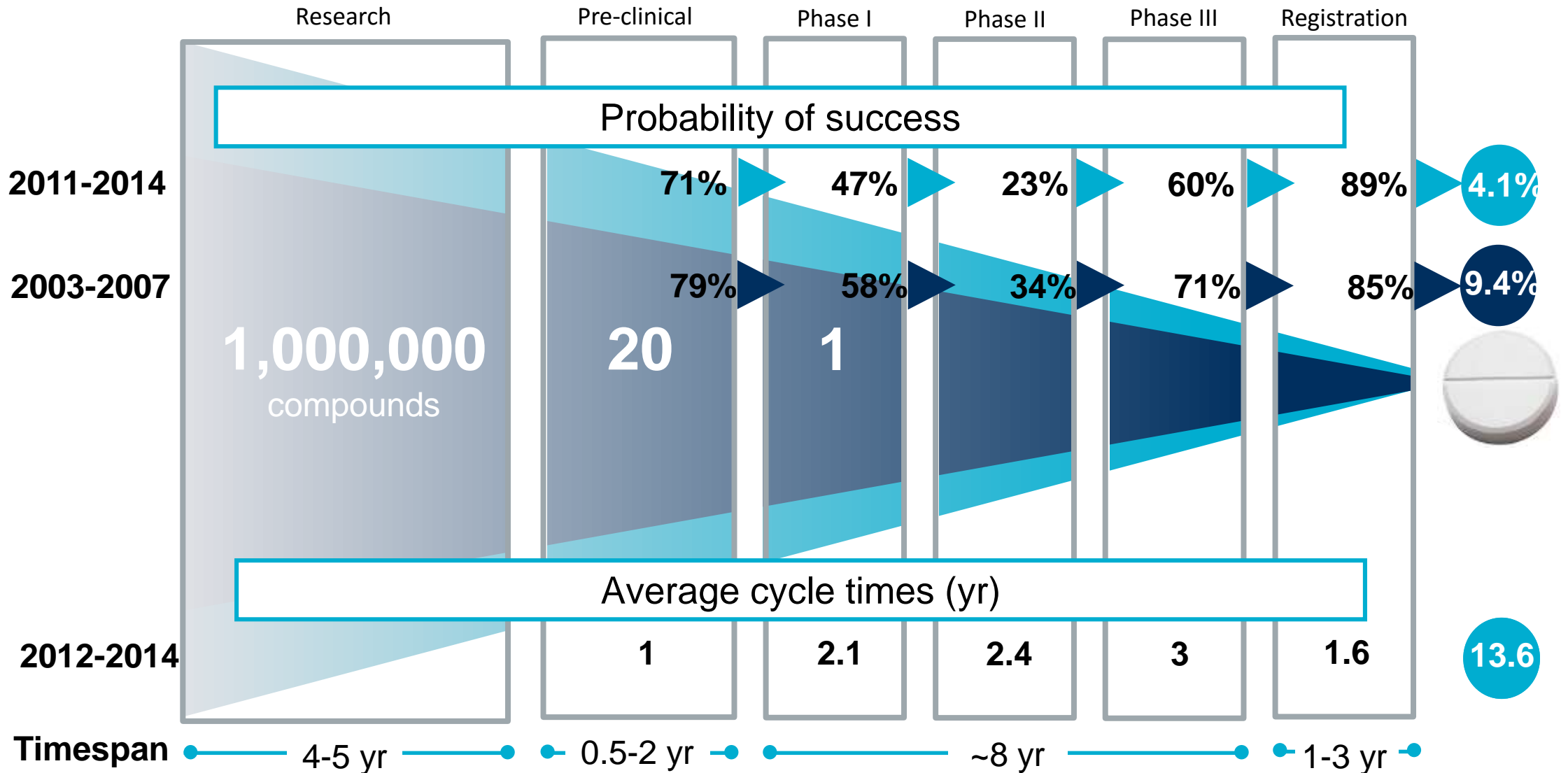
The R&D environment is increasingly challenging



The drug discovery funnel



As an industry we fail more often than we succeed





\$1.8-2.6 bn



Outline



Introduction to our industry



Reshaping our pipeline



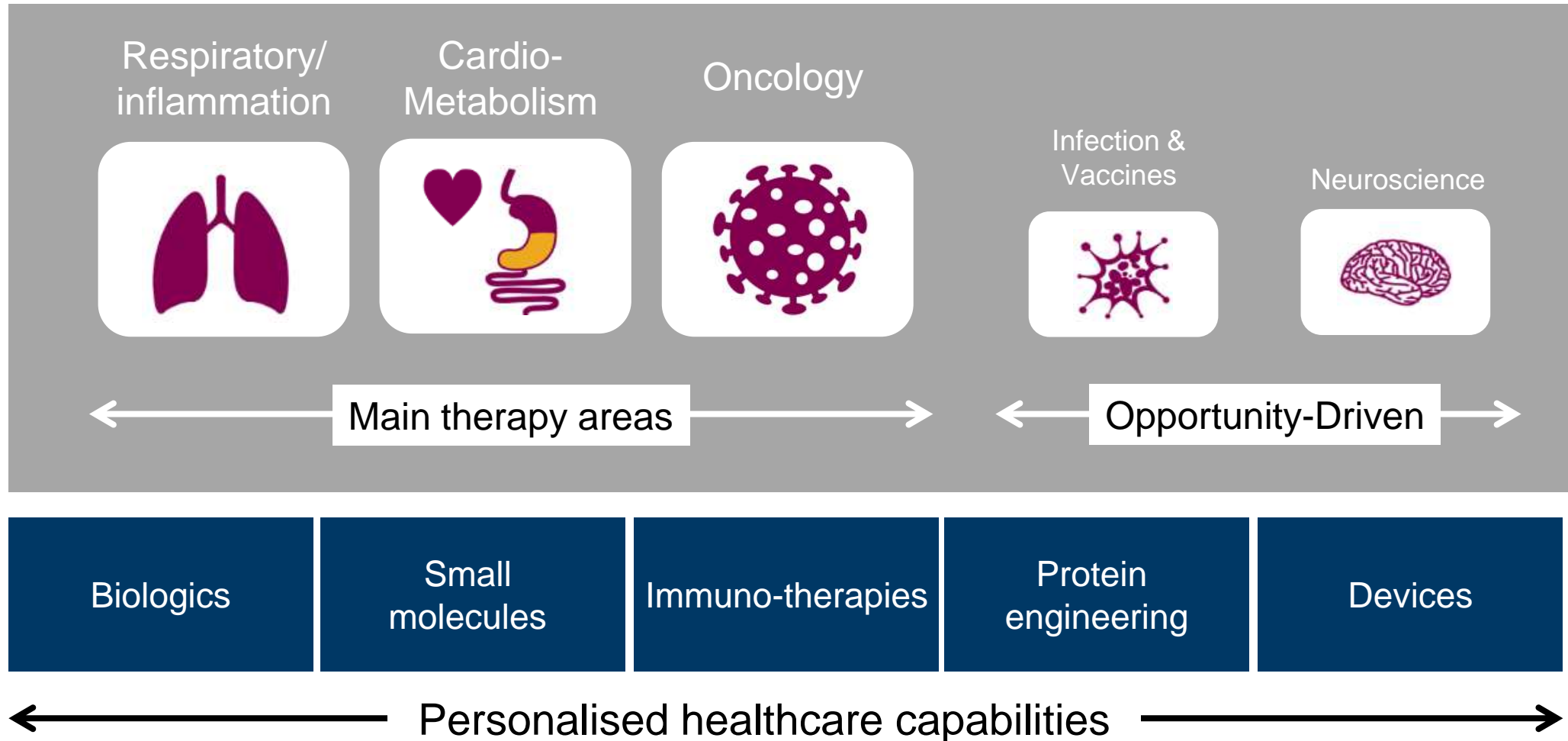
Following the science



Future of healthcare

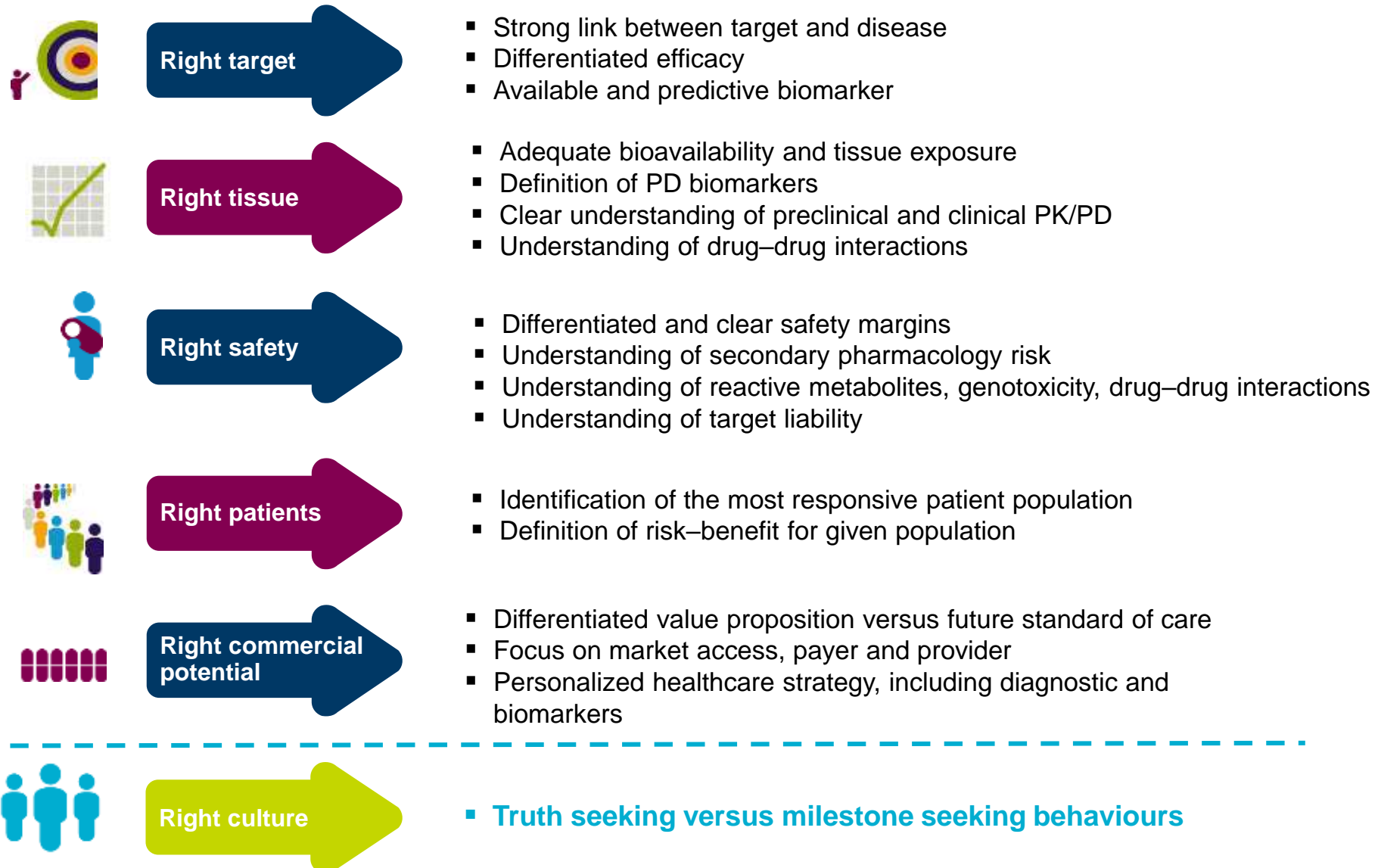


Our focus is on achieving success in three core therapeutic areas





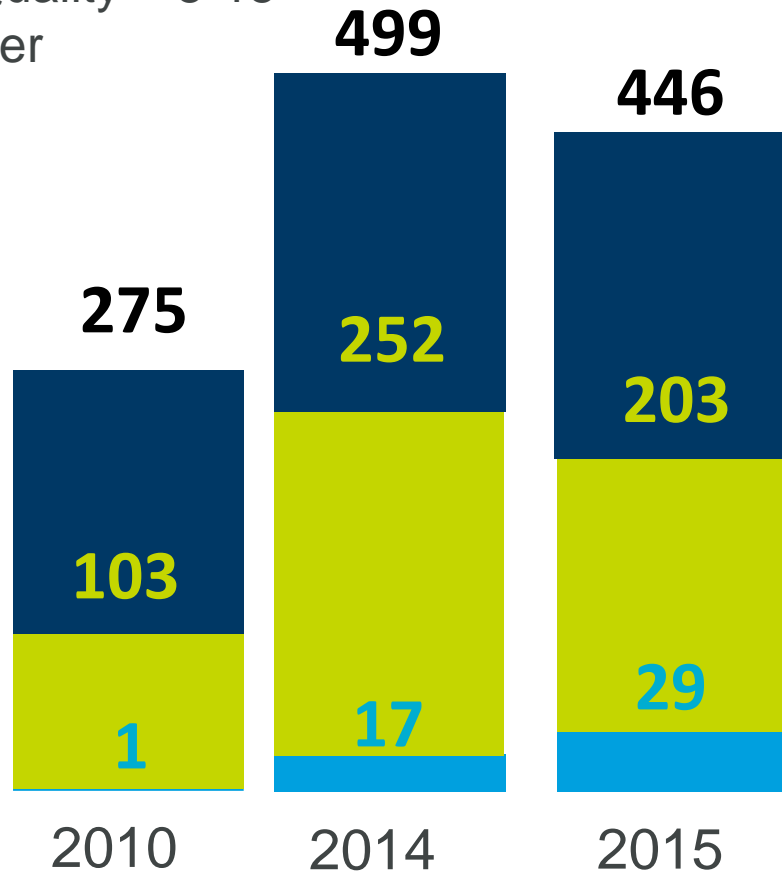
Our 5R framework has helped us drive quality not quantity



We are more committed than ever to basic science and publishing our breakthrough research

- High Impact = >15
- High Quality = 5-15
- All Other

No. of publications



Cancer Cell
Acetyl-CoA Synthetase 2 P Utilization and Maintains C under Metabolic Stress

nature COMMUNICATIONS
Aberrant splicing of U12-type introns is the hallmark of ZRSR2 mutant myelodysplastic syndrome

nature REVIEWS DRUG DISCOVERY
BIOBUSINESS BRIEFS
MARKET WATCH
Therapeutic area 'hea for emerging markets

nature REVIEWS CANCER
MEK1 and MEK2 inhibitors and cancer therapy: the long and winding road

nature REVIEWS DRUG DISCOVERY
OPINION
ESKAPeIng the labyrinth of antibacterial discovery

nature COMMUNICATIONS
Responding to the ch untreatable gonorrh a first-in-class agent mechanism-of-action bacterial Type II top

JOURNAL OF CLINICAL ONCOLOGY
Randomized, Double-Blind Phase II Trial With Classification by ATM Protein Level to Predict and Tolerability of Olaparib Plus Fuzesid in Recurrence of Metastatic Gastric Cancer

Science Advances
Structural basis of Lewis^b antigen *Helicobacter pylori* adhesin BabA

nature REVIEWS DRUG DISCOVERY
An analysis of the attrition of drug candidates from four major pharmaceutical companies

JOURNAL OF CLINICAL ONCOLOGY
Molecular Profiling and Targeted Thoracic Malignancies: A Biomultihistology Phase II Basket Tr

nature
Patient-centric tr development in p

nature medicine
Acquired EGFR C797S mutation mediates resistance to AZD1775 in non-small cell lung cancer harboring EGFR L790M

JNCI Journal of the National Cancer Institute
PI3K Inhibitor: AZD1208 for Treatment of MYC-Driven Prostate Cancer

Molecular Cell
Targeting the DNA damage response in Mark's cancer

Cancer Cell
Feedback Suppression of PI3K α Signaling in PTEN-Mutated Tumors Is Relieved by Selective Inhibition of PI3K β

Molecular Psychiatry
ers to dopamine and serotonin in human brain

Angewandte Chemie International Edition
Stable Synthesis of Piperazines Enabled by Visible-Light Irradiation Aluminum Organometallics

nature
Patient-centric trials for therap development in precision oncol

nature COMMUNICATIONS
Structural and dynamic insights into the energetics of activation loop rearrangement in c-MYC kinase

Science
A sustainable model for antibiotics

nature medicine
c-kit⁺ cells adopt vascular endothelial but not epithelial cell fates during lung maintenance and repair

European Heart Journal
Effect of genetic variations on triglyceride levels and clinical outcomes

AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE
Role of B Cell-Activating Factor in Pulmonary Disease

EUROPEAN JOURNAL OF CELL BIOLOGY
A Randomised Phase 2 Study of AZD2

The NEW ENGLAND JOURNAL OF MEDICINE
AZD9291 in EGFR Inhibitor-Resistant Non-Small-Cell Lung Cancer



...and we have a strong and well balanced pipeline

Phase I

30 New Molecular Entities

Small molecule	Large molecule
AZD1419# TLR9 asthma	MEDI4920 CD40L-Tn3 pSS
AZD7986 DPP1 COPD	MEDI5872# B7RP1 SLE
AZD8999 MABA asthma/COPD	MEDI7836 IL-13 asthma
AZD9977 MCR diabetic kidney disease	MEDI0382 GLP-1/glucagon diabetes/obesity
AZD3759 or AZD9291 BLOOM EGFR NSCLC brain mets	MEDI6012 LCAT ACS
AZD5312# androgen receptor prostate	MEDI8111 Rh-Factor II trauma/bleeding
AZD6738 ATR solid tumours	MEDI0562# hOX40 solid tumours
AZD8186 PI3Kβ solid tumours	MEDI0639# DLL-4 solid tumours
AZD8835 PI3Kα solid tumours	MEDI0680 PD-1 solid tumours
AZD9150# STAT3 haems & solids	MEDI3617# ANG-2 solid tumours
AZD9496 SERD ER+ breast	MEDI-565# CEA BITE GI tumours
ATMAVI# BL/BLI SBI	MEDI6383# Ox40 FP solid tumours
AZD8108 NMDA suicidal ideation	MEDI9447 CD73 solid tumours
	MEDI1814 amyloidβ Alzheimer's
	MEDI3902 Psl/PcrV pseudomonas
	MEDI-550 pandemic influenza virus vaccine
	MEDI8852 influenza A treatment

Phase II

25 New Molecular Entities

Small molecule	Large molecule
AZD7594 Inhaled SGRM asthma	AZD9412# Inhaled β1FN asthma/COPD
abediterol (AZD0548) LABA asthma/COPD	mavrilimumab# GM-CSFR rheumatoid arthritis
AZD7624 Inhaled p38 inhibitor COPD	MEDI2070# IL-23 Crohns
RDEA3170 URAT-1 hyperuricemia/gout	MEDI-551# CD19 neuromyelitis optica
AZD4901ψ PCOS	abrilumab# α4β7 Crohns/ulcerative colitis
AZD1775# Wee-1 ovarian	MEDI9929# TSLP asthma/atopic dermatitis
AZD2014 mTOR 1/2 solid tumours	MEDI-551# CD19 DLBCL
AZD4547 FGFR solid tumours	MEDI-573# IGF metastatic breast cancer
AZD5363# AKT breast cancer	susatoxumab (MEDI4893) staph alpha toxin SSI
savolitinib# MET pRCC	MEDI7510 sF+GLA-SE RSV prevention
AZD3241 MPO Multiple System Atrophy	MEDI8897# RSV passive prophylaxis
AZD3293#* BACE Alzheimer's	
AZD5847 oxazolidinone TB	
CXL# BLI/cephalosporin MRSA	

Phase III

10 New Molecular Entities

Small molecule	Large molecule
PT010 LABA/LAMA/ICS COPD	anifrolumab# TULIP IFNαR SLE
roxadustat# HIFPH anaemia CKD/ESRD	benralizumab# IL-5R severe asthma
selumetinib# SELECT-1 MEK 2L KRAS+ NSCLC	brodalumab# IL-17R psoriasis
	tralokinumab IL-13 severe asthma
	durvalumab# ATLANTIC† PD-L1 3L NSCLC
	moxetumomab# CD22 HCL
	tremelimumab DETERMINE† CTLA-4 mesothelioma

Applications Under Review

5 New Molecular Entities

Small molecule	Large molecule
PT003 PINNACLE LABA/LAMA COPD	
lesinurad URAT-1 gout	
AZD9291 AURA, AURA 2 EGFR T790M NSCLC >2L	
cediranib ICON 6 VEGF PSR ovarian	
CAZ AVI# BLI/cephalosporin SBI/cIAI/cUTI	

■ RIA
 ■ CVMD
 ■ Oncology
 ■ Infection, Neuroscience, Gastrointestinal

¹ Includes significant fixed dose combination projects, and parallel indications that are in a separate therapeutic area (See LCM chart for other parallel indications and oncology combination projects)

Partnered; *Partnered with Lilly; † Registrational P2/3 study. Selumetinib (AZD6244, ARRY-142886)



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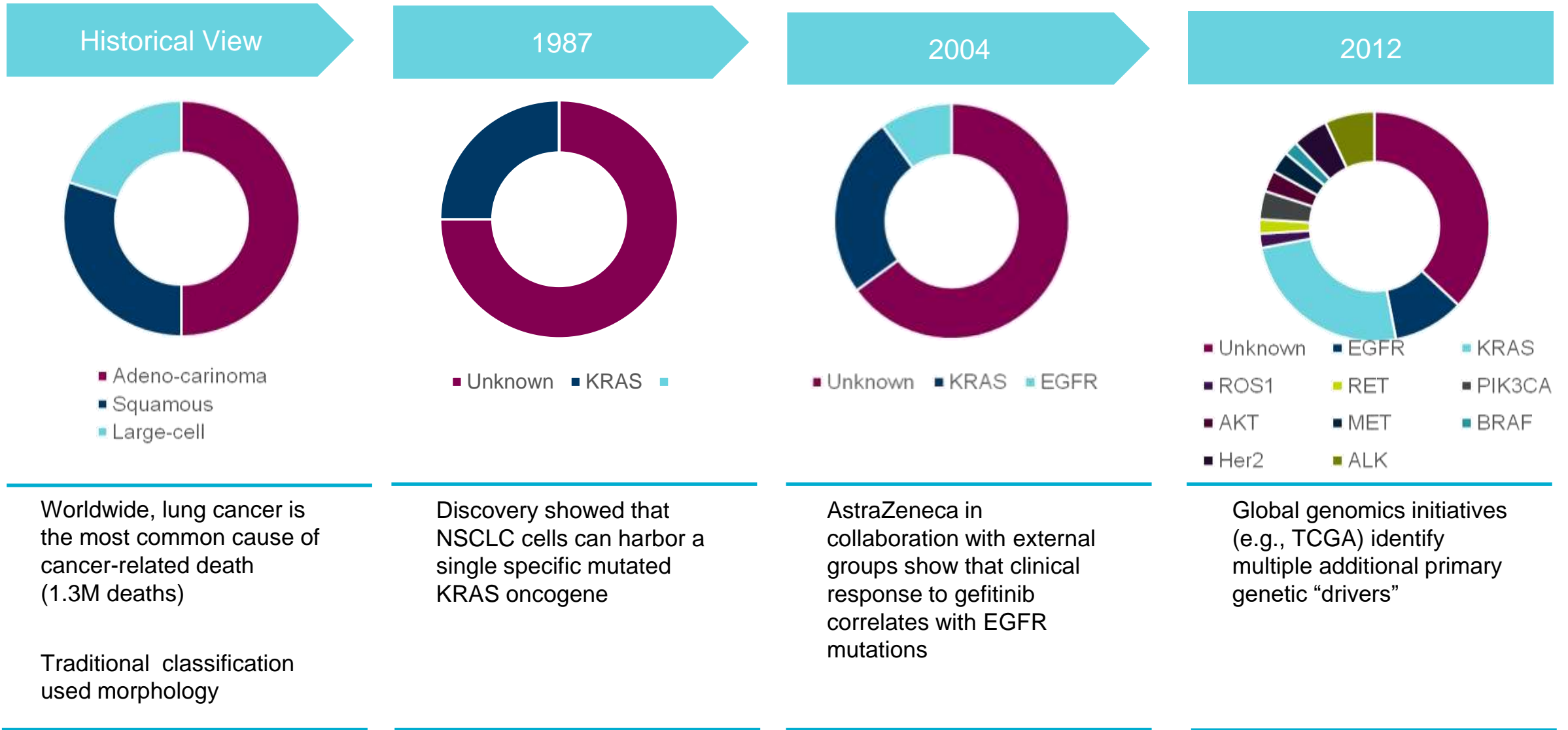
Future of healthcare



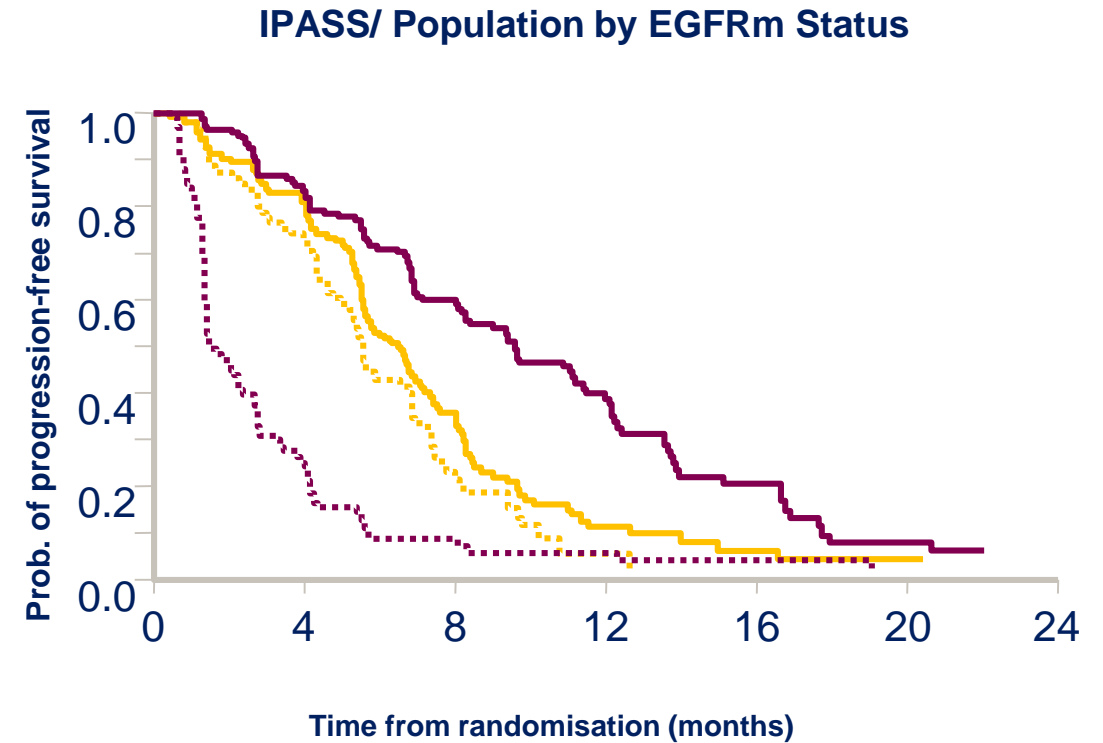
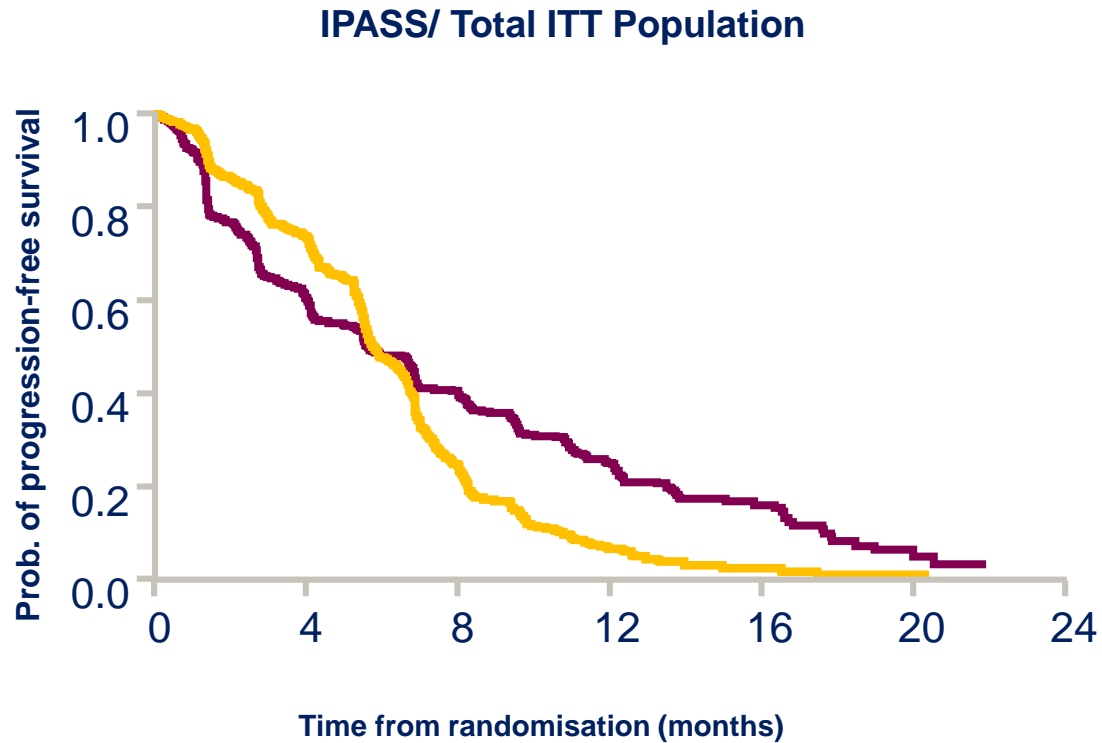
Case study 1

Osimertinib for non-small cell lung cancer

The evolution of genomics in lung cancer diagnosis



The first EGFR inhibitors highlighted the importance of identifying the right patient

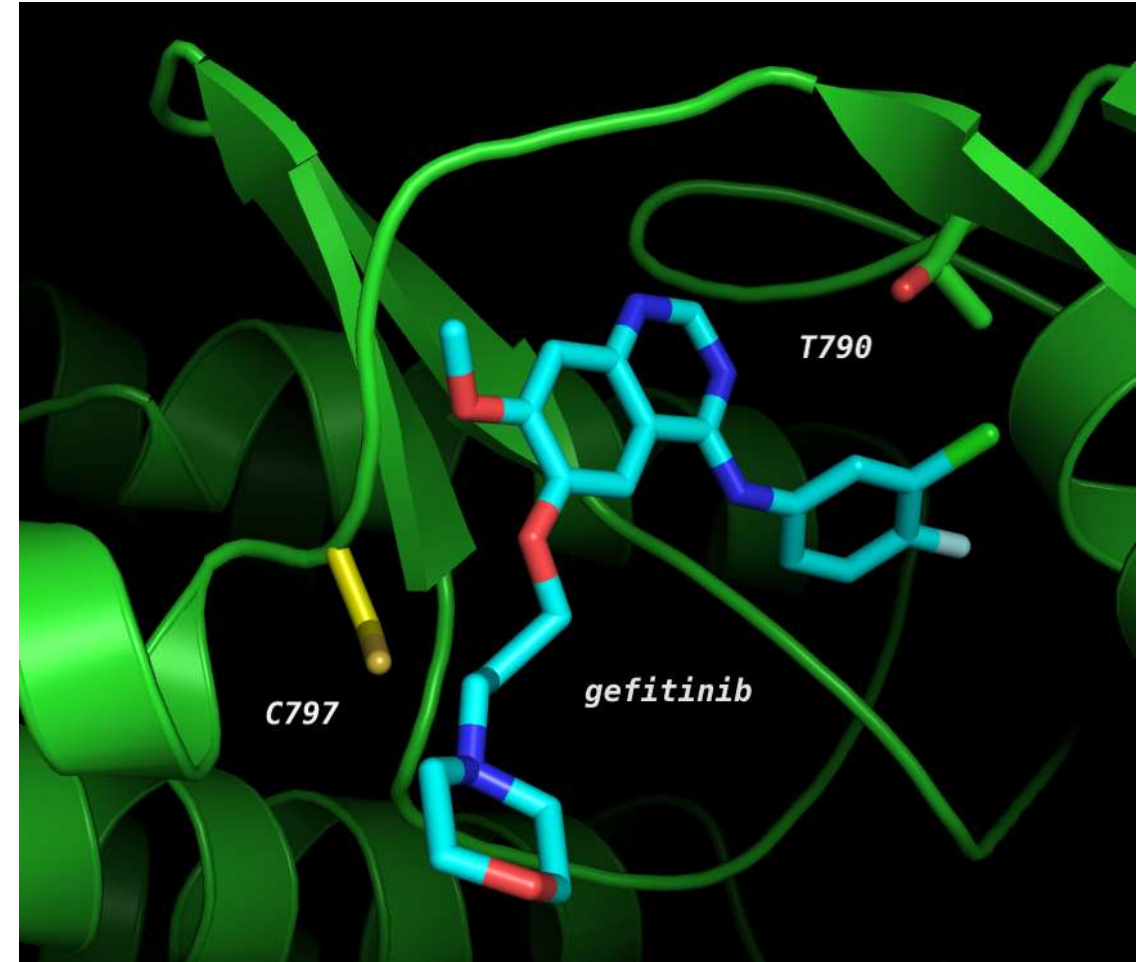


— Gefitinib EGFR M+ ··· Gefitinib EGFR M- — C/P M+ ··· C/P M-



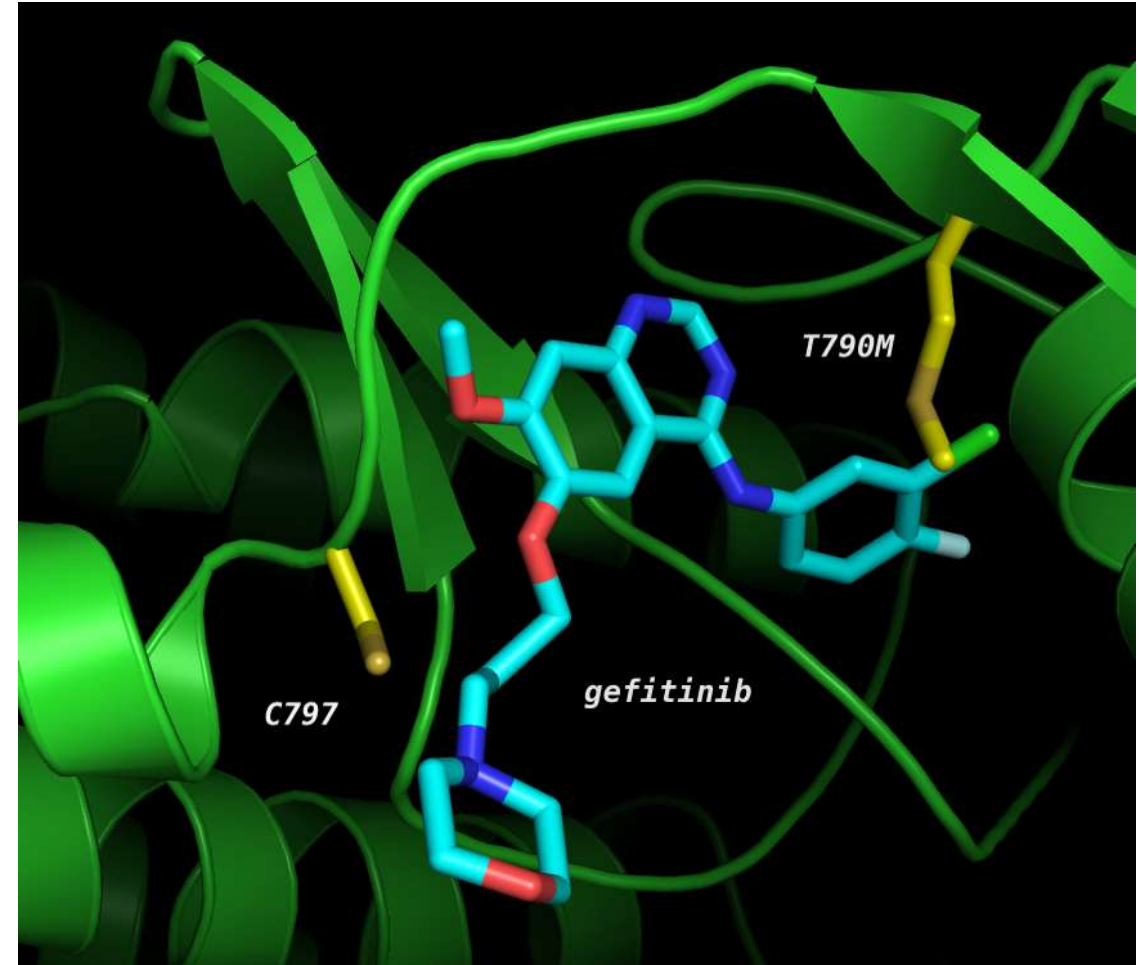
Structure-based design underpins the accelerated progress of osimertinib

- Mutations in EGFR leads to an oncogenic phenotype & acquired resistance
- Drugs like gefitinib & Tarceva® face resistance with new mutations in EGFR
- 66% of acquired resistance due to T790M in exon 20 of EGFR (gatekeeper mutation)
- Osimertinib designed to target T790M



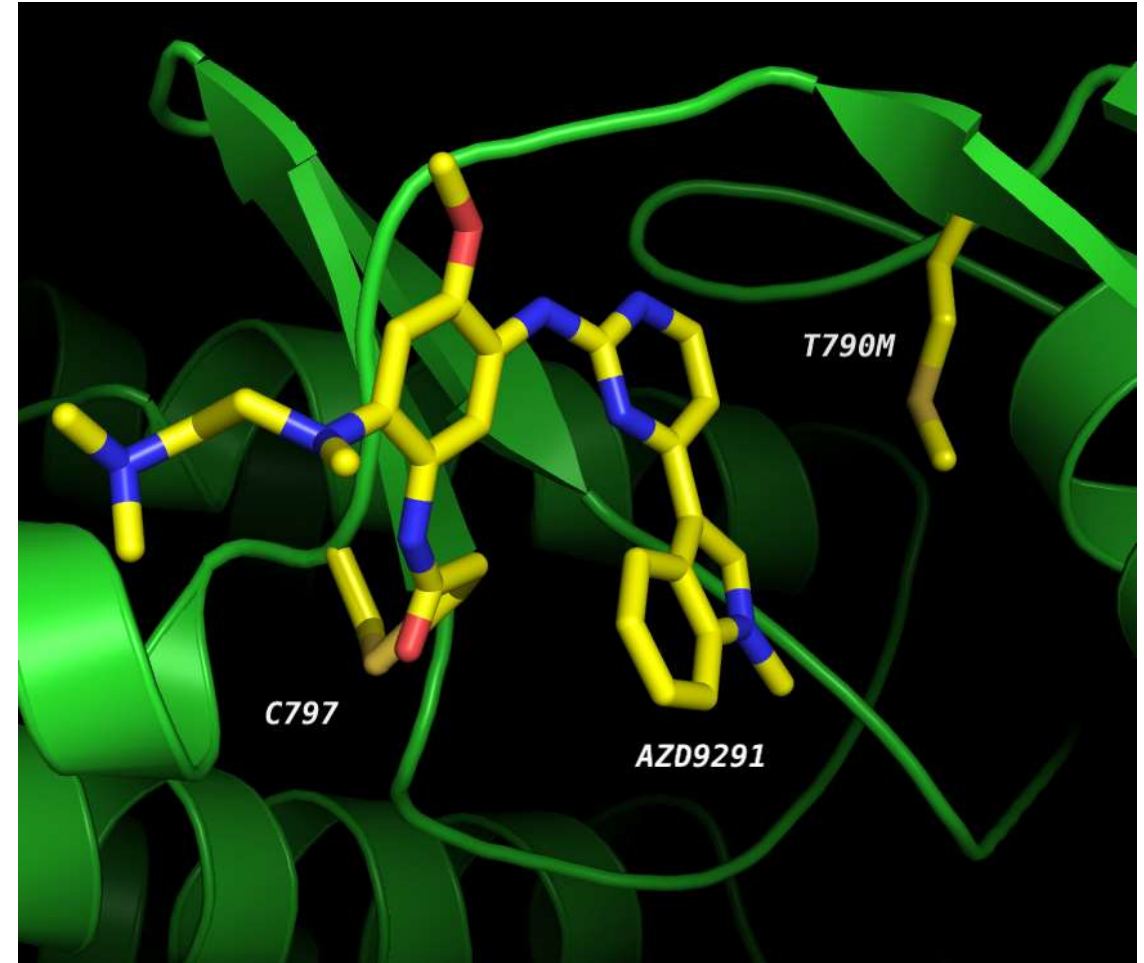
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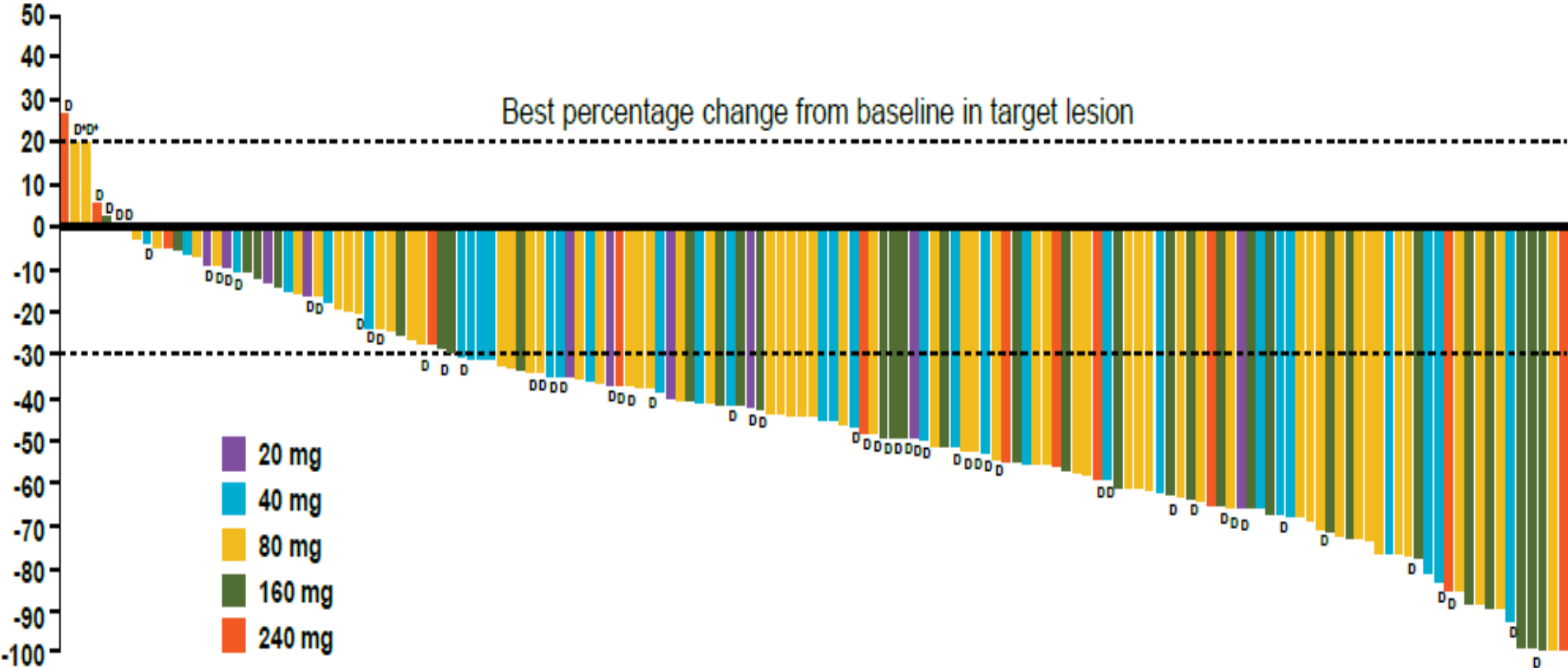
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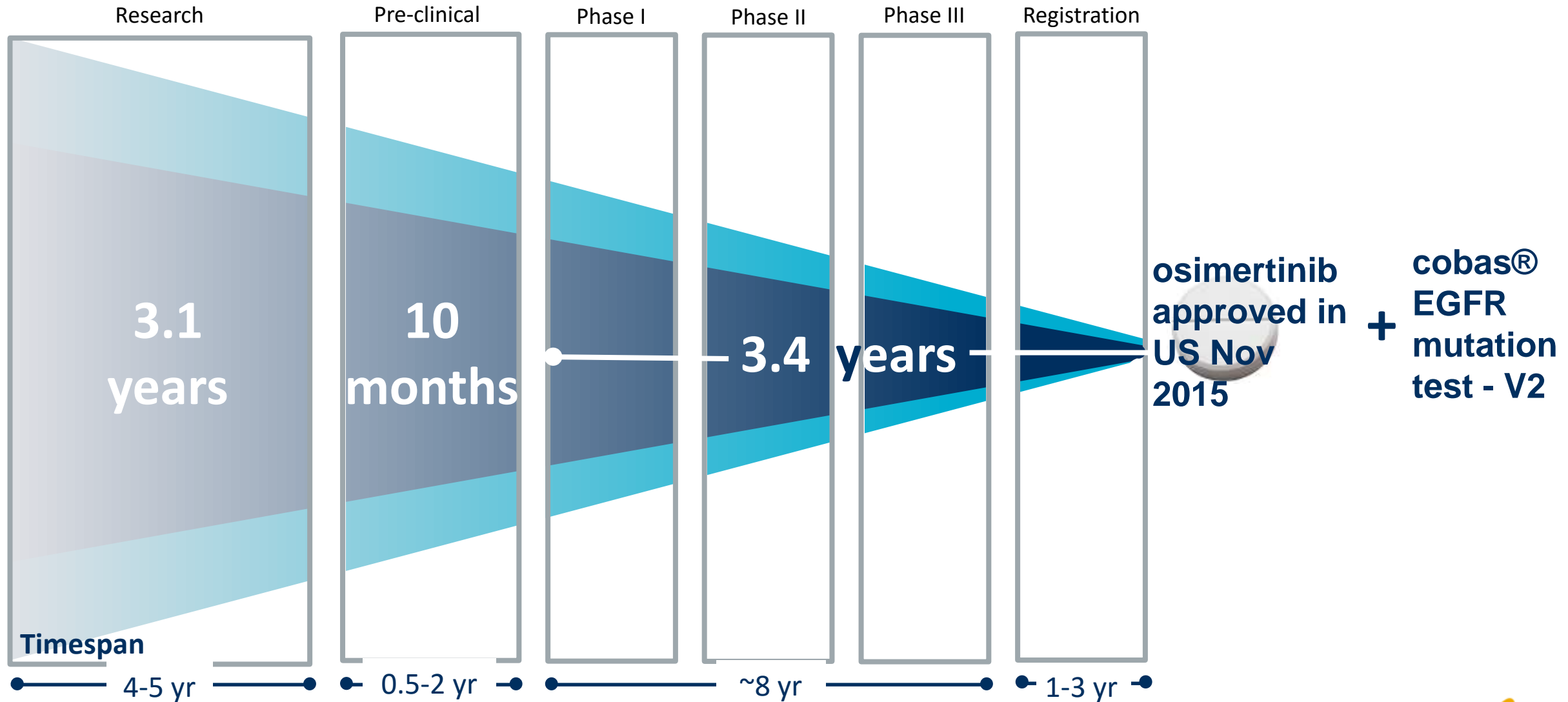


Osimertinib: Overall response rate* 64% in T790M+

Longest response > 9 months and ongoing



Ground-breaking timelines from discovery to approval together with the world's first plasma and tissue diagnostic approved



We continue to understand resistant mechanisms to osimertinib to prolong patient benefit

- MET amplification (10–15% patients)
- MEK/ERK pathway switching
- Combination with immune-oncology molecules
- Treating EGFRM+ NSCLC with brain metastasis
- C797S EGFR (~40% patients)
Nature Medicine, Thress et al, 2015

Early responses with savolitinib (MET inhibitor) / osimertinib combo in NSCLC



Pre-treatment



4 weeks

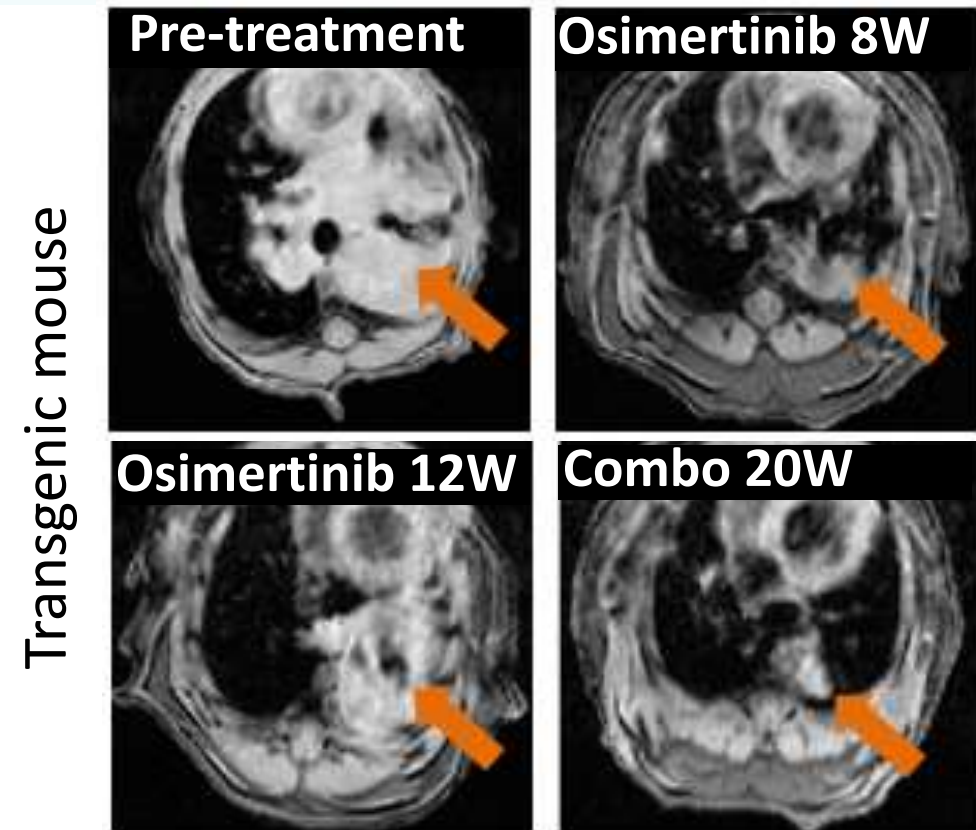
**32-yr female showing neck metastasis
with high MET-amplification**



We continue to understand resistant mechanisms to osimertinib to prolong patient benefit

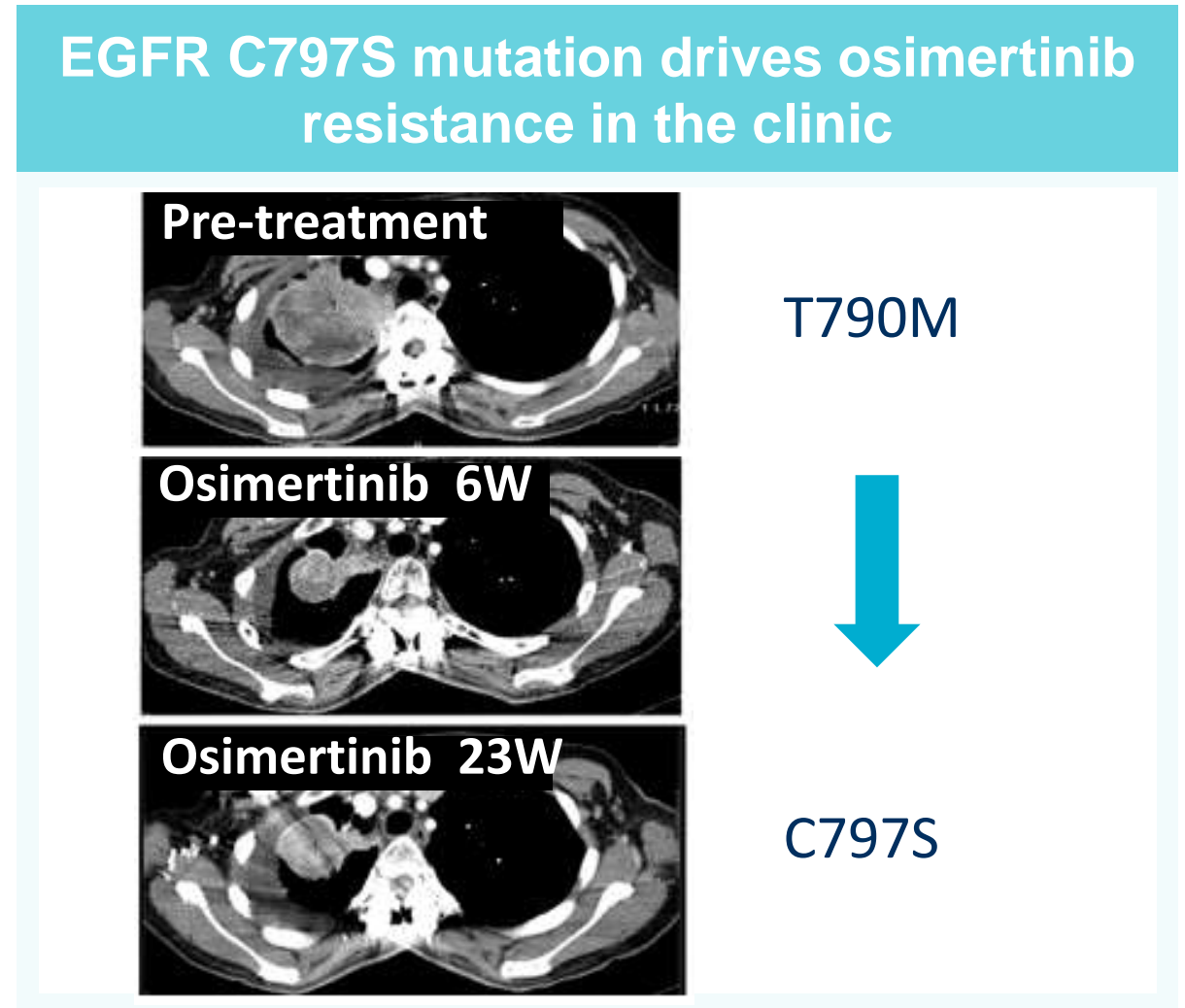
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Nature Medicine, Thress et al, 2015

Osimertinib/ selumetinib combo restores tumour regression in EGFR T790M



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Nature Medicine, Thress et al, 2015



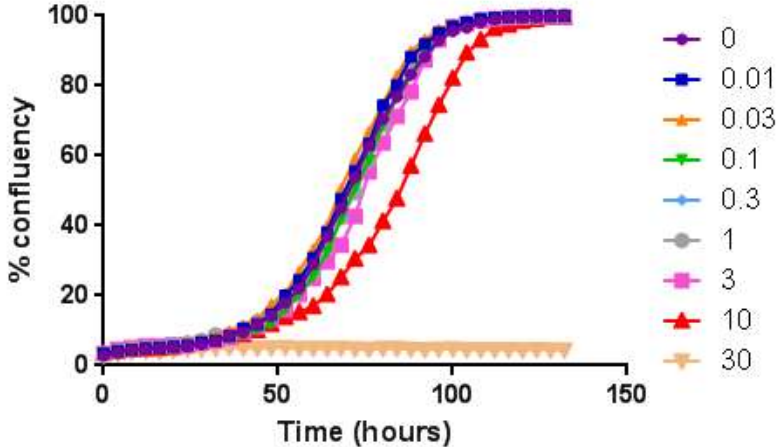
Generation of an EGFR C797S cellular model through gene editing to identify next generation inhibitors

T790M

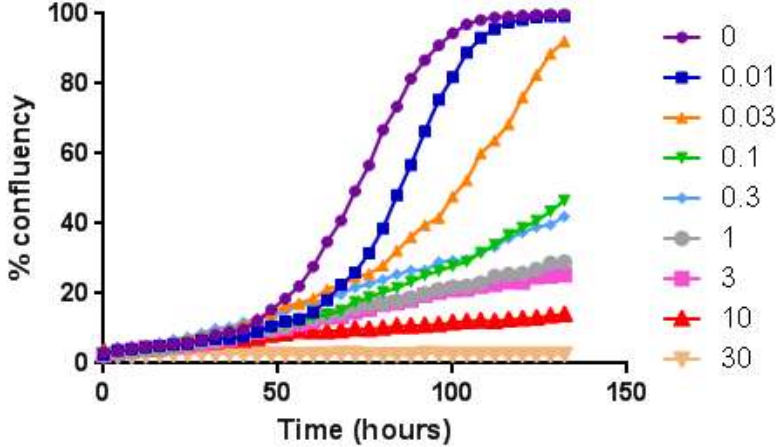


C797S

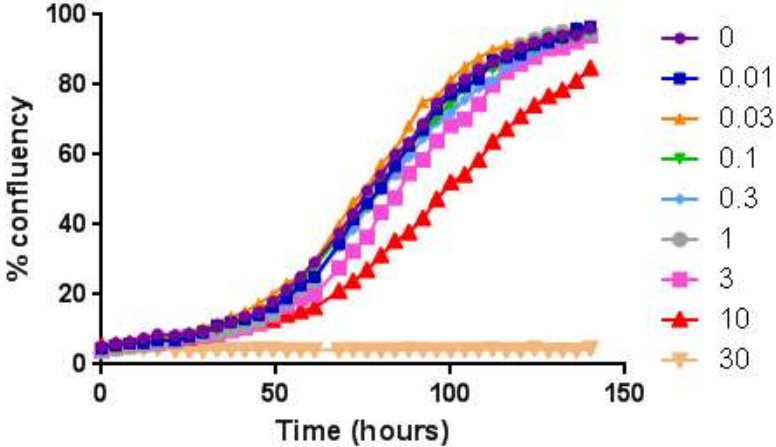
gefitinib resistant



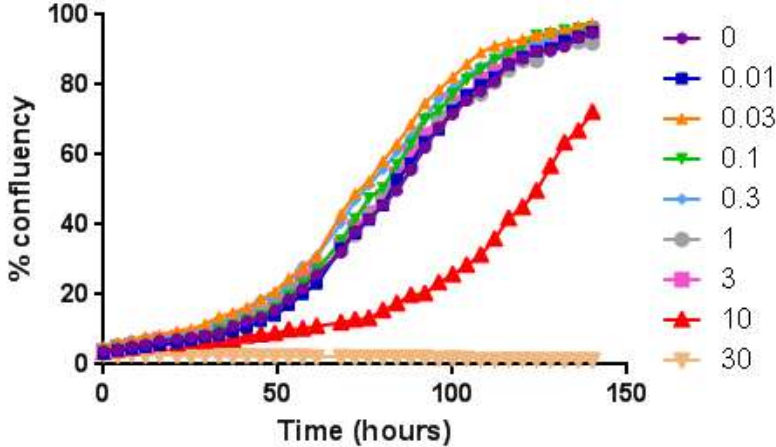
osimertinib sensitive



gefitinib resistant



osimertinib sensitive



Case study 2

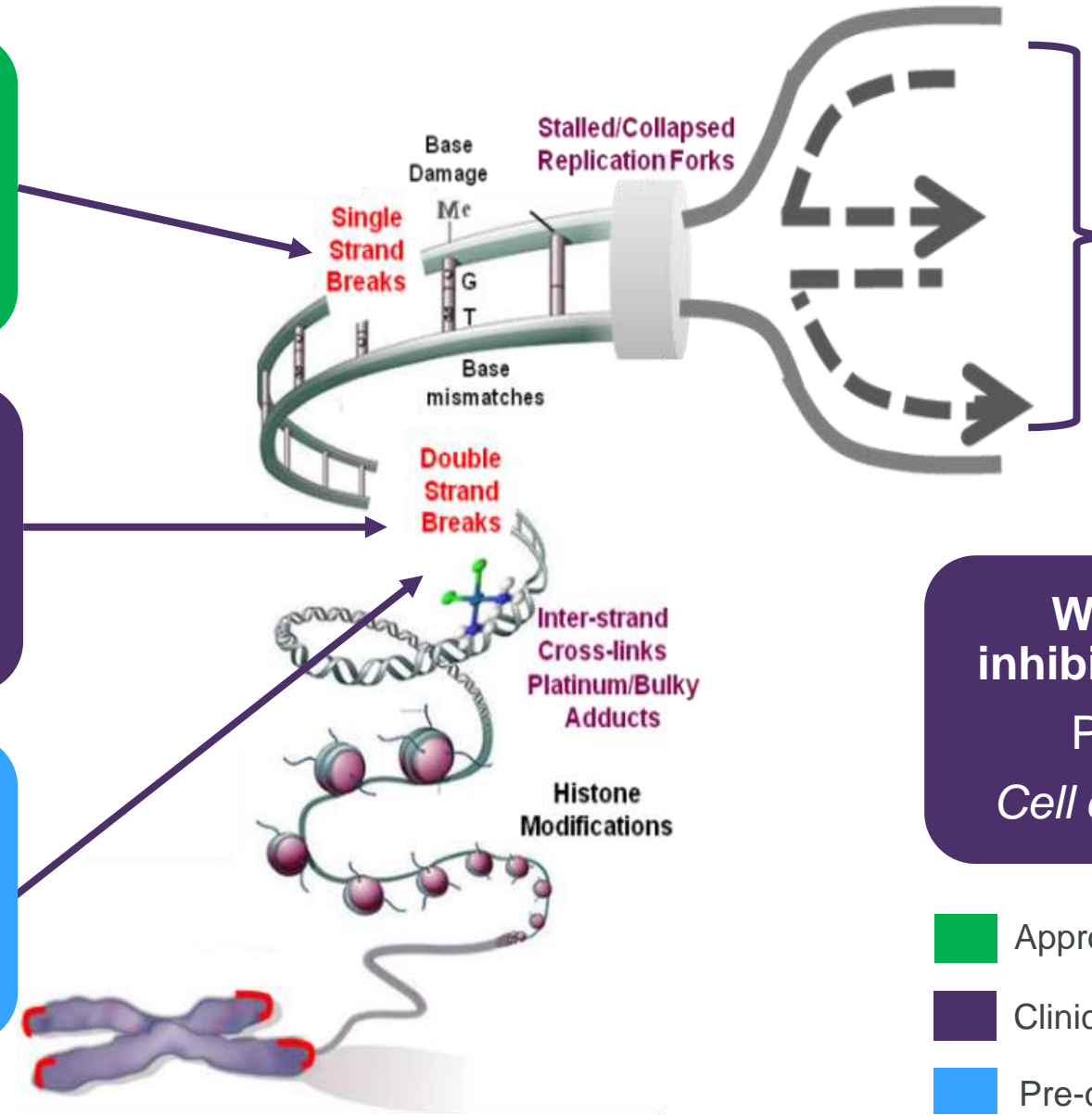
DNA damage response therapies

Our DNA damage response (DDR) portfolio is world leading

PARP inhibitor (olaparib)
Approved
Single strand DNA break repair

ATM kinase inhibitor (AZD0156)
Phase I
Double strand DNA break repair

DNA-PK
Lead optimisation
Double strand end joining



ATR kinase (AZD6738)
Phase I
DNA replication & double strand break repair

Wee1 kinase inhibitor (AZD1775)
Phase I & II
Cell cycle regulator

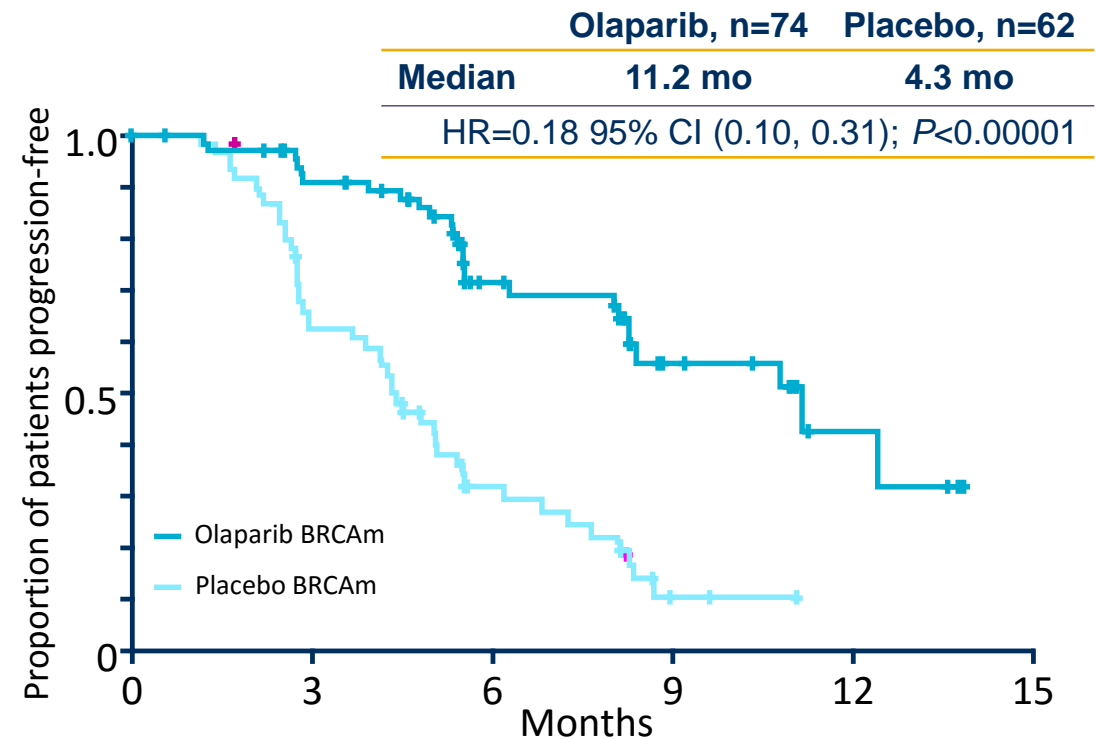
- Approved
- Clinical
- Pre-clinical (Lead optimisation)



Olaparib is a first-in-class PARP inhibitor for BRCAm ovarian cancer

- Exploits tumours with defective DNA repair mechanism
- Initial research by Professor Steve Jackson at University of Cambridge
- Discovered and developed by KuDOS and AZ scientists
- Approved in US and EU Q4 2014

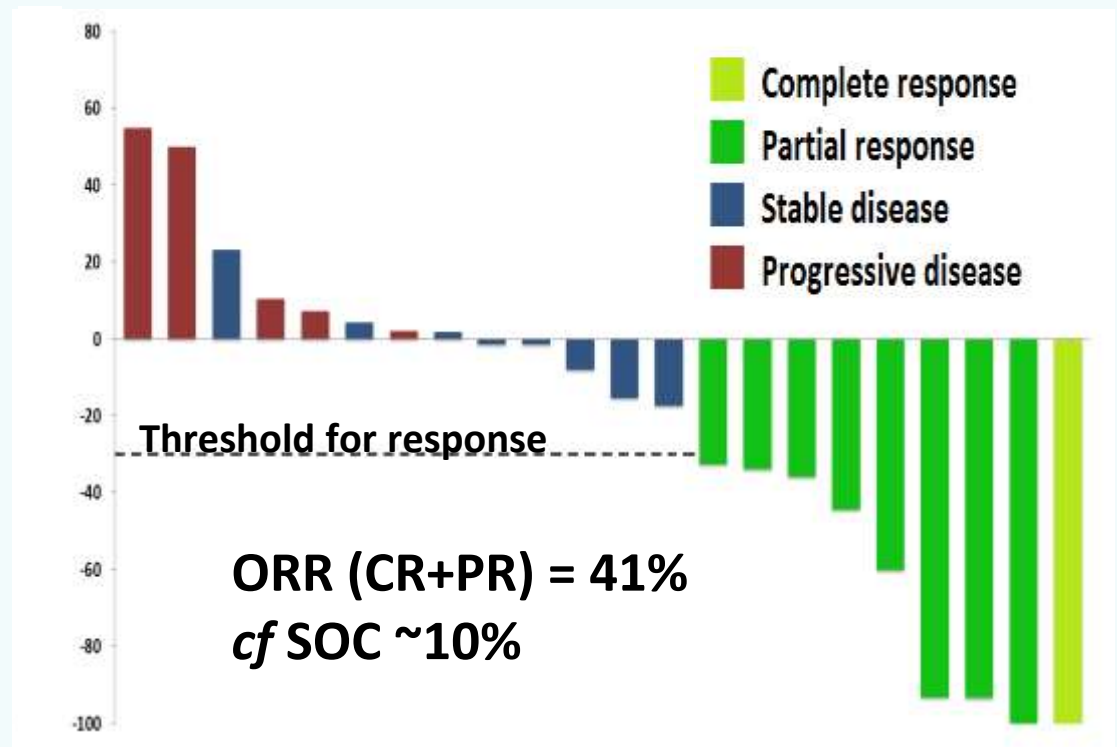
Clinical benefit in BRCAm ovarian cancer



AZD1775 (Wee1) expands therapeutic opportunity beyond chemo combination for multiple untreatable cancers

- Wee1 inhibition drives cell to catastrophic cell death
- Ph2 efficacy in platinum resistant ovarian cancer
- Emerging data
 - Potential in breast, ovarian and lung cancer
 - Combination with olaparib or olaparib failures
 - Combination with IO molecules

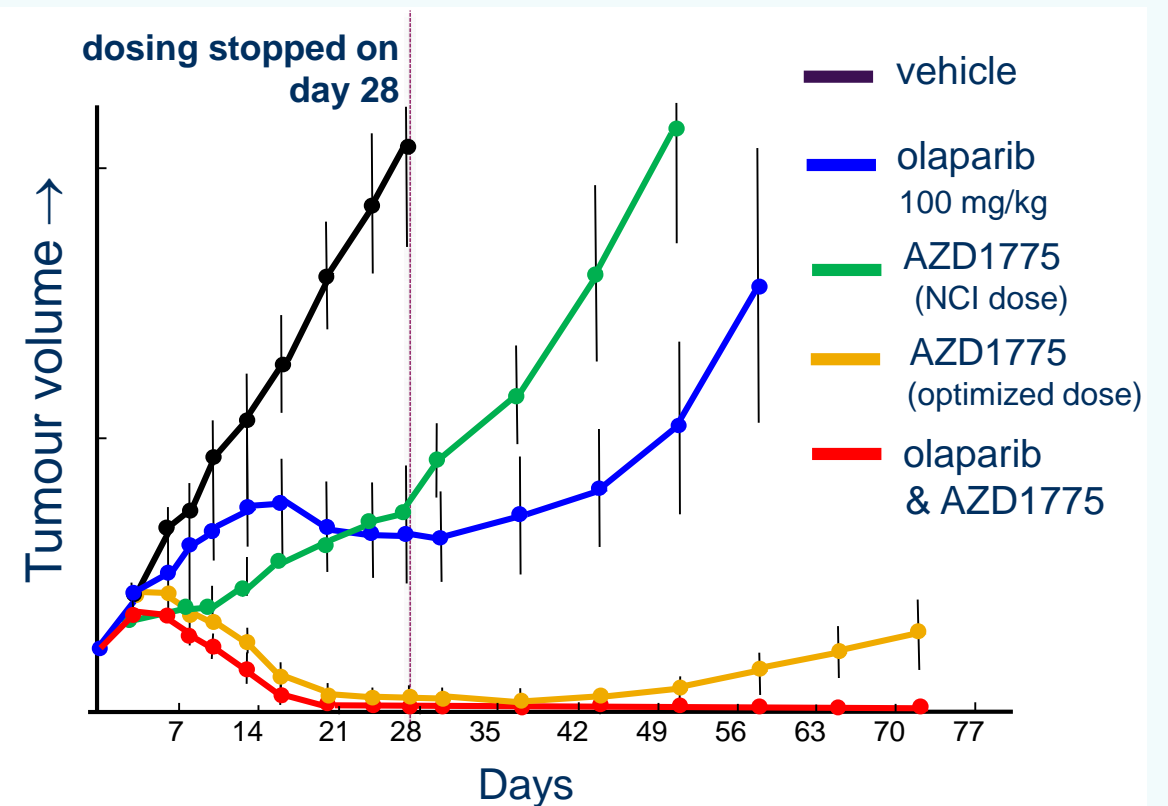
AZD1775 improves on SOC for platinum resistance ovarian cancer



AZD1775 (Wee1) expands therapeutic opportunity beyond chemo combination for multiple untreatable cancers

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 - Combination with IO molecules

AZD1775 combined with olaparib has superior efficacy in a variety of models

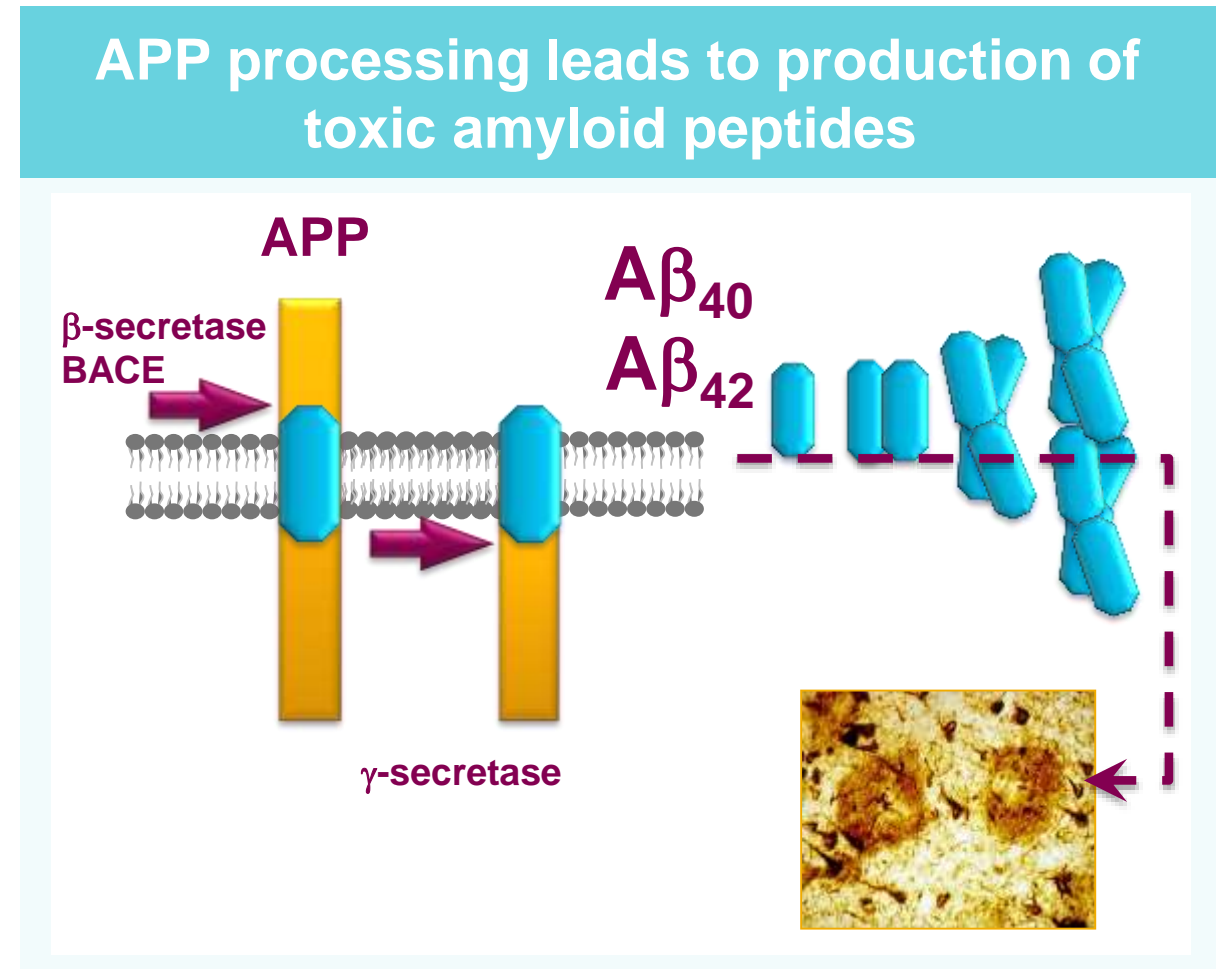


Case study 3

AZD3293 for Alzheimer's disease

β -secretase (BACE1) is a key processing enzyme of amyloid precursor protein

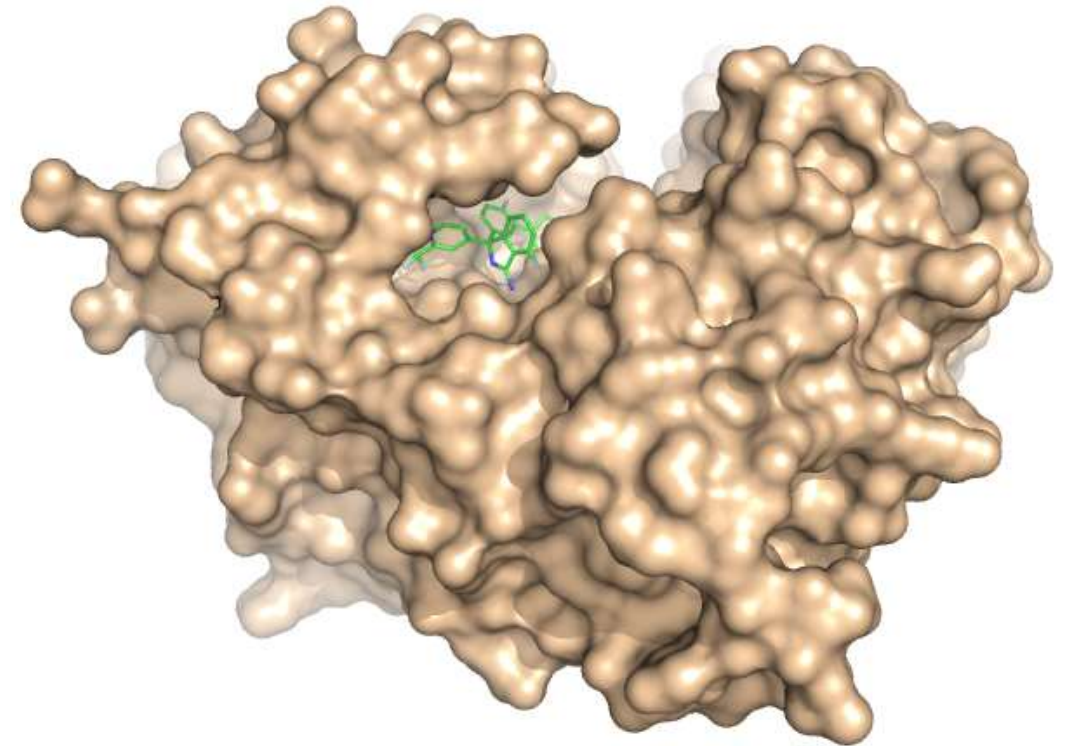
- Mutations in APP and PS linked directly to familial AD
- Mutation in APP that reduces BACE activity protects from AD
- Mutations in APP result in increased BACE activity and A β production
- BACE1 inhibition to reduce A β production and reduce disease progression
- Targeting BACE1 has its challenges
 - Large binding pocket
 - Compound must cross BBB
 - Previous failed compounds due to QT effects



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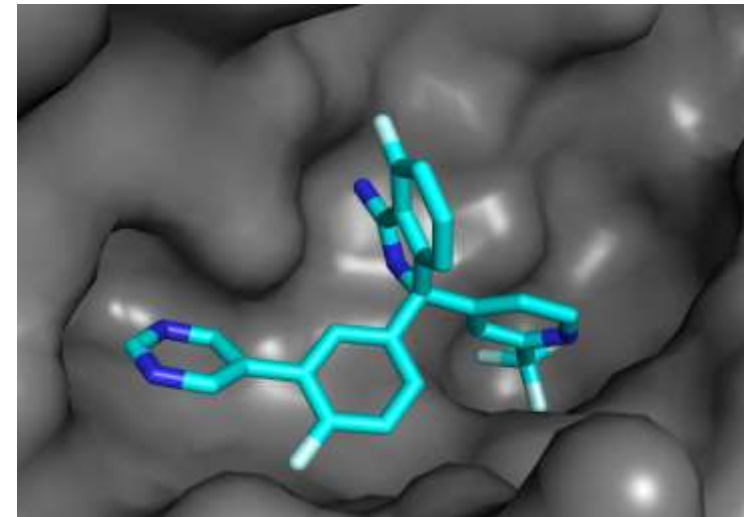
Crystal Structure of AZD3839 (yellow) in complex with BACE1 (grey)



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Crystal Structure of compounds bound to the catalytic site of BACE1



PDB:4AZY Ref: Swahn et.al, (2012) J.Med.Chem.55: 9346

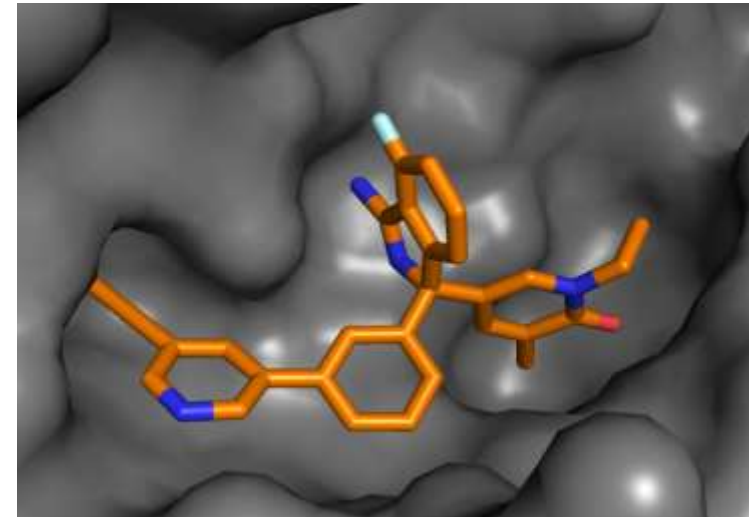
IC50-BACE (nM)	IC50 hERG (μ M)	Margin
125	7.9	63x



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Crystal Structure of compounds bound to the catalytic site of BACE1



PDB:4B00 Ref: Swahn et.al, (2012) *J.Med.Chem.* 55: 9346

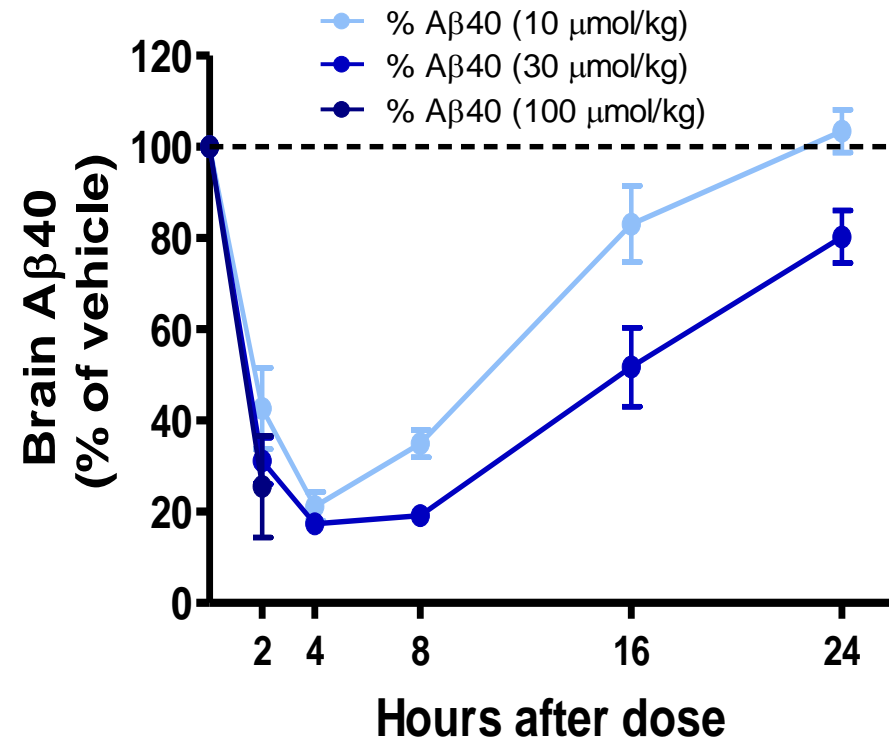
IC50-BACE (nM)	IC50 hERG (μ M)	Margin
2.4	2.8	1167x



β -secretase (BACE1) is a key processing enzyme of amyloid precursor protein

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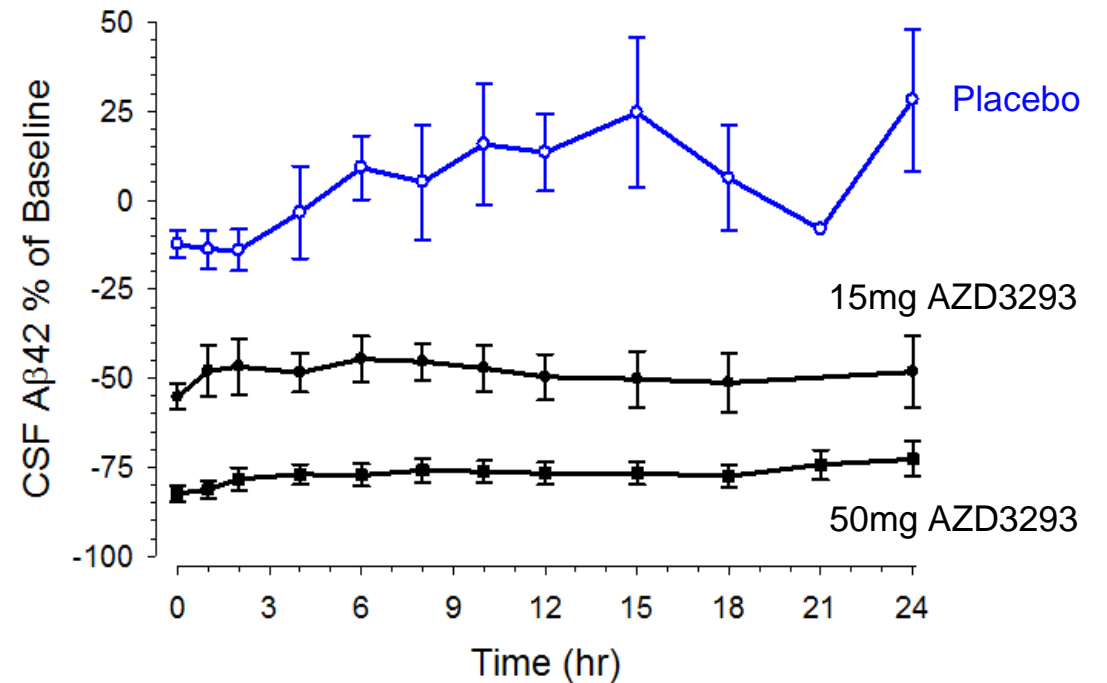
Time and dose dependent inhibition of amyloid generation in guinea pig brain



β -secretase (BACE1) is a key processing enzyme of amyloid precursor protein

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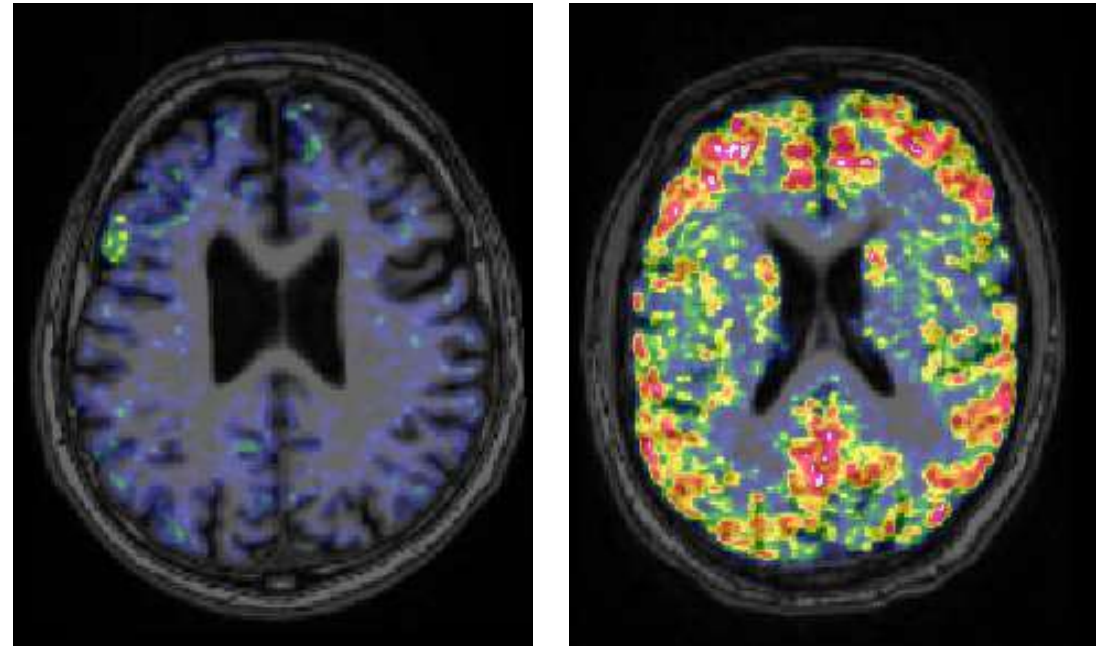
Reduction of A β in CSF in Healthy Volunteers – continuous sampling



No single cognitive test to diagnose prodromal Alzheimer's Disease

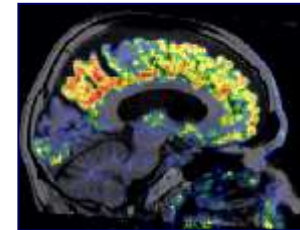
- Routes for patient selection criteria:
 - PET imaging
 - CSF biomarkers
 - ApoE genotype
 - Volumetric MRI
 - Family history

PET radioligand visualise amyloid plaques in Alzheimer's disease brains



Agreement with Lilly to jointly develop AZD3293

- Combining AZ science with Lilly experience in late stage AD development
- Future development costs and revenues to be shared equally
- Phase II/III clinical trial in patients with early Alzheimer's disease
- Lilly will lead clinical development, working alongside researchers from AZ Neuroscience iMed



Outline



Introduction to our industry



Reshaping our pipeline



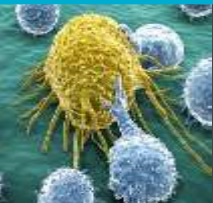
Following the science



Future of healthcare



Great science is redefining the future of healthcare



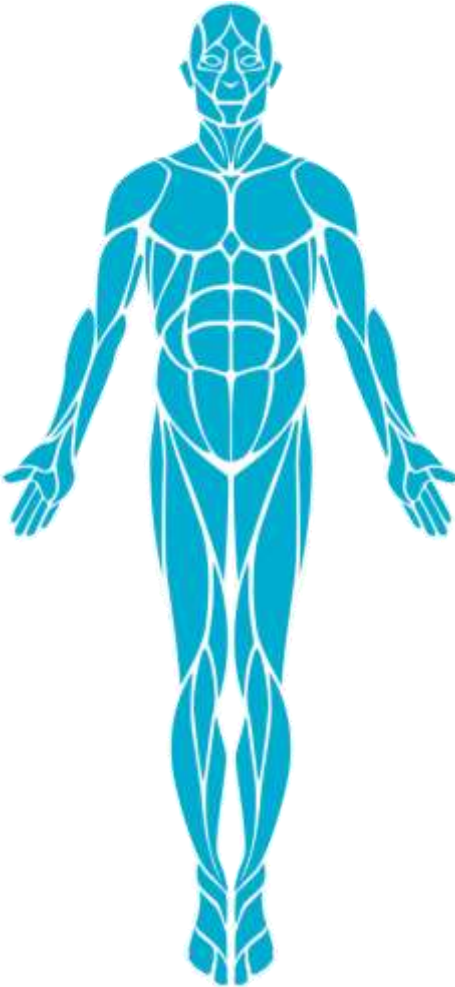
Immune system therapies



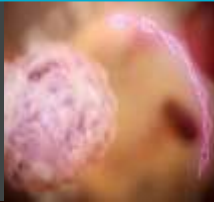
Novel drug platforms



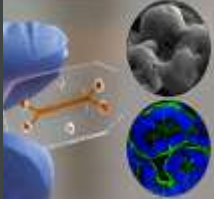
Intelligent medicines



Personalised healthcare



Human cell technology



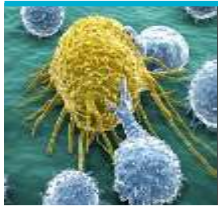
Genome editing



...and AstraZeneca can continue to lead the way



Great science is redefining the future of healthcare



Immune system therapies



Novel drug platforms



Intelligent medicines

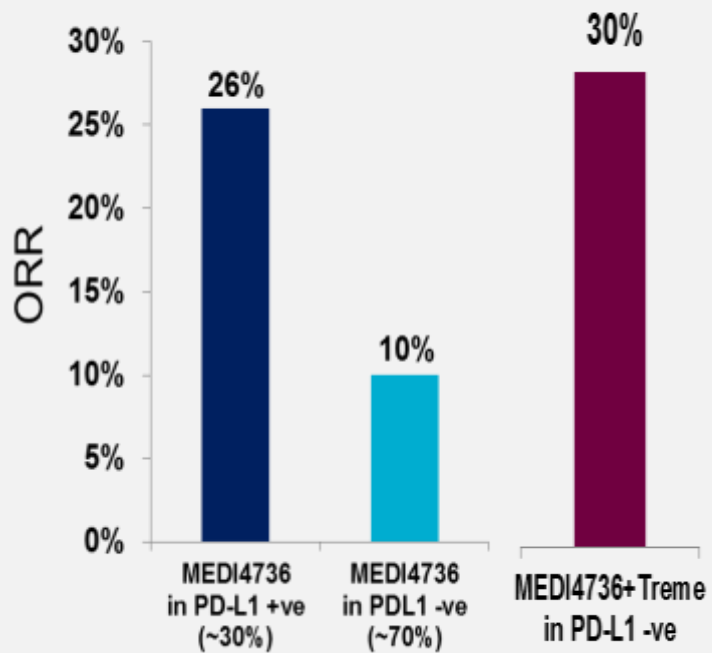
The immune system plays a pivotal role across multiple diseases

- Immuno-oncology is one of the most promising therapeutic modalities in the fight against cancer
 - Capitalising on our depth of immunological understanding across the company
 - Building collaborations and understanding across therapeutic areas
-



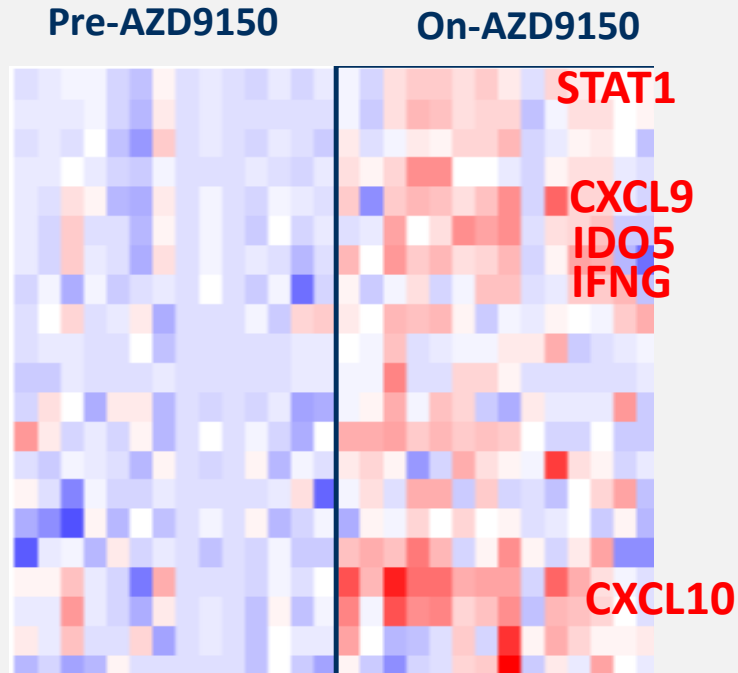
Bringing forward the next generation of immune therapies

Durva/ Treme (PD-L1/ CTLA-4, mAb) in immuno-oncology



Clinical activity 2L/3L NSCLC
new treatment paradigm (Ph3)

AZD9150 (STAT3, antisense) in immuno-oncology



Potential to enhance
durvalumab response (Ph1/2)

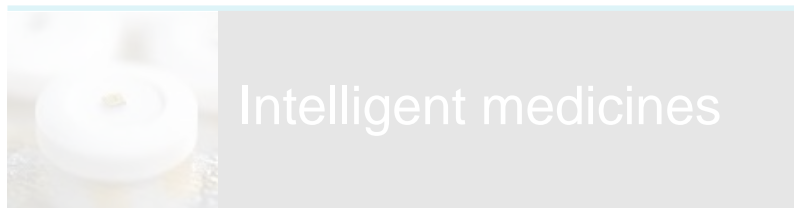
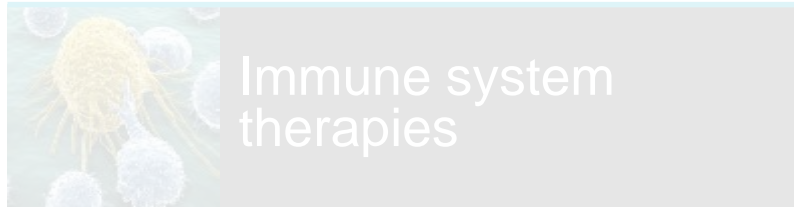
Anifrolumab (IFNAR1, mAb) in lupus



Significant & sustained
improvement in lupus (Ph3ID)



Great science is redefining the future of healthcare



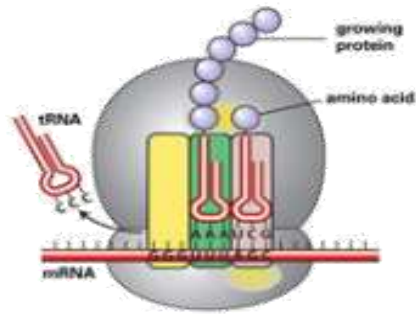
Innovative platform technologies allow us to rapidly and efficiently create new drug candidates

- Oligonucleotide therapies
- Targeted drug delivery – nanomedicine, dendrimers, viral vectors, antibody drug conjugates
- Protein engineering – bispecific/ biparatropic antibodies



Exclusive agreement with Moderna to harness pioneering messenger RNA technology

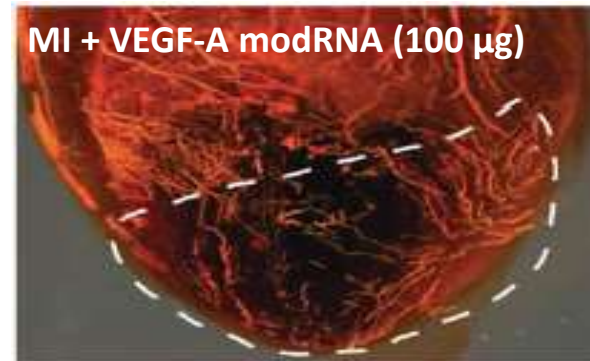
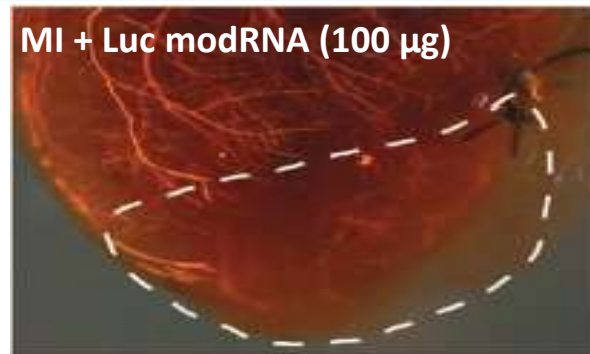
Intracellular translation



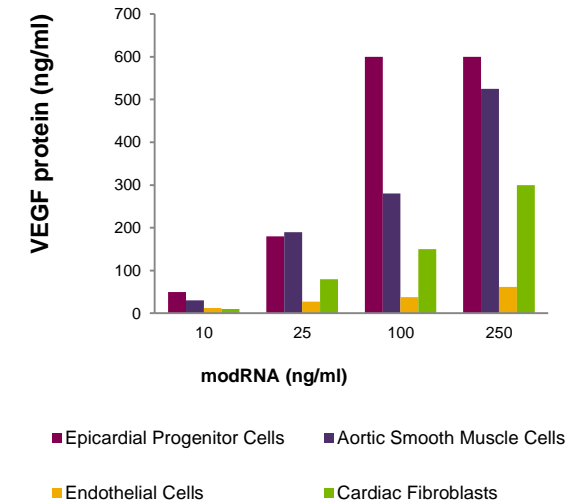
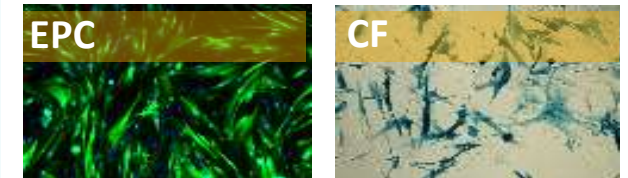
Protein expression



Regenerating blood vessels and cardiomyocytes*



Expresses in a variety of CV cell types

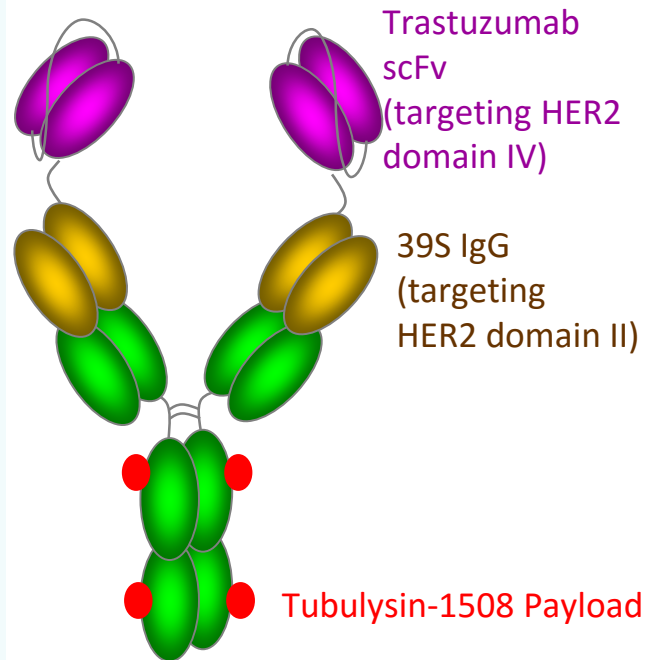


* Lior Zangi et al. Nature Biotechnology (2013)

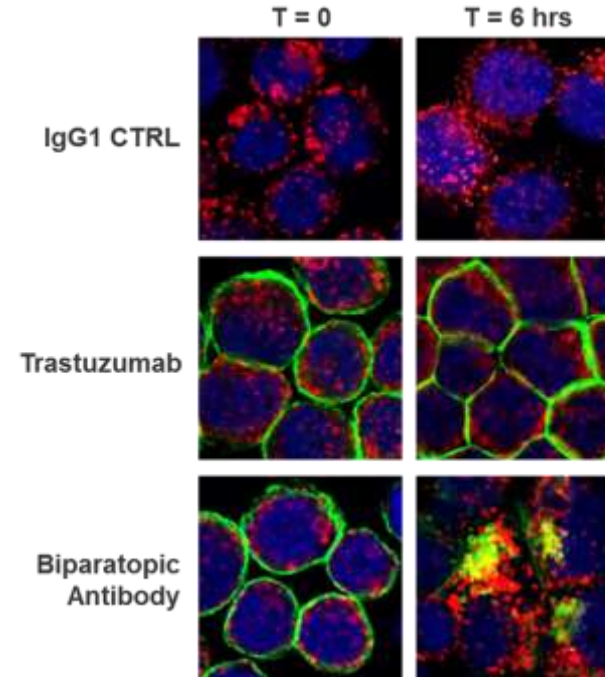


MEDI4726 a novel bispecific HER2 biosuperior antibody-drug-conjugate enters Phase 1

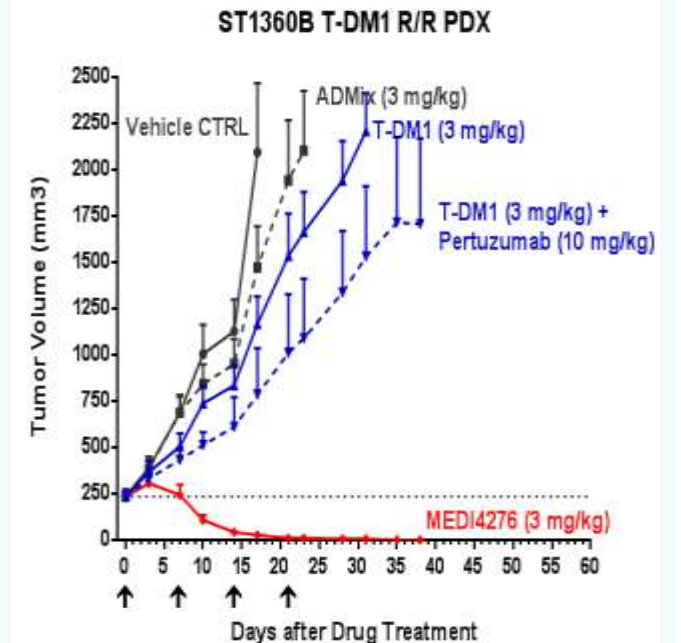
Bispecific ADC molecule



Rapid biological effect



Sustained activity



Great science is redefining the future of healthcare

Personalised medicine is becoming a healthcare reality for payers, physicians and patients

- More than 80% of our clinical pipeline currently has a PHC component
- 1st circulating tumour DNA test approved
- 7 diagnostic approvals in 2015 alone
- 50% of pipeline will have a diagnostic at launch over next 5 years (~30 launches)

Personalised
healthcare



Human cell technology



Genome
editing



Great science is redefining the future of healthcare

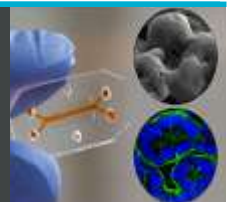
Human tissue systems have the potential to redefine R&D

- Creation of microchips that mimic the structure and function of living organs
- “organs-on-chips” technology could accelerate drug development and reduce animal use
- AZ scientists with our partners are leading the science in this space

Personalised
healthcare



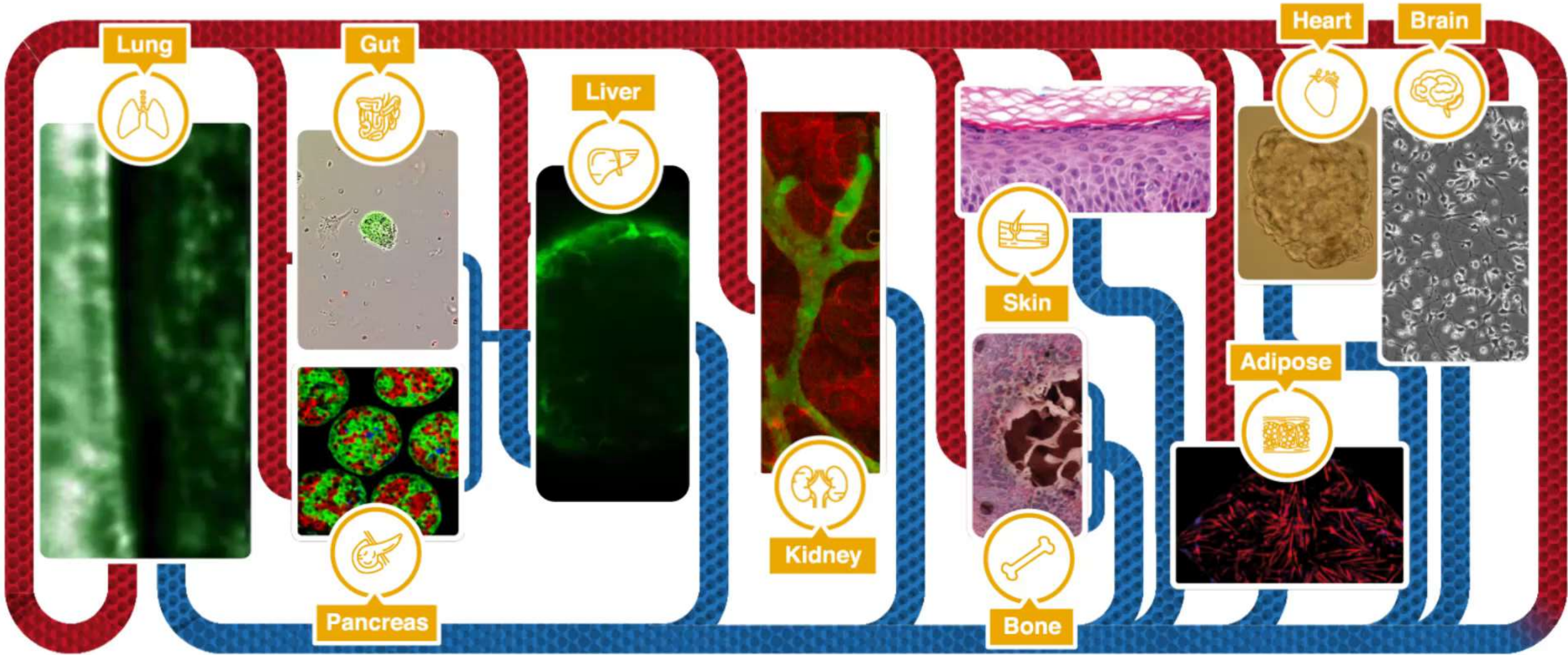
Human cell technology



Genome
editing



Working to create the first 'human body-on-a-chip'



Great science is redefining the future of healthcare

Ability to edit the human genome could have almost limitless potential for medical research

- Basic biological research opens up new opportunities for treatment
- **Clustered regularly interspaced short palindromic repeats (CRISPR)** - able to achieve highly flexible and specific targeting

Personalised healthcare

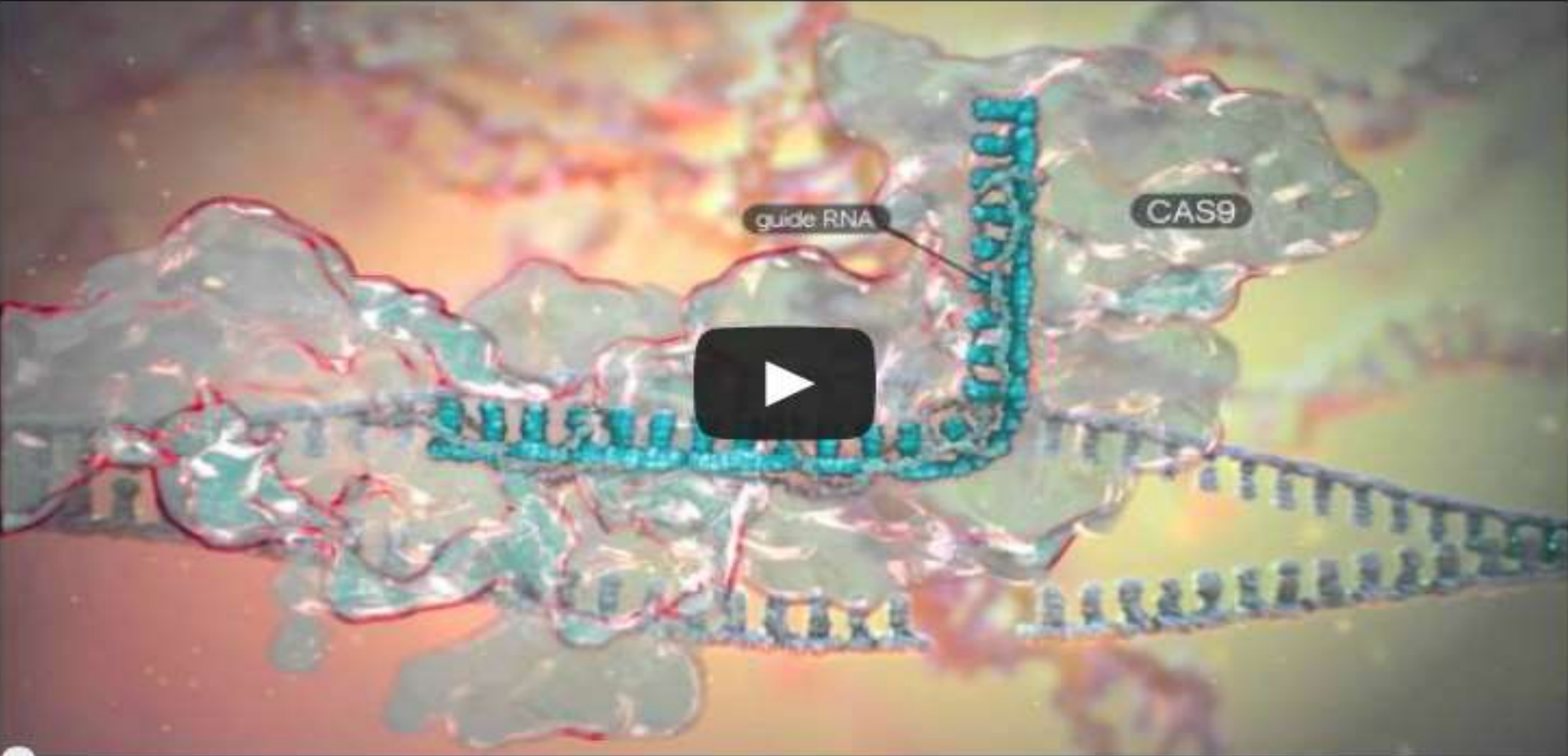


Human cell technology



Genome editing





guide RNA

CAS9



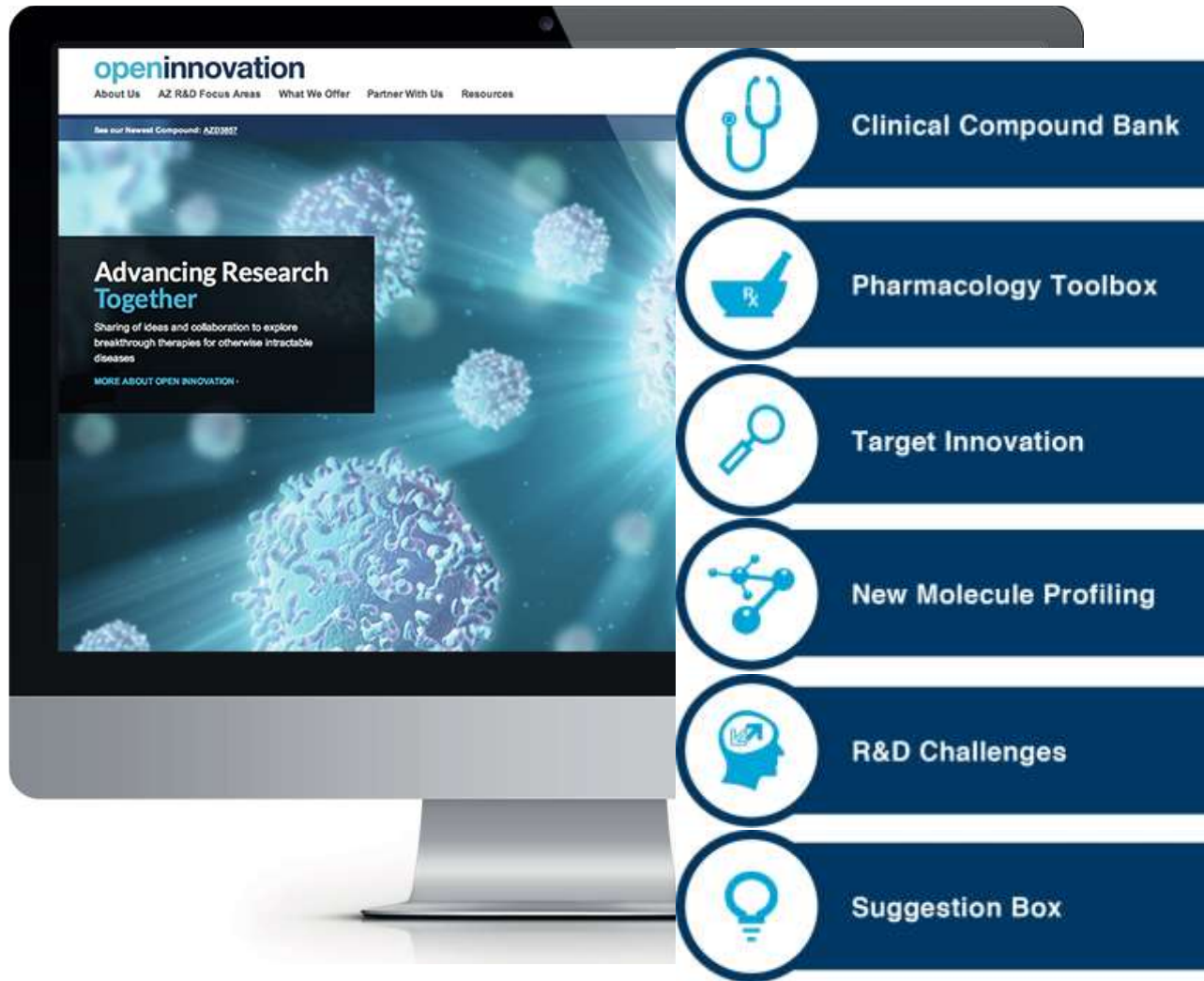
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YouTube



Identifying new partnerships through our open innovation portal



Interest:

- >10,000 web portal visits
- > 345 proposals reviewed

Outcomes:

- > 20 clinical trials
- > 80 preclinical studies
- 13 novel targets screened
- > 30,000 novel compounds
- 12 R&D challenges
- \$43.9M from public funding

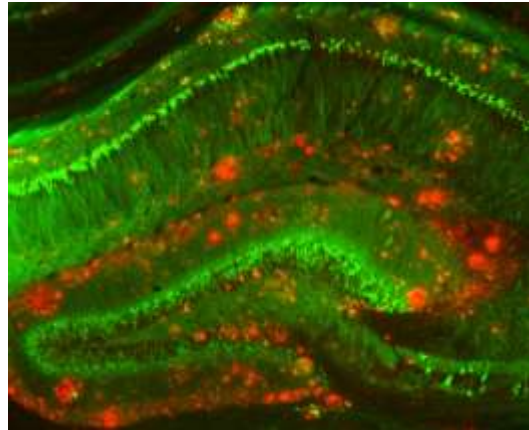
openinnovation.astrazeneca.com



...has uncovered potential new treatments for patients

AZD0530 in clinical trials for Alzheimer's Disease

- Fyn kinase inhibitor - developed to target cancer
- Yale scientists explored for AD by blocking Fyn activity
- Compound successfully reversed brain problems in mouse models
- Phase 1 trial showed compound reaches the brain at levels similar to those beneficial in mice



Alzheimer's disease mouse model, amyloid beta plaques (red) build up among neurons (green) in a memory-related area of the brain.



AZD3355 in clinical trials for chronic cough

- GABA-B receptor agonist developed to treat heartburn
- University of Manchester explored for chronic cough treatment
- Findings on GABA-B receptor mechanisms in human cough reflex presented at the BTS
- Phase 1 trial showed good tolerability - second study recruiting

“Getting access to the compound means an enormous amount. There have been no new treatments for cough in over 50 years, so there is so much potential for patients.”

Professor Jacky Smith,
University of Manchester



Our new Cambridge research centre will be a catalyst for innovation and collaboration

