Pipeline: Oncology

Susan Galbraith, Head of Innovative Medicines Oncology iMed
Mohammed Dar, Vice President, Oncology Clinical Development

AstraZeneca Oncology

Common vision

Redefine cancer treatment paradigm
Restore patients' lives
Eliminate cancer as cause of death

Bold ambition

By 2020, we will be a recognised leader in oncology, delivering 6 new medicines to patients

4 key MoA & platforms

4 core disease areas

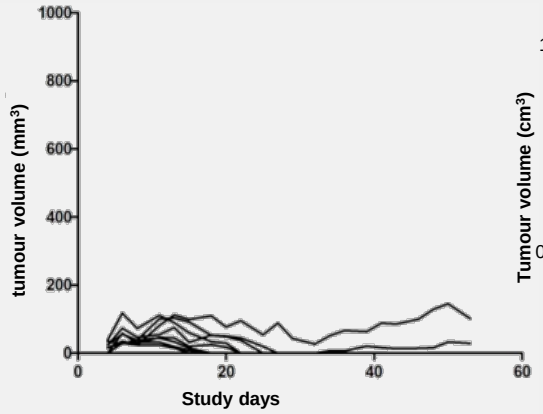
Combinations

Personalised healthcare

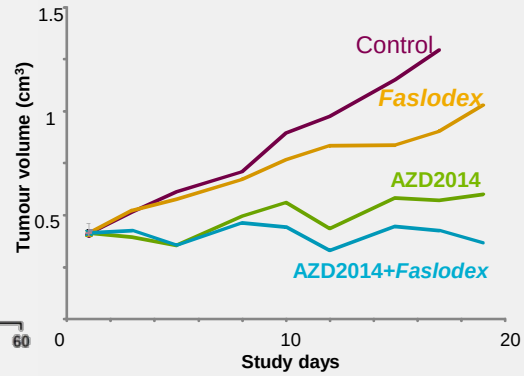
Smart development crucial to leadership

Oncology:
Combine therapies to change treatment paradigm

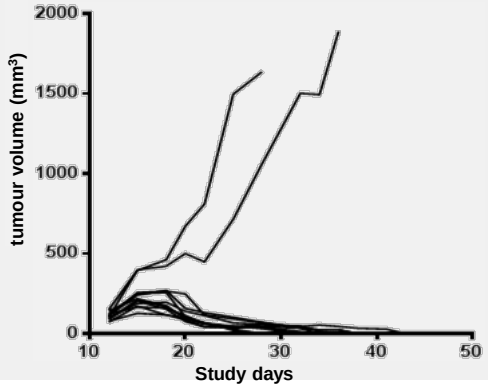
PD-L1 + CTLA-4



TORC1/2 + *Faslodex*



OX40 + CTLA-4

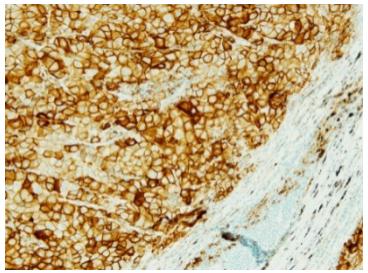


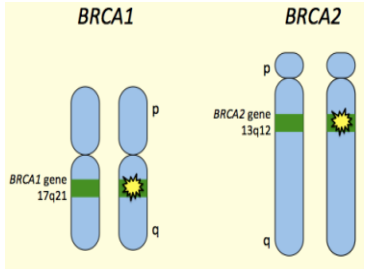
Combination therapies may enhance efficacy by:

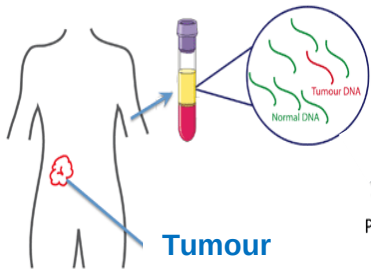
- Targeting complementary pathways
- Establishing synergistic effects
- Overcoming resistance to monotherapy
- Improving risk / benefit profile

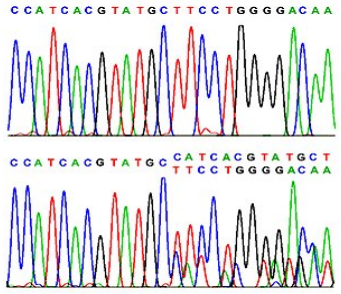
Oncology:
Personalised healthcare as key driver

Tissue-based assay	*Single-gene mutation analysis*	*Circulating tumour DNA*	*Next-generation sequencing*
MEDI4736 (PD-L1)	***Lynparza***	***Iressa* / AZD9291**	**Oncology portfolio**









VENTANA
A Member of the Roche Group

MYRIAD®

QIAGEN

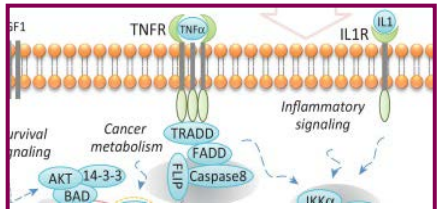
Roche

illumina®

Oncology:
Smart development crucial to leadership

AZD9291	**Potential filing less than 2½ years from first dose**
MEDI4736 (PD-L1) PACIFIC study	**Leapfrog competition into early line of therapy**
***Iressa* / AZD9291**	**First in ctDNA diagnostic testing**
MEDI4736 BRAF / MEK	**Good combinability enables novel triplet combination**

Scientific leadership: Four key platforms

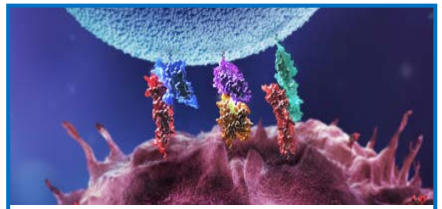


Tumour drivers and resistance

- AZD9291 (EGFRm)
- Selumetinib (MEK)
- AZD2014 (TORC1/2)
- AZD4547 (FGFR)
- AZD5363 (AKT)
- AZD6094 (cMET)
- AZD8186 (PI3Kβ)
- AZD8835 (PI3Kα)
- MEDI0639 (aDLL4)
- MEDI-573 (aIGF1/2)
- AZD9496 (SERD)
- AZD5312 (AR antisense)

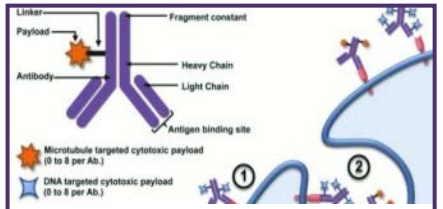
DNA damage repair

- Olaparib (PARP)
- Cediranib (VEGF)**
- AZD1775 (Wee1)
- AZD6738 (ATR)
- AZD0156 (ATM)*
- AZD2811 (AKB)*



Immunotherapy

- MEDI4736 (PD-L1)
- Tremelimumab (CTLA-4)
- MEDI0680 (PD-1)
- MEDI6469 (murine OX40)
- MEDI6383 (OX40 Fusion Protein)
- MEDI0562 (OX40 humanised mAb)
- AZD9150 (STAT3)
- AZD5069 (CXCR2)

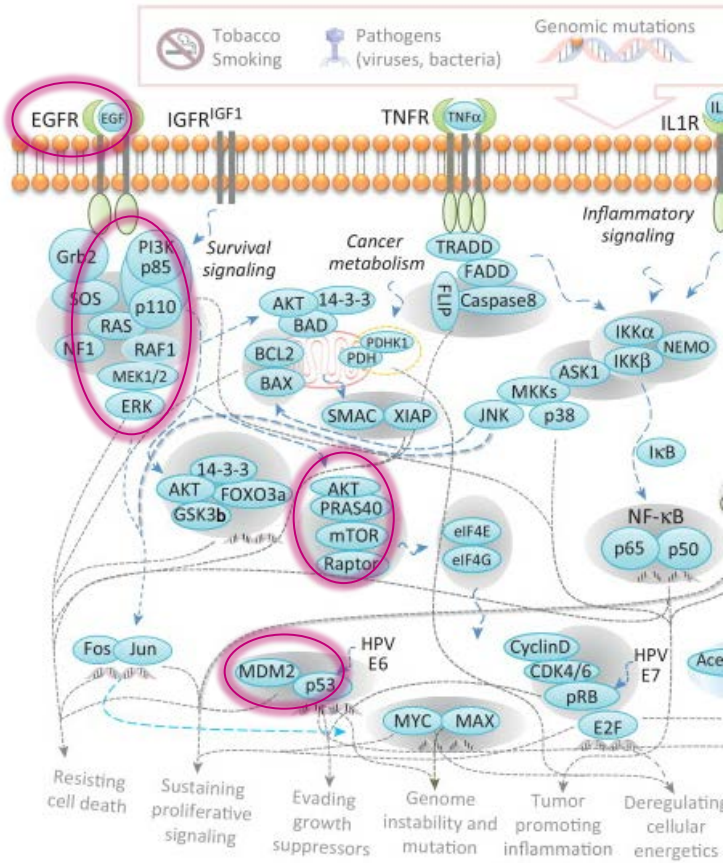


Antibody drug conjugates

- Moxetumomab (CD22)
- ADC-Spirogen*
- ADC-Bispecific*

* Preclinical
** Combination with DDR

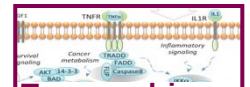
Scientific leadership:
Tumour drivers & resistance



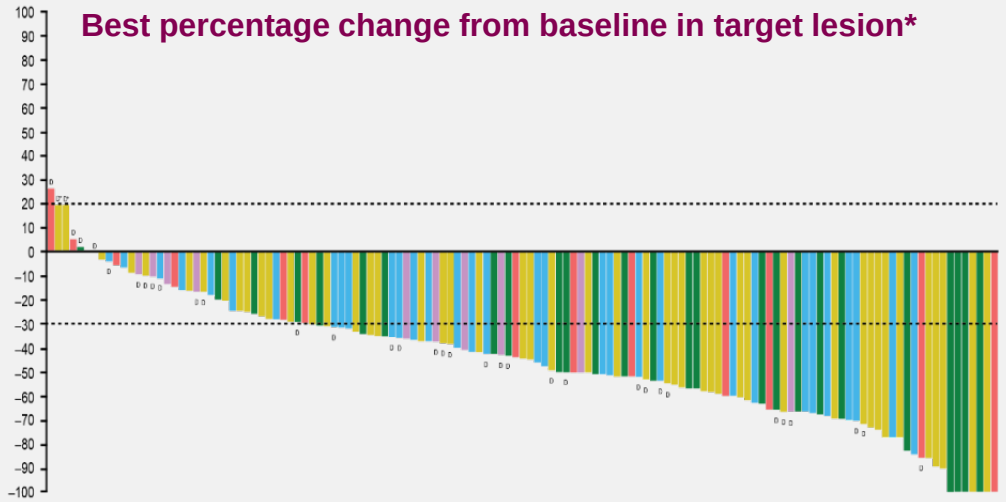
Tumour

- Highly altered signalling pathways in cancer
- Interconnected pathways allow resistance / escape mechanisms
- Multiple targets identified as potential tumour driver mutations

AZD9291:
EGFR mutant selective inhibitor in lung cancer



Strong evidence of monotherapy activity

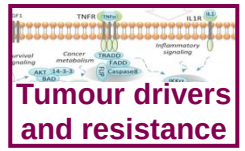


- Potentially first irreversible selective inhibitor of double EGFR mutations
- Awarded FDA Breakthrough Therapy Designation
- FSI 1st line Phase III Q4 2014, data expected 2017
- Combinations with MEDI4736 (PD-L1), MET (cMET) and selumetinib (MEK) ongoing (FSI Q3 2014)

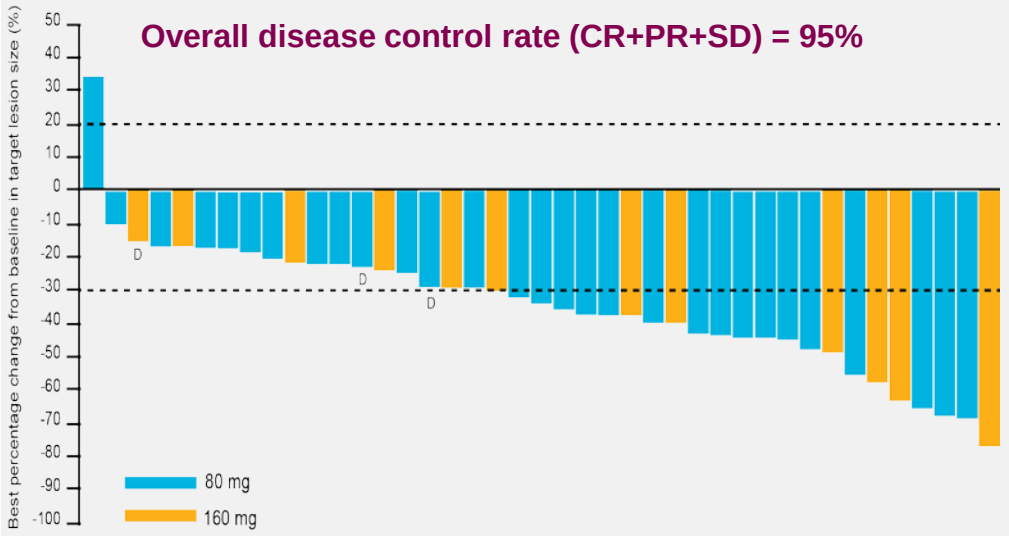
US NDA submission expected Q2 2015 in NSCLC 2L

* ESMO 2014

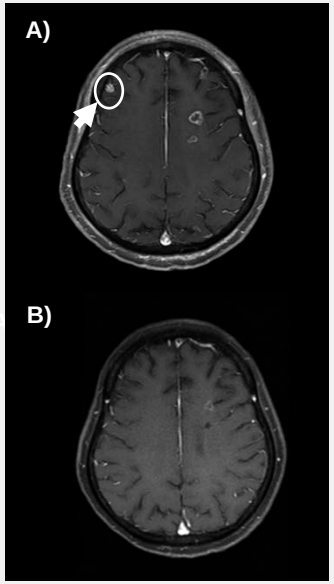
AZD9291:
Early efficacy in 1st line EGFRm NSCLC

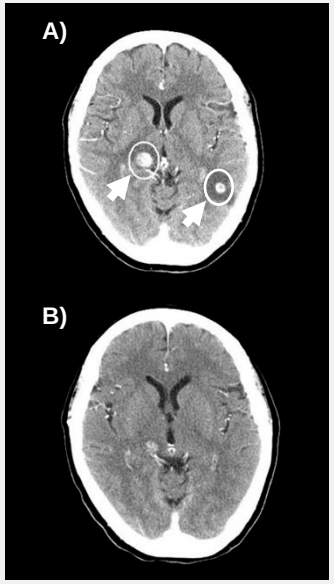


1st line EGFRm



Preliminary evidence of activity in NSCLC brain mets

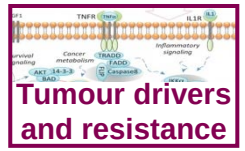




Clinical activity of AZD9291 in brain mets has been observed in a Phase I study in patients with acquired resistance to current EGFR-TKIs.

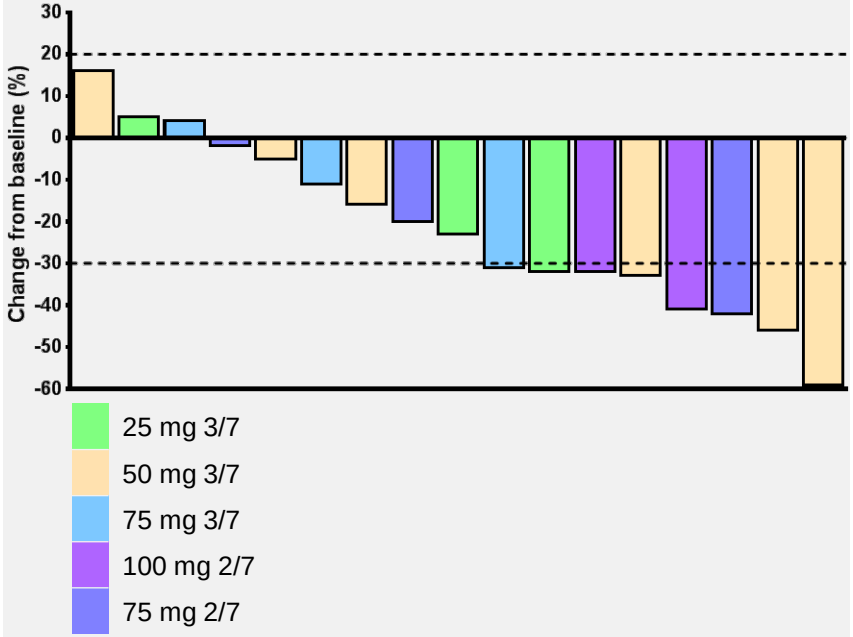
FLAURA: Phase III NSCLC 1L EGFRm H2H vs 1st gen. TKI to start Q4 2014

AZD2014:
Dual TORC1/2 inhibitor



Strong evidence of activity

Dual TORC1/2 + paclitaxel*



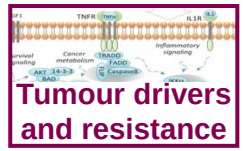
Differentiated clinical activity

- Broad potential in breast, lung, ovarian cancer and lymphoma
- Dual TORC1/2 and intermittent weekly dosing schedule to deliver better efficacy and tolerability
- Potential accelerated Phase III investment decision in 2015

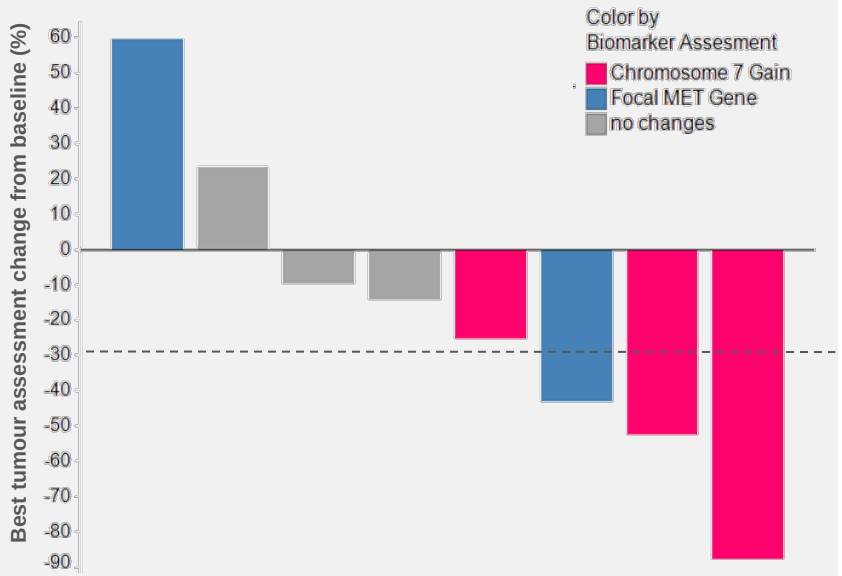
Combination with *Faslodex* in ER+ breast cancer to be submitted for presentation in 2015

*Basu et al ESMO 2014

AZD6094:
Potent, selective cMET inhibitor of MET-driven tumours



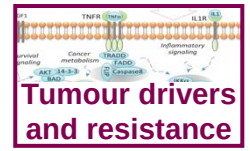
Activity in MET-driven papillary renal cell cancer (PRCC)



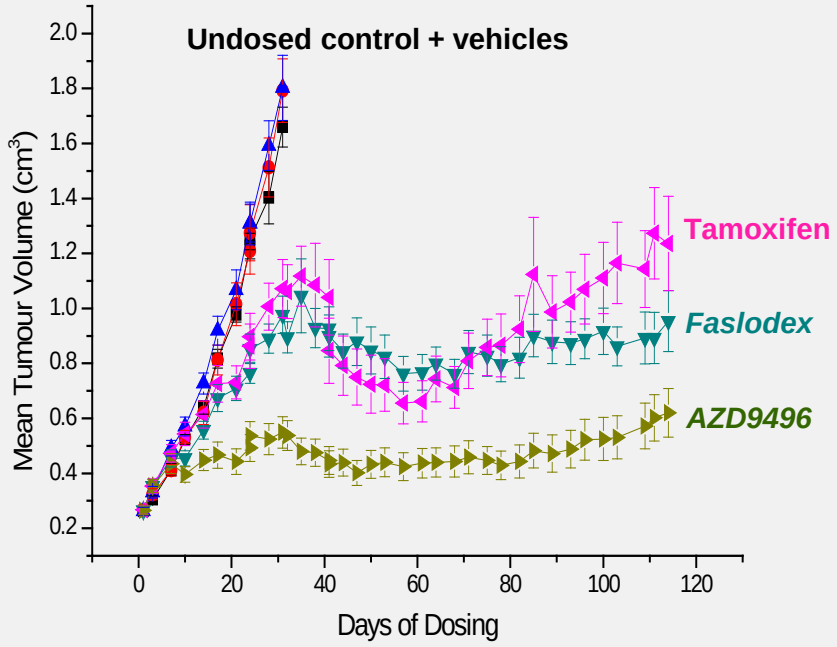
- Active in MET amplified and MET-mutant settings
- First-in-class opportunity in papillary renal cell cancer (PRCC)
- Phase II trial in PRCC ongoing
- Phase II trial in MET-amplified gastric and lung cancer ongoing
- Combination with AZD9291 in 2nd line EGFR mutant lung cancer ongoing

Gan et al ASCO 2014

AZD9496:
Oral selective estrogen receptor degrader (SERD)

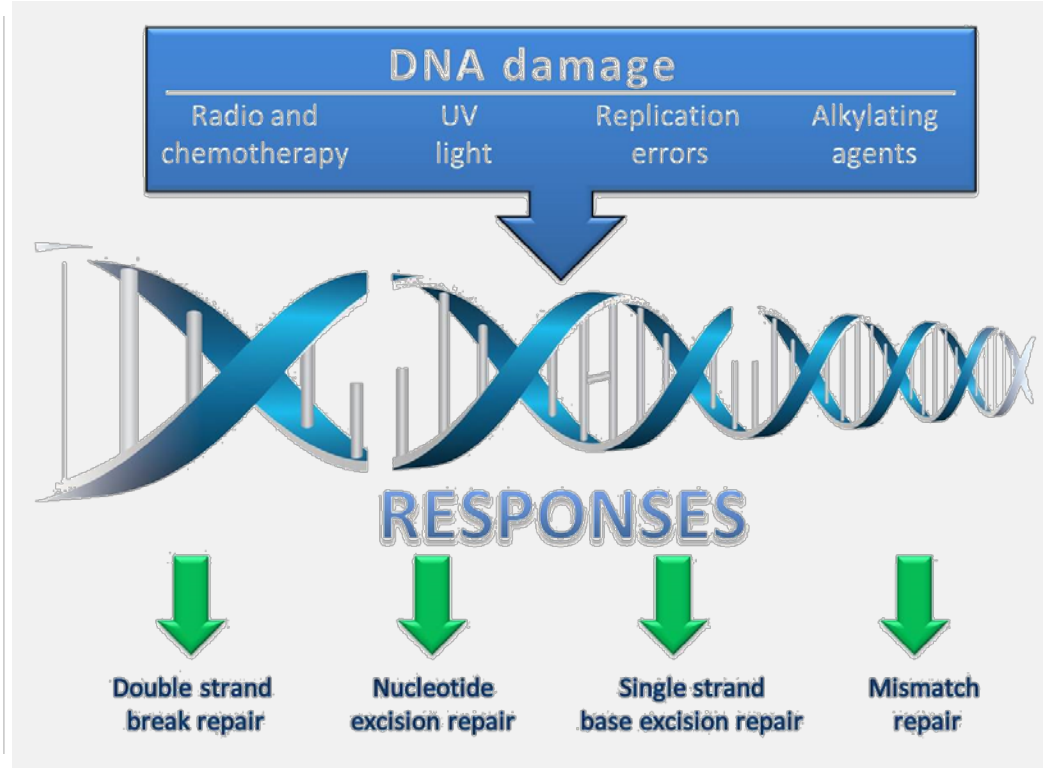


Greater tumour inhibition than *Faslodex*



- Improved potency and bioavailability allows greater estrogen receptor (ER) knockdown
- Oral formulation
- Clinical development started Q4 2014
- Pharmacological data submitted for AACR 2015

DNA Damage Repair (DDR): Targeting the Achilles heel of cancer

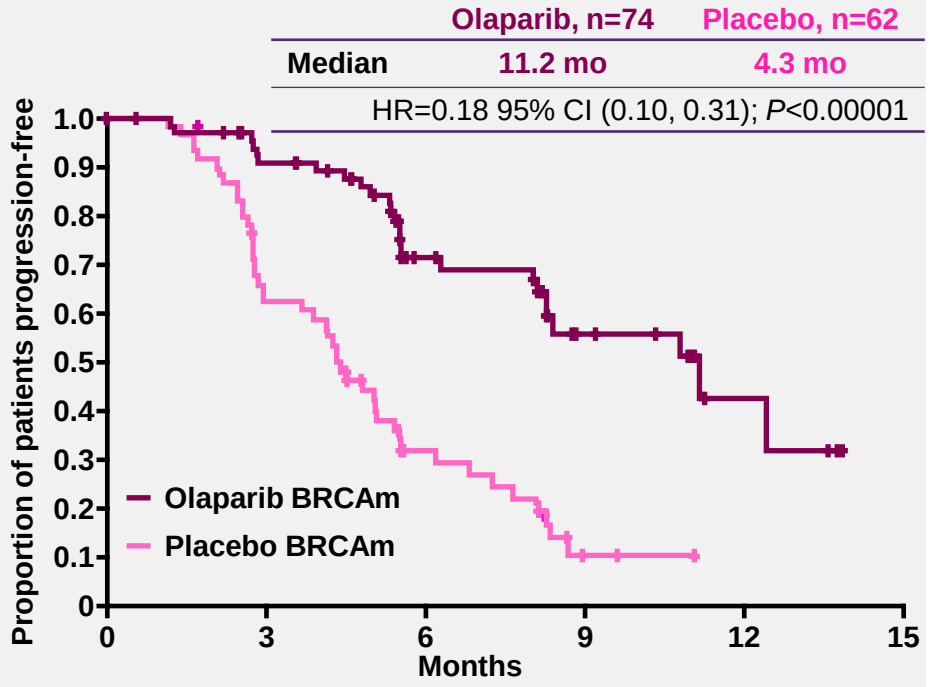


- Highly altered pathways in cancer
- Traditional chemotherapies depend on DDR pathways
- Most extensive portfolio of DDR agents in the industry

Lynparza (olaparib): First-in-class PARP inhibitor

DNA damage repair

Clinical benefit in BRCAm ovarian cancer



Ongoing Phase III programmes

- BRCAm ovarian cancer: SOLO-2 (2015*), SOLO-1 (2016*)
- BRCAm breast cancer: OlympiAD (2016*)
- Gastric cancer: GOLD (2017*)
- BRCAm pancreatic cancer: POLO (FSI Q4 2014)
- Promising activity in late-stage prostate cancer (10/30 RR, ESMO 2014)

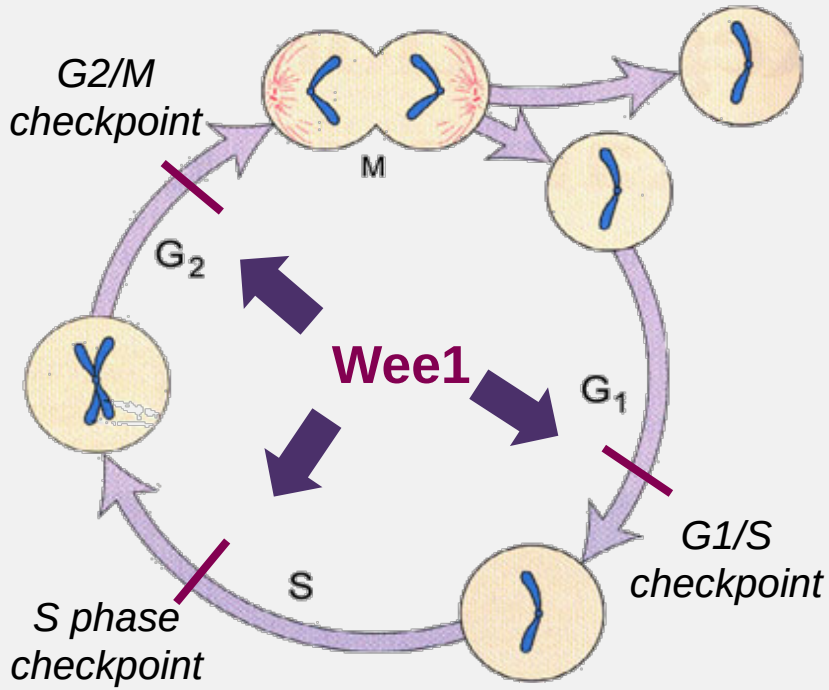
EU: Positive CHMP opinion
US: PDUFA 3 January 2015

*Data available

AZD1775:
Wee1 inhibitor; encouraging data in ovarian cancer

DNA damage repair

Wee1: Role in cell cycle progression and DNA damage checkpoints



Platinum-sensitive relapsed ovarian cancer

- 11/14 RECIST responses
- PFS 10.8 months
- 13/14 GCIG responses (includes CA125 responses)
- Phase II study in ovarian; *Lynparza* combination due to start Q1 2015
- Phase I/II trials in NSCLC

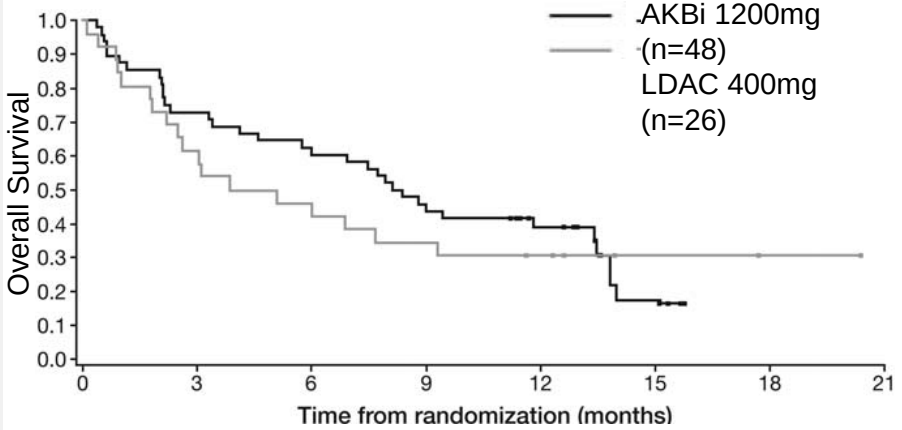
Phase III ovarian cancer investment decision expected 2015

AZD2811:
Aurora Kinase B inhibitor (AKBi): AML proof of concept

DNA damage repair

Phase II: AKBi vs low-dose cytarabine (LDAC) in elderly unfit AML

	AKBi vs LDAC
OCRR (+Cheson)	+30%
Overall Survival (HR)	0.88 (0.49-1.58)

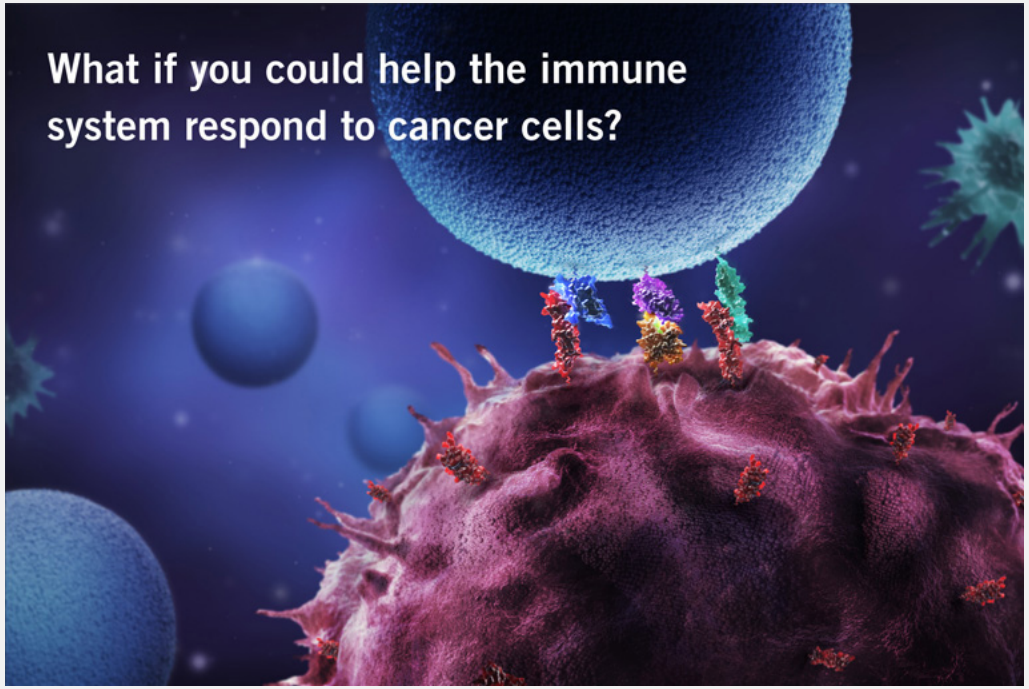


Differentiated profile

- Novel mechanism of action: Regulates mitosis and chromosomal segregation
- Nanoparticle formulation in development*
- Potential in DLBCL and AML
- Plan to discuss further steps with regulators early in 2015

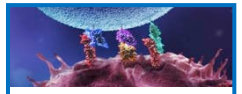
Kantarjian et al Cancer 2013;119:2611-19
* In collaboration with BIND Therapeutics

Immuno-oncology (IO):
Changing the treatment paradigms for cancer



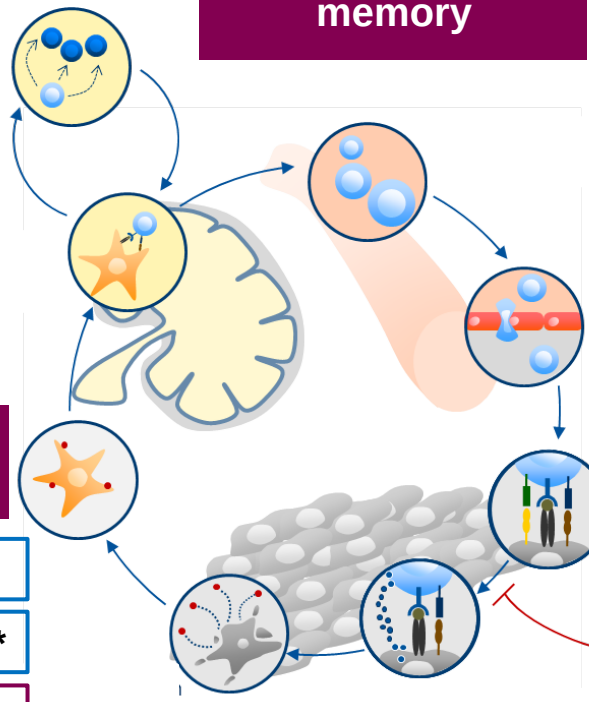
- An effective immune response is durable - possibly life-long
- Cancer hijacks many immune pathways to escape destruction
- Our robust pipeline allows identification of combinations that restore the immune response

Immuno-oncology (IO):
Three major components to cancer immune response



2. Optimizing T cell function and memory

- OX40
- PD-L1
- PD-1
- CTLA-4
- NME-4
- NME-5



1. Antigen presentation

- HPV Vaccine*
- AZD9291
- Radiotherapy
- BRAF/MEK*
- Iressa
- NME-1
- NME-2
- NME-3

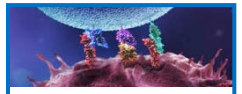
3. Inhibition by microenvironment

- IDO*
- CXCR2
- CCR4*
- STAT3
- NME-6
- NME-7
- NME-8

Clinical | Preclinical

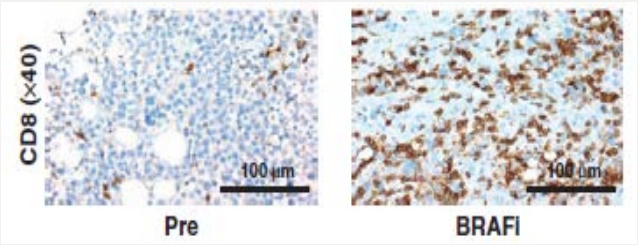
* Clinical collaborations

MEDI4736 (PD-L1):
Triplet w/dabrafenib and trametinib in BRAFm melanoma

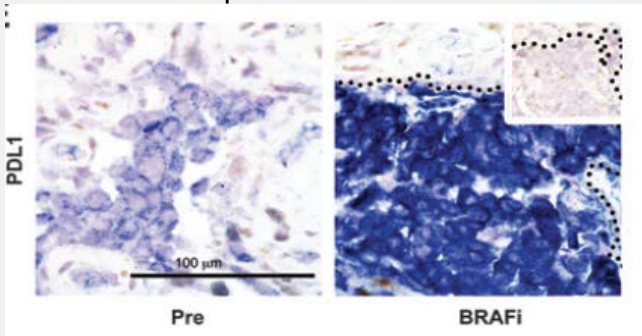


BRAFi/MEKi treatment effect

Increase in CD8 Tumour Infiltrated Lymphocytes (TILs)



Increase in PD-L1 expression



Frederick et al, 2013

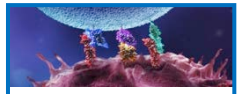
Potential for well-tolerated, durable benefit in BRAFm melanoma

- Clinical data for BRAFi/MEKi provide rationale for “triplet” combination
- Potential for durable response in 1L BRAFm melanoma patients
- Phase I “triplet” combination well tolerated at full monotherapy doses; MTD not reached

Presentation of Phase I “triplet” combination planned for H1 2015

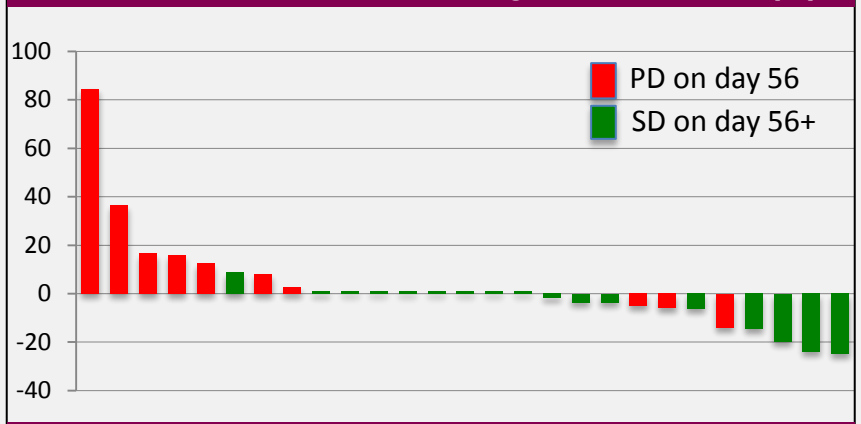
In collaboration with GSK

MEDI6383 (OX40):
Pathway drives potent, durable anti-tumour T cell immunity

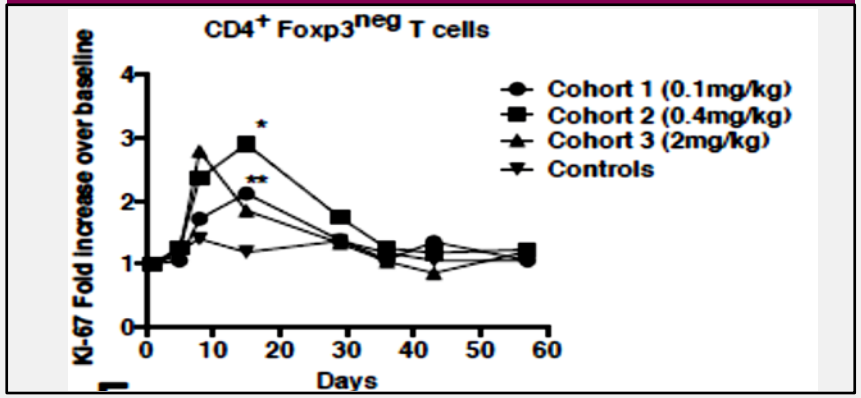


Murine OX40: Phase I evidence of activity

Best tumour assessment change from baseline (%)



Stimulatory activity in periphery

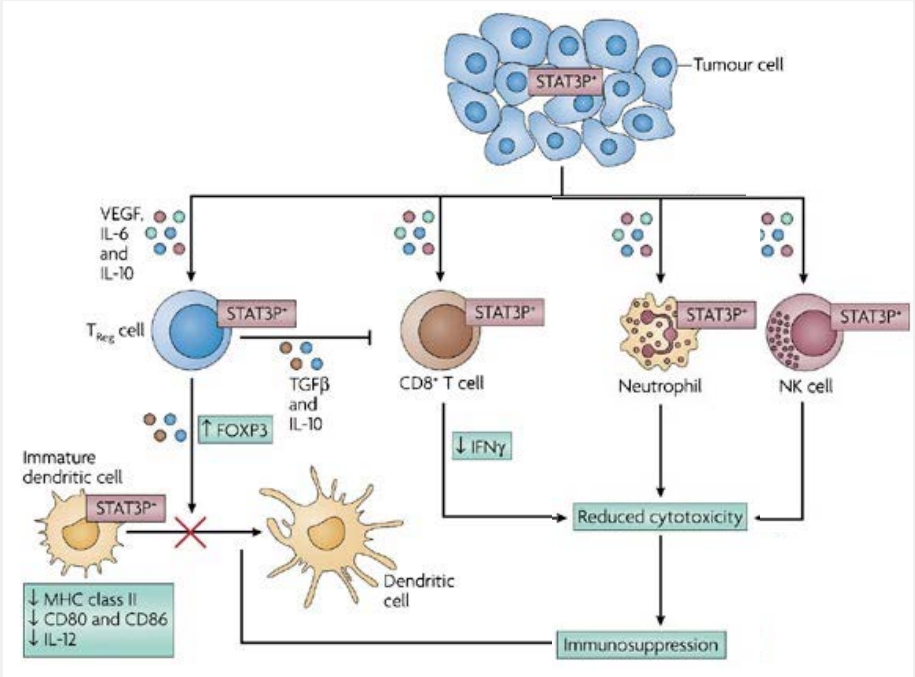


3 unique OX40 molecules with distinctive biology

- Murine anti-human OX40 (active in monotherapy; in combination with MEDI4736 now)
- Human OX40L fusion protein (currently in dose escalation)
- OX40 (FSI Q1 2015)

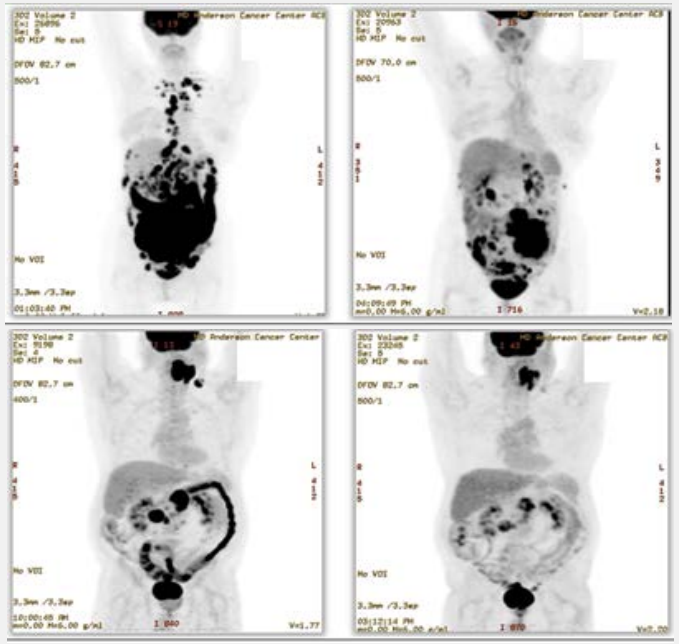
AZD9150:
STAT3 and roles in tumour microenvironment

STAT3 inhibition decreases immune tolerance in tumour microenvironment



Nature Reviews Immunology 7, 41-51

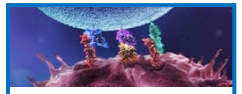
Durable responses in Phase I monotherapy studies



A CR and PRs lasting > 1year in lymphoma and liver cancer studies

Phase I oral presentation in plenary session at EORTC 19 Nov 2014
STAT3 + MEDI4736 Phase I study start H1 2015

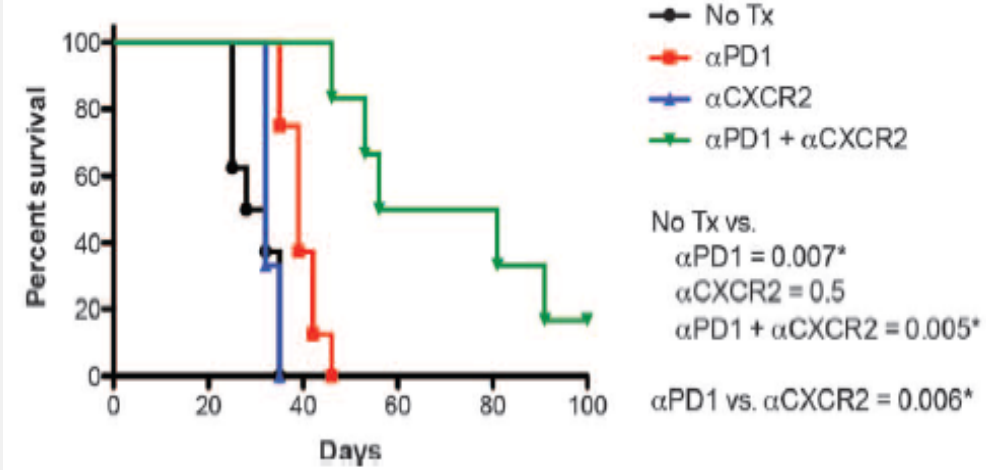
AZD5069:
CXCR2 affects myeloid-derived suppressor cell trafficking



Disruption of CXCR2-Mediated MDSC Tumor Trafficking Enhances Anti-PD1 Efficacy

Steven L. Highfill, Yongzhi Cui, Amber J. Giles, Jillian P. Smith, Hua Zhang, Elizabeth Morse, Rosandra N. Kaplan, Crystal L. Mackall*

Science Translational Medicine
AAAS



- First-in-class CXCR2 antagonist in oncology
- Potential synergistic activity with MEDI4736 (PD-L1)
- Phase I combination study of CXCR2 + MEDI4736 (PD-L1) expected to start in H1 2015

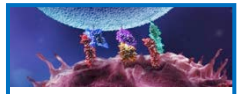
Immuno-oncology (IO): Combinations address multiple immune pathways

Antigen presentation		
PD-L1	**EGFR**	T-cell activation combined with increased tumour visibility
PD-L1	**MEK/BRAF**	T-cell activation combined with increased antigen presentation
PD-L1	**HPV Vaccine**	T-cell activation combined with increased priming
T-cell killing and memory		
CTLA-4	**PD-L1**	Increased T-cell activation through blocking multiple inhibitory pathways
PD-1	**PD-L1**	Increased T-cell activation through complete blockade of the PD-1/PD-L1 axis
PD-L1/CTLA-4	**OX40**	Increasing T cell number, function and memory
Tumour microenvironment		
PD-L1	**IDO**	T-cell activation combined with removal of inhibition
PD-L1	**CCR4**	T-cell activation combined with T-reg depletion
PD-L1	**CXCR2**	T-cell activation combined with reduced MDSC suppression
PD-L1	**STAT3**	T-cell activation combined with myeloid reprogramming

DEFINIENS
the tissue phenomics company

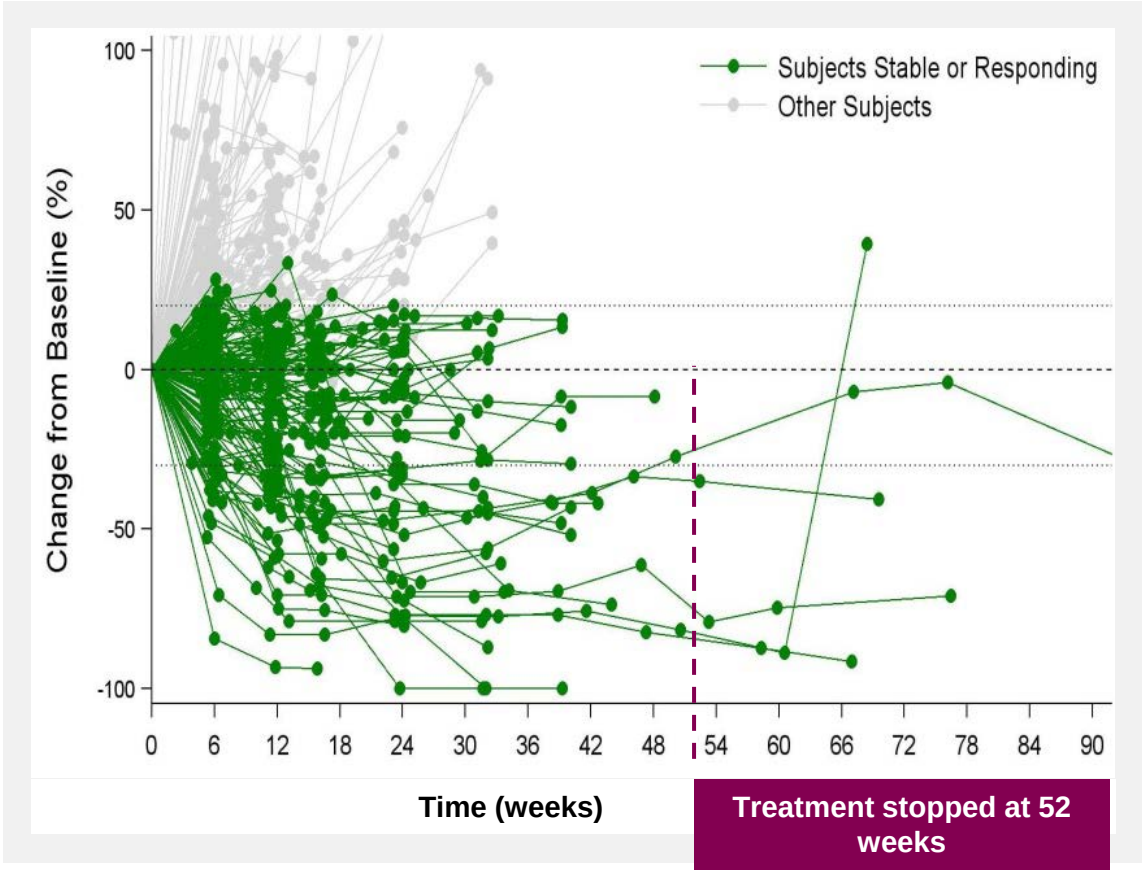
Enables precise identification, location and relationship between multiple components of tumour microenvironment

Immuno-oncology (IO):
Unique indications, novel combos, speed of execution



1 Speed	2 Differentiation	3 Leadership
Quickest path to approval	• Rapid program expansion • Adaptive decision-making • Patient selection	First or best-in-class agents
Monotherapy MEDI4736 (PD-L1) • Late-stage NSCLC • 2L head/neck (SCCHN) **MEDI4736 (PD-L1) / tremelimumab combo** • Late-stage NSCLC • 2L head/neck (SCCHN)	**Differentiated tumour types and biomarker subsets** **High value leapfrog indications:** • Stage 3 unresectable NSCLC • Adjuvant NSCLC	**Combinations** • MEDI4736 (PD-L1) + tremelimumab • MEDI4736 (PD-L1) + AZD9291 **Three OX-40 antibodies** • Murine, humanised, fusion • Monotherapy, combination

MEDI4736 (PD-L1):
Monotherapy; early, durable activity in multiple tumours*

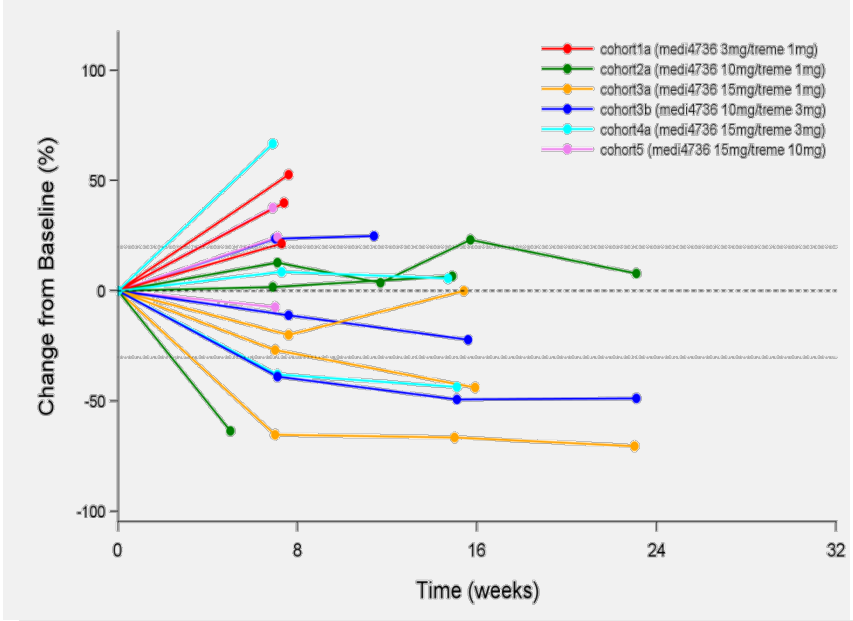


Total study population (10 mg/kg q2w)	
Ongoing responders	
Total	92% (33/36)
RECIST response	
PD-L1+	22% (18/81)
PD-L1-	5% (12/233)
Total	10% (36/352)
Disease control rate at 12 weeks	
PD-L1+	47% (38/81)
PD-L1-	28% (64/233)
Total	33% (115/352)

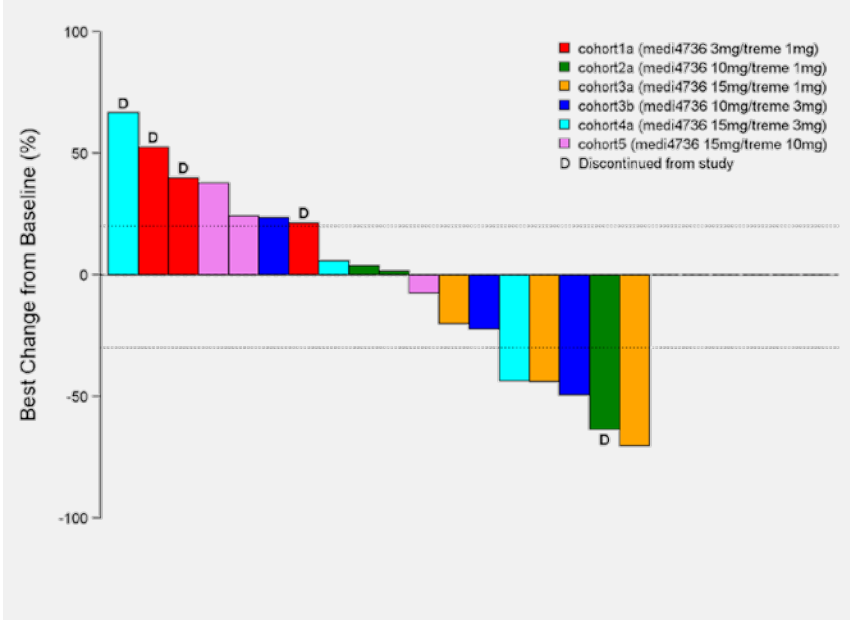
* Patients with baseline and ≥1 on-treatment scan; disease assessment at 6 weeks, 12 weeks, 16 weeks, and then every 8 weeks
Data cut-off: 21 August, 2014

MEDI4736 (PD-L1) + tremelimumab: Encouraging efficacy for combination in NSCLC

Tumour shrinkage by dose cohort (n=18)

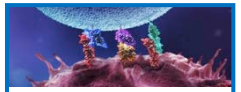


Best change in tumour size by dose cohort (n=18)

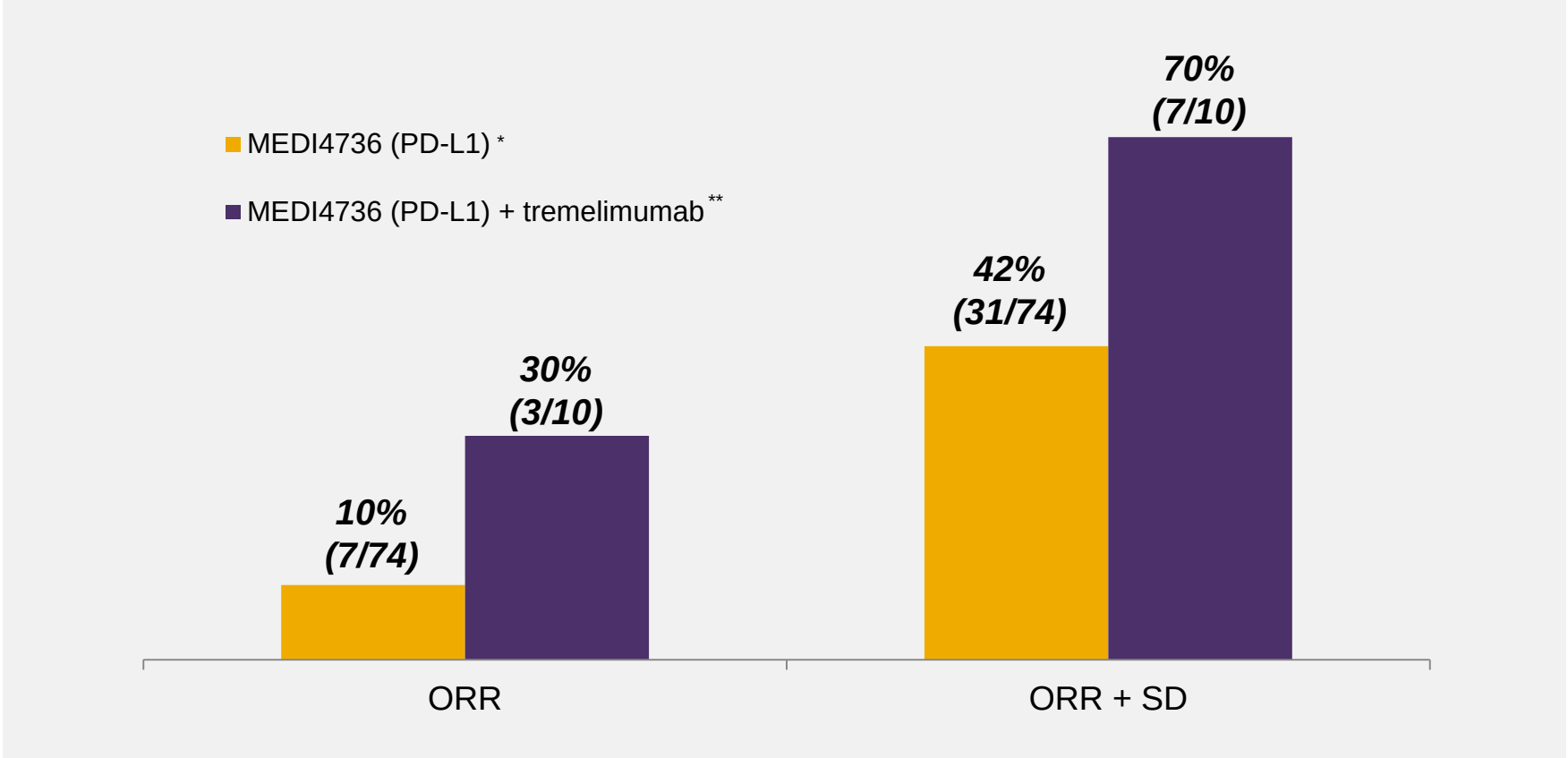


All patients	ORR	Stable disease
MEDI4736+tremelimumab	28% (5/18)	28% (5/18)

MEDI4736 (PD-L1) + tremelimumab: Potentially better response in PD-L1 negative tumours

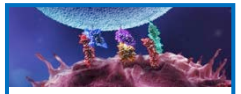


PD-L1 negative patients in NSCLC



* Mono: ORR 10% (7/74), 95%CI (3.9%, 18.5%) SD≥12weeks 32.4% (24/74), 95%CI (22.0%, 44.3%)
** Combination: ORR 30% (3/10), 95%CI (6.7%, 65.2%) SD≥12weeks 40% (4/10), 95%CI (12.2%, 73.8%)

MEDI4736 (PD-L1): Development in NSCLC

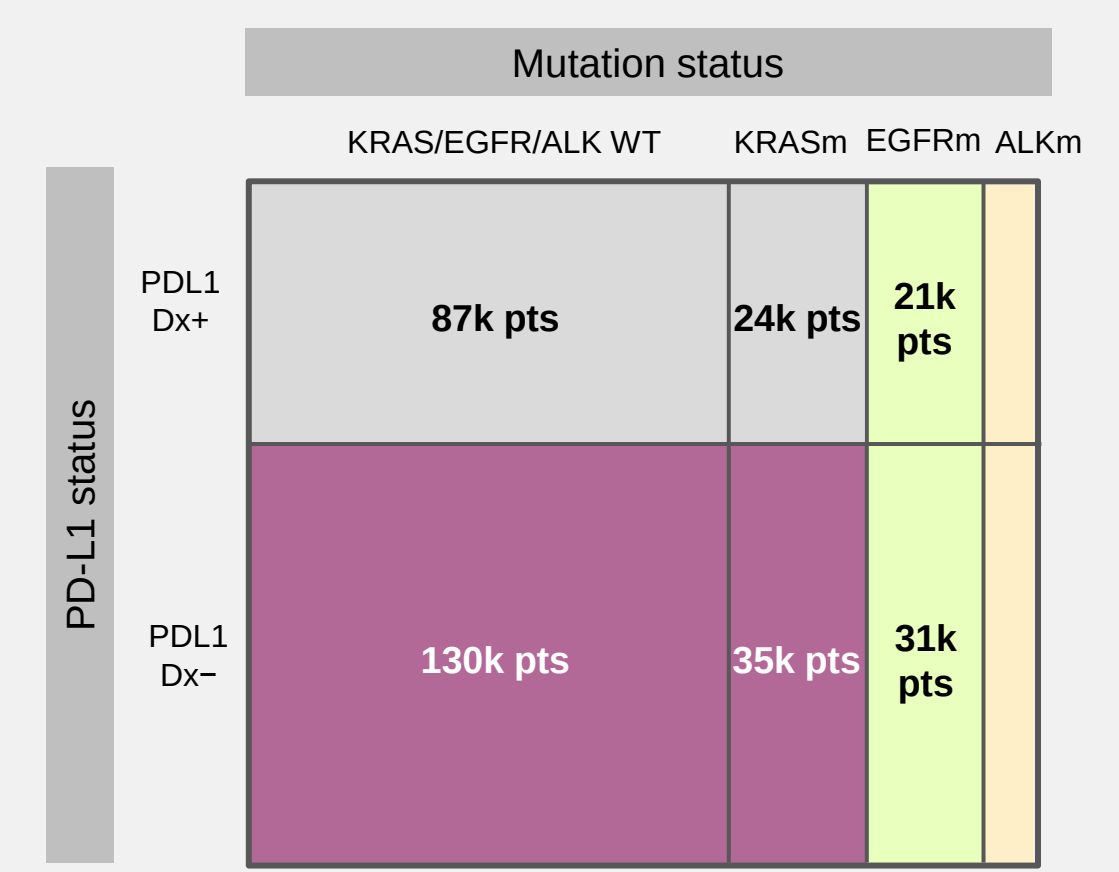


Fast-to-market monotherapy		First-mover advantage Early NSCLC	
ATLANTIC	**ARCTIC**	**PACIFIC**	**ADJUVANT**
Phase II 3L NSCLC PD-L1 -positive	Phase III 3L NSCLC	Phase III Stage 3 unresectable NSCLC	Phase III Adjuvant NSCLC PD-L1 positive and unselected
MEDI4736 (PD-L1) monotherapy	MEDI4736 (PD-L1) monotherapy; treme combination	MEDI4736 (PD-L1) monotherapy	MEDI4736 (PD-L1) monotherapy
Single-arm Phase II	Randomised vs. SOC*	Randomised vs. SOC*	Randomised vs. SOC*
Data: 2015	Data: 2017	Data: 2017	Data: 2020

Phase III MEDI4736 (PD-L1) + tremelimumab to start early 2015

*SOC = standard of care

Non-small cell lung cancer (NSCLC): Focus on medical need in PD-L1 negative disease

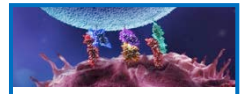


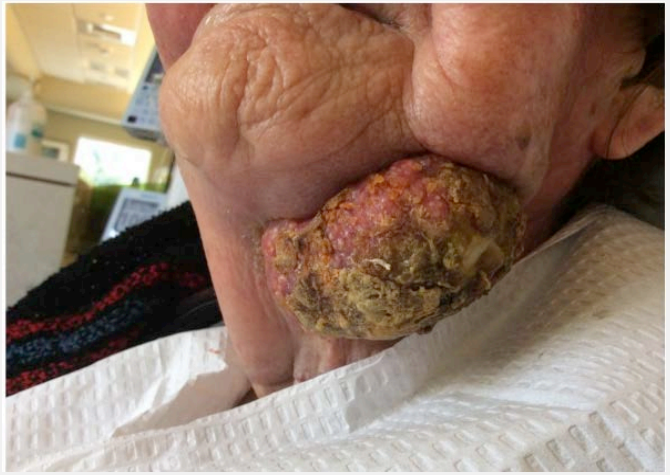
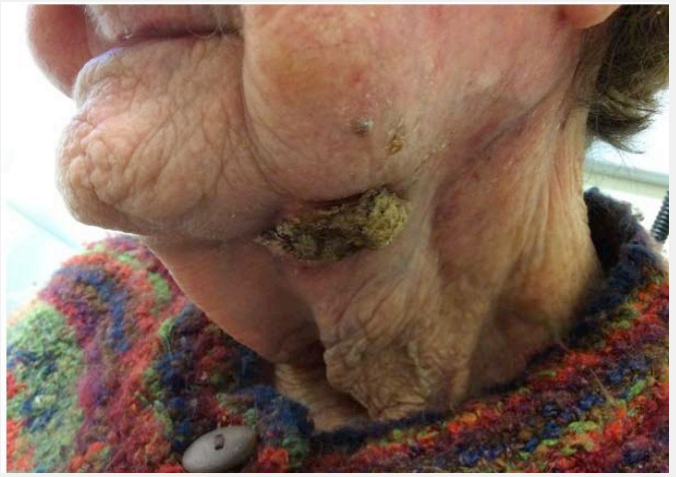
PD-L1 negative NSCLC

- Largest segment of NSCLC
- Not addressed by marketed targeted therapies (EGFR, ALK)
- Significant unmet medical need remains

EGFRm16%; KRASm 18%; ALKm 3%; EGFR/ALK/KRAS wt 63% (Kantar and AZ estimates 2020)

MEDI4736 (PD-L1): Head and neck cancer (SCCHN)

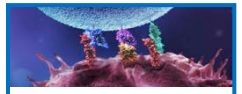


Before MEDI4736 (PD-L1) infusion	After two MEDI4736 (PD-L1) infusions (30 days)
	

96 year old patient who had progressed on cetuximab prior to study entry (HPV negative, PD-L1 positive)

SCCHN=Squamous cell carcinoma of head and neck

MEDI4736 (PD-L1): Head and neck cancer development



Fast-to-market monotherapy	First-mover advantage combination therapy	
HAWK	**CONDOR**	**EAGLE**
Phase II Platinum failures PD-L1 positive	Phase II Platinum failures PD-L1 negative	Phase III Platinum failures Unselected
MEDI4736 (PD-L1) monotherapy	MEDI4736 (PD-L1) + tremelimumab	MEDI4736 (PD-L1) + tremelimumab
Single-arm Phase II	Contribution of component study	Randomised study vs. SOC
Data: 2015	Data: 2016	Data: 2017

Phase III monotherapy and combination with tremelimumab to start early 2015

Immuno-oncology (IO): 13 ongoing and 16 planned combinations to address multiple immune pathways

Ongoing studies

PD-L1	Ph III	NSCLC
tremelimumab	Ph III	Mesothelioma
Seq. AZD9291/selumetinib + docetaxel/*Iressa*/CTLA-4 & PD-L1	Ph II	NSCLC
PD-L1	Ph II	Solid tumours
PD-L1	Ph II	SCCHN
PD-L1 + mOX40	Ph I/II	Solid tumours
PD-L1	Ph I/II	MDS
PD-L1 + tremelimumab	Ph I	NSCLC
PD-L1 + tremelimumab	Ph I	Solid tumours
PD-L1 + BRAFi + MEKi PD-L1 + MEKi	Ph I	Melanoma
PD-L1 + Iressa	Ph I	EGFRm NSCLC
PD-L1 + PD-1	Ph I	Solid & haems
PD-L1 + AZD9291	Ph I	EGFR M+ NSCLC
tremelimumab + *Iressa*	Ph I	EGFRm NSCLC
OX40 fusion protein	Ph I	Solid tumours

Planned studies

PD-L1 + tremelimumab	Ph III	3L NSCLC
PD-L1 +/- tremelimumab	Ph I/II/III	SCCHN
PD-L1 +/- tremelimumab	Ph I/II	Solid tumours
mOX40 + rituximab	Ph I/II	Haematological
CD19 + PD-1	Ph I/II	Haematological
PD-L1 + STAT3	Ph I/II	Solid/haem tumours
PD-L1 + CXCR2i	Ph I/II	Solid tumours
PD-L1 + INCB024360 (IDO1)	Ph I/II	Solid tumours
PD-L1 + mogamulizumab (CCR4)	Ph I/II	Solid tumours
tremelimumab + mogamulizumab (CCR4)	Ph I/II	Solid tumours
PD-L1 + ADXS-HPV	Ph I/II	HPV-cervical & H&N
mOX40 + tremelimumab	Ph I/II	Solid tumours
PD-L1 + ibrutinib (BTKi)	Ph I/II	Haematological
PD-L1 + radiation	Ph I	Solid tumours
PD-L1 + tremelimumab + radiation	Ph I	Solid tumours
PD-L1 + tremelimumab	Ph I	Haematological
OX40	Ph I	Solid tumours

New since ESMO 2014

Summary

Oncology poised to be transformational for the company

Broad pipeline addresses multiple mechanisms and allows for optimal combination therapies to improve patient benefit

Leadership in next-generation of science in oncology

Q&A

Mondher Mahjoubi, *moderator*
Susan Galbraith
Mohammed Dar
Antoine Yver