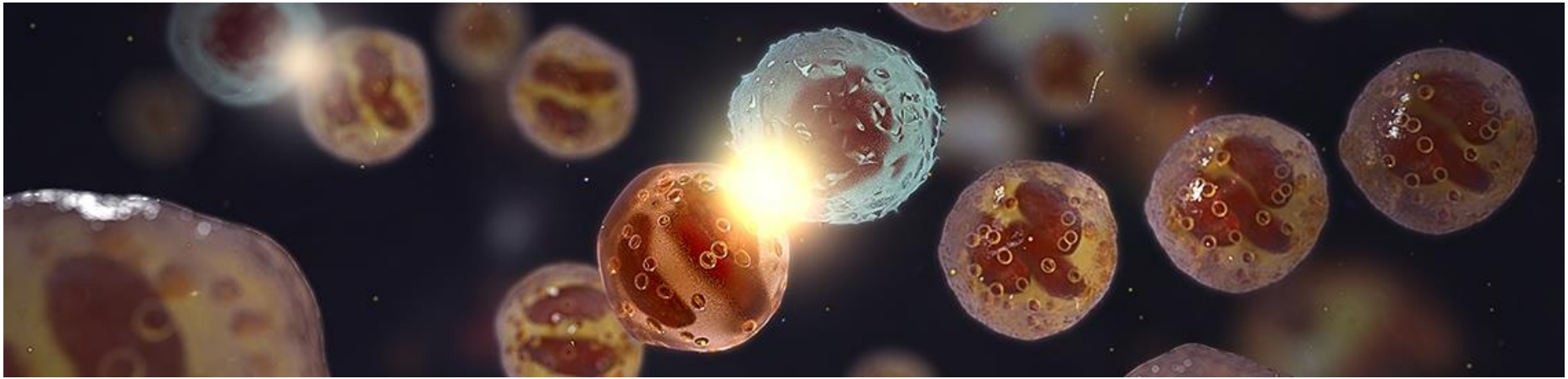
AstraZeneca/MedImmune Combinations Alliance Expressions of Interest Call – October 2017

Brief Overview of Compounds for Consideration

October 2017



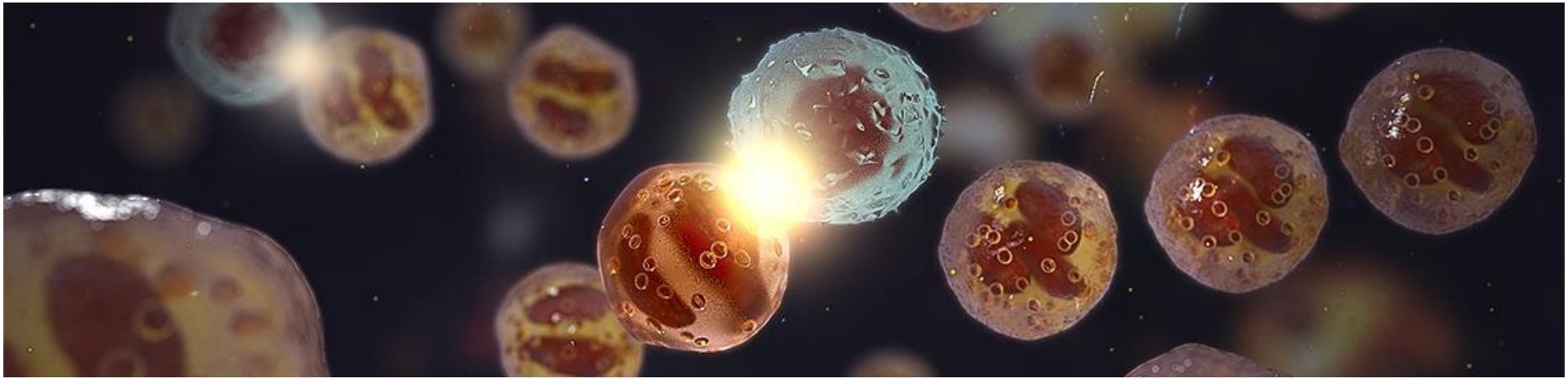
Compounds agreed for EoI Call – October 2017

Molecule	Primary AZ Contact
AZD9150 (STATi)	Esha Gangolli esha.gangolli@astrazeneca.com
AZD0156 (ATMi)	Andrew Reynolds andrew.reynolds1@astrazeneca.com
AZD6738 (ATRi)	Simon Smith simon.a.smith@astrazeneca.com
Acalabrutinib (BTKi)	Edwin Clark, Allard Kaptein, Sarang Abhyankar Edwin.Clark@astrazeneca.com a.kaptein@acerta-pharma.com sarang.abhyankar@acerta-pharma.com
Durvalumab (Imfinizi; anti-PD-L1) – with or without tremelimumab	Asud Khaliq Asud.Khaliq@astrazeneca.com
Tremelimumab (anti-CTLA-4) – only in combination with durvalumab or another AZ/MedI molecule	Asud Khaliq Asud.Khaliq@astrazeneca.com

AZD9150 (STAT3 antisense oligonucleotide)

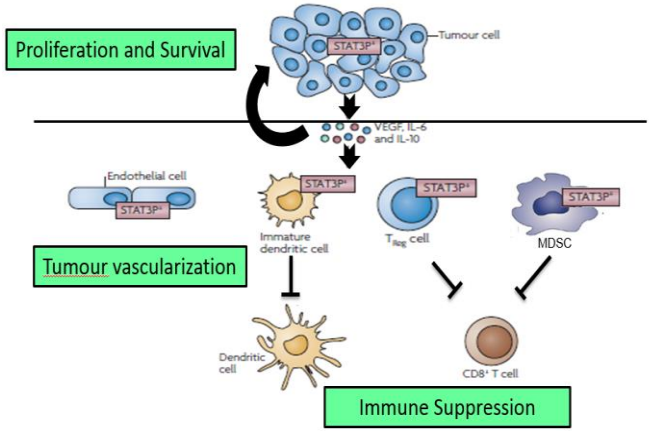
Esha Gangolli

October 2017



AZD9150 – STAT3

Key Data	
Primary pharmacology	STAT3 mRNA and protein reduction in a variety of cell types, with IC50s as low as 10nM
Dose range explored	1-4 mg/kg/week
RP2D	3 mg/kg/week, monotherapy or combination with durvalumab
Clinical PoM	Circulating leukocytes; tumor biopsies (knockdown in microenvironment)
Clinical DLT	Thrombocytopenia, liver enzyme increases
PK	Clinical $t_{1/2}$ = 2-3h (plasma); accumulates in tissues – tissue half-life > 1 week

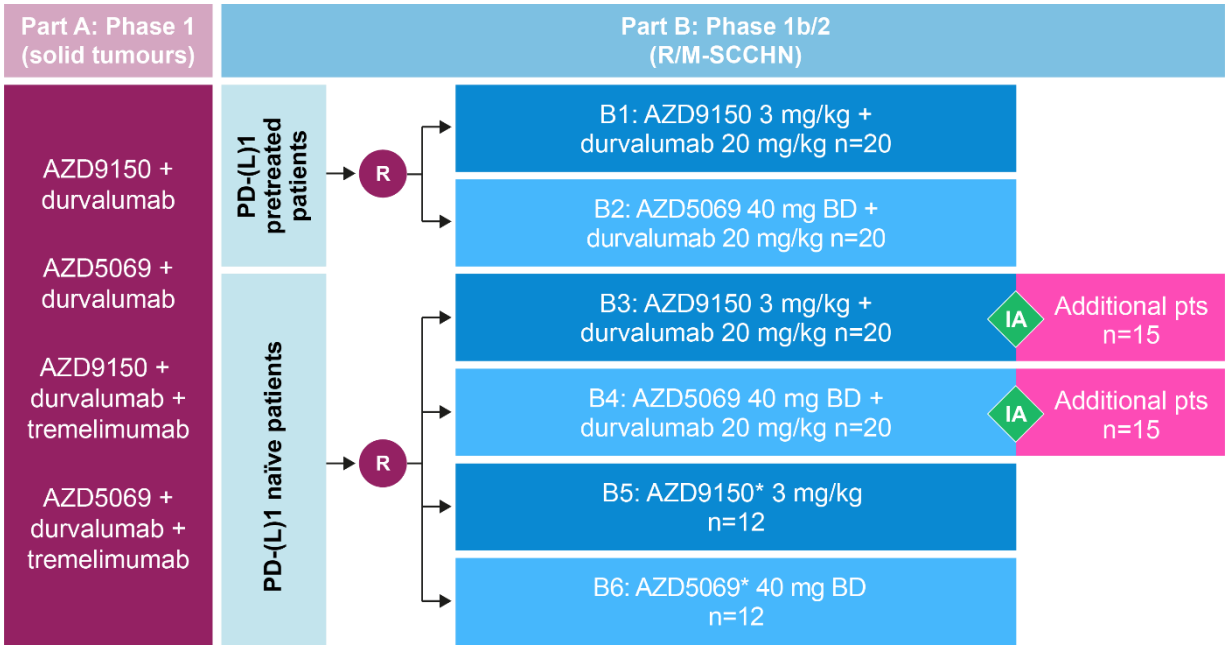


- STAT3
  - Broadly modulates immune system function
  - Contributes to immunosuppressive tumour microenvironment
  - Is inhibited in stromal and immune cells by AZD9150, an antisense oligonucleotide, with monotherapy activity in DLBCL
- AZD9150
  - STAT3 antisense oligonucleotide licensed from IONIS with broad therapeutic potential
  - Inhibits STAT3 in stromal and immune cells, activity with durable responses in R/R DLBCL and HCC populations
  - Clinical activity in multiple tumour types in combination with durvalumab
- Clinical biomarker data support an immune mechanism of action
  - On-treatment clinical samples demonstrate:
    - Intense and broad ASO staining of tumor stromal and immune cells in biopsies (DLBCL)
    - STAT3 knockdown in tumor stroma (DLBCL)
    - STAT3 knockdown and relevant gene expression changes in peripheral blood leukocytes (HCC)
- Development strategy focused on tumour-extrinsic role of STAT3
  - Offers immuno-oncology approach that may complement checkpoint inhibition
  - Pursuing phase 1b/2 trials of AZD9150 + MEDI4736 in DLBCL and HNSCC

IONIS PHARMACEUTICALS

SCORES Study Design

(STAT3 or CXCR2 in COmbination with DuRvalumab in HEad & Neck CancerS)



- Phase 1b/2:
  - Phase 1b: dose, PK, safety in solid tumours
  - Phase 2: RCT in second-line R/M-SCCHN patients
- Part B primary objectives
  - ORR
- Part B secondary objectives
  - Safety
  - DCR
  - DOR
  - PFS
  - OS
  - PK/PD

*Monotherapy arms allow addition of durvalumab on progression.

BD=twice daily; DCR=disease control rate; DOR=duration of response; IA=interim analysis; ORR=objective response rate; OS=overall survival; PD-(L)1=programmed death-(ligand) 1; PD=pharmacodynamics; PFS=progression-free survival; PK=pharmacokinetics; R=randomisation; R/M=recurrent/metastatic; RCT=randomised controlled trial; SCCHN=squamous cell carcinoma of the head and neck.

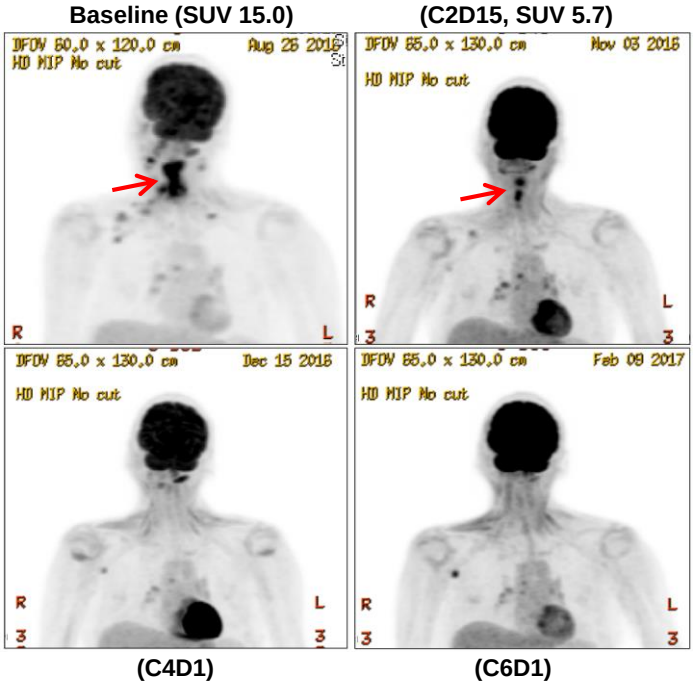
AZD9150

Response in multiple tumour types by treatment group

- **Part A (dose escalation in solid tumours)**
  - AZD9150 + durvalumab : PR in multiple tumour types and 1 CR in prostate cancer (>64 weeks on treatment)
  - AZD9150 + durvalumab + tremelimumab: PR - sarcoma at 12 weeks

- **Part B AZD9150 + durvalumab responses in R/M-SCCHN patients**

Arm	Dosed & evaluable	CR	PR	Response (%)	DCR, n/ total evaluable* (%)
B1: PD-L1 pretreated AZD9150 + durvalumab	18	1 CMR †	1	2 (11)	8/18 (44)
B3: PD-L1 naïve AZD9150 + durvalumab	28	3	5‡	8 (29)	16/28 (57)
B5: PD-L1 naïve AZD9150 monotherapy	12	0	0	0	0



Data cut-off date: 20 July 2017, unvalidated data by best response.
Images courtesy of G. Falchook
*Evaluable patients with first reassessment visit or met with an event prior to the first reassessment visit
†Complete metabolic response (CMR) by PERCIST and Illustrated in PET images here; ‡Includes 1 CR in target lesions.
C=cycle; CR=complete response; CMR=complete metabolic response; D=day; DCR=disease control rate; PD-L1=programmed death-ligand1; PR=partial response; R/M=recurrent/metastatic; SCCHN=squamous cell carcinoma of the head and neck; SUV=standardised uptake values.

AZD9150: STAT3 antisense oligonucleotide

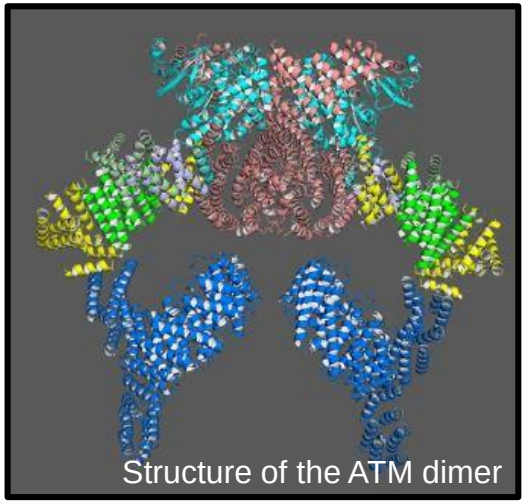
Settings not available	Comments
Monotherapy in solid tumor settings	Mechanistically unproven
Combination with PD-L1 therapy in SCCHN (1st and 2nd line metastatic), DLBCL (2nd line), bladder (1st line), NSCLC (1st line), TNBC	Core AZ development
Combination with PD-L1/CTLA-4 therapy in SCCHN (2nd line metastatic)	Core AZ development
Combination with PD-L1 therapy in advanced NSCLC, pancreatic and MSI-high CRC	Committed ESR program

Areas of Interest	Comments
I/O Combinations in settings other than unavailable ones	
Chemotherapy or radiation combinations	Dose/schedule-finding needed, with mechanistic/translational support for immune regulation in microenvironment

AZD0156

Andrew Reynolds

ATM inhibitor



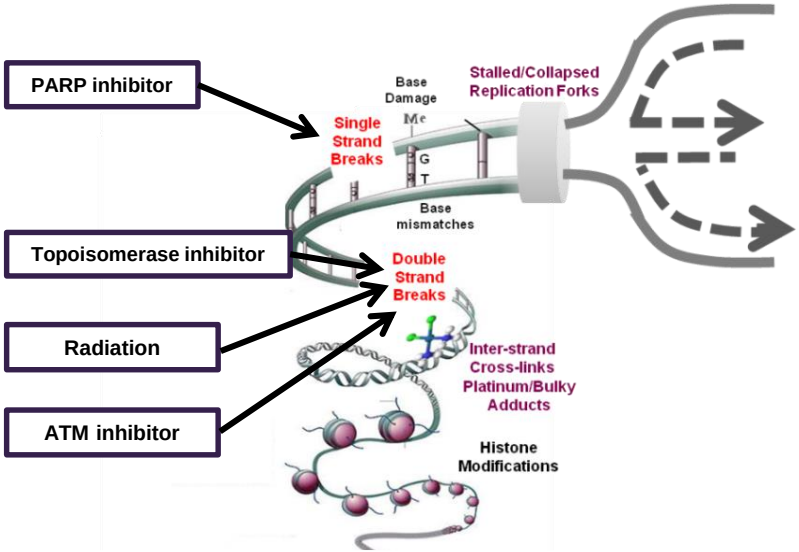
Structure of the ATM dimer

AstraZeneca

AZD0156: ATM inhibitor

Background

- ATM (ataxia-telangiectasia mutated) is a serine/threonine kinase activated by DNA double strand breaks (DSBs) and oxidative stress
- ATM coordinates the repair of DNA double strand breaks
- AZD0156 is an orally available, potent and selective inhibitor of ATM kinase activity, currently undergoing investigation in phase 1 by AZ
- Primary hypothesis for AZD0156 is to combine with agents causing double strand breaks



Current state of clinical development

Phase 1 dose escalation of AZD0156 in combination with the PARP inhibitor olaparib in solid tumours (currently underway)

- **Hypothesis:** combination of AZD0156 with olaparib should sensitise otherwise olaparib-insensitive tumours to olaparib

Phase 1 dose escalation of AZD0156 in combination with irinotecan in solid tumours (begins October 2017)

- **Hypothesis:** since irinotecan induces double strand breaks, AZD0156 should sensitise tumours to irinotecan

AZD0156: ATM inhibitor

ESR strategy: to expand scientific knowledge regarding the clinical use of AZD0156 through well-conducted research

Settings not available for collaboration :

- Paediatric tumours – not considered at this stage of clinical development
- AZD0156 in combination with olaparib
- AZD0156 in combination with irinotecan

Settings available for collaboration :

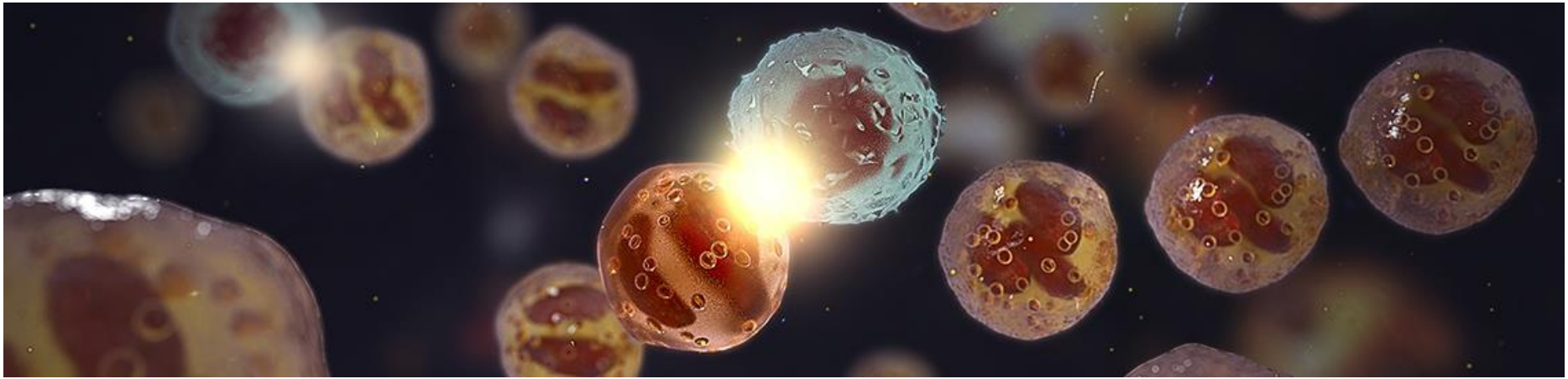
- AZD0156 monotherapy
- AZD0156 in combination with DNA damaging chemotherapy (but not irinotecan)
- AZD0156 in combination with radiation
- AZD0156 in combination with immunotherapy
- Window of opportunity studies, or other innovative study designs, with the potential to elucidate AZD0156 mechanism of action and / or discover predictive biomarkers of response for AZD0156

Additional notes:
(1) Setting could be a solid tumour type or a haematological malignancy
(2) Studies should select a well-defined patient segment supported by a strong hypothesis pertaining to why these patients would be likely to respond to an ATM inhibitor (in this regard, supporting preclinical data would be desirable)
(3) We also encourage studies with a strong translational component, with the potential to (a) elucidate mechanism of action, and / or (b) identify predictive biomarkers of response
(4) We encourage investigators to consider the line of sight – if their study was successful, what study would they do next?

AZD6738 (ATR inhibitor)

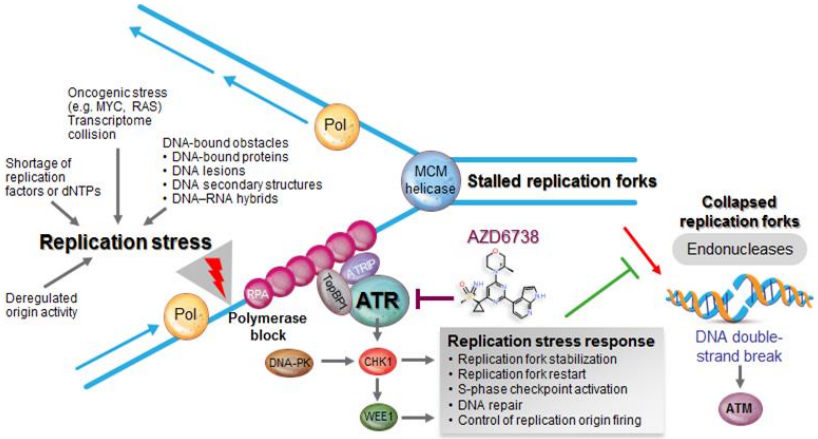
Simon Smith

October 2017



AZD6738 – ATR inhibitor

Key Data	Oral inhibitor of Ataxia Telangiectasia and Rad3 related (ATR) kinase
Primary pharmacology	ATR enzyme kinase IC_{50} = 1 nM ATR cell CHK1 pSer345 (ATR substrate): IC_{50} = 74 nM, IC_{90} = 0.67 uM
Pre-clinical DLT	Bone marrow, gastro intestinal tract
Dose range explored	AZD6738 mono-therapy: 20-240 mg BD AZD6738+carboplatin: 20-80 mg BD and 20-40 mg OD + carbo AUC5, Q21d AZD6738+olaparib: 80-240 mg OD + olaparib 100-300 mg BD Q28d AZD6738+durvalumab: 80-160 mg BD and 320 mg OD + 1500mg durva d1 Q28d; RPh2D not yet defined AZD6738+paclitaxel: 40-80 OD d1-21,160 mg OD d1-7 +paclitaxel 80 mg/m2 d1, 8, 15 Q28d; RPh2D not yet defined
Potential Ph2 regimens	AZD6738+olaparib: available AZD6738+durvalumab: available Mono-therapy
Clinical PoM	Under investigation in current study
Clinical DLT	Neutropenia, thrombocytopenia and anaemia
Clinical PK	Rapid oral absorption & half life 11-16 h



AZD6738 is an inhibitor of ATR which suppresses signalling, cell cycle checkpoints, repair and recovery from replication associated DNA damage (stalled replication), leading to collapsed replication forks and mitotic cell death

ATR is activated and signals the replication stress response caused by replicative DNA damage:
- Directly at stalled replication forks (replication stress) with long stretches of RPA coated ssDNA
- Indirectly when DNA double strand breaks (DSB) are resected into ssDNA, activating ATR

ATR controls (in response to replication stress):
- Replication fork origins firing and speed of replication fork progression to prevent collapse
- S/G2-phase cell cycle checkpoints preventing progression into mitosis and giving time for repair

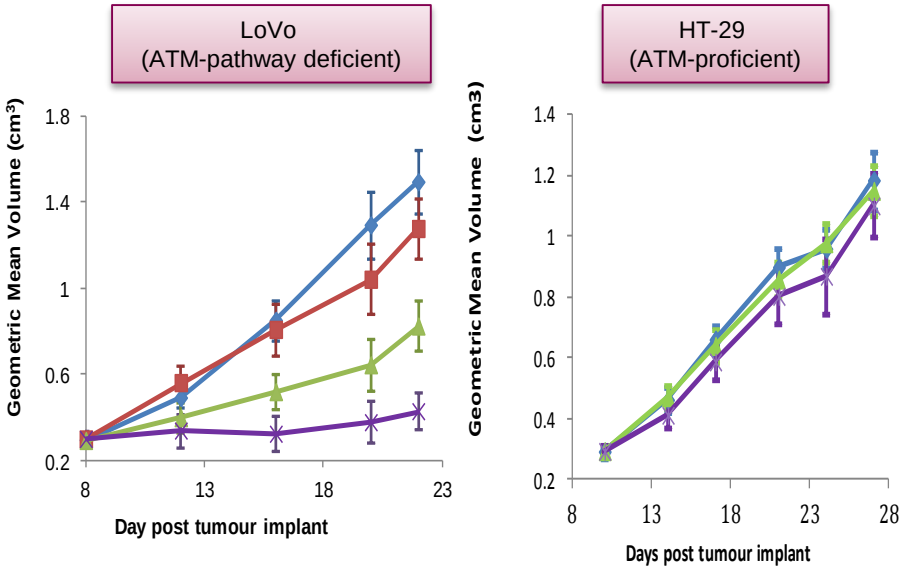
ATR inhibition leads to:
- **Single agent and combination activity** in cells with defects in ATM, cell cycle checkpoint or with high replication stress which causes an increased dependency on ATR activity for survival
- **Potential for combination with immuno-oncology agents** due to increased cell stress/death and/or neo-antigens, changes PD1/PD-L1 expression and increased IFN and immune response

CNS penetration:
Physchem, *in vitro* and rat PK data would suggest poor BBB permeability therefore AZD6738 unlikely to penetrate CNS in human

Foote *et al*. 2015, Vendetti *et al*. 2015, Kwok *et al*. 2016, Yap *et al* 2016)

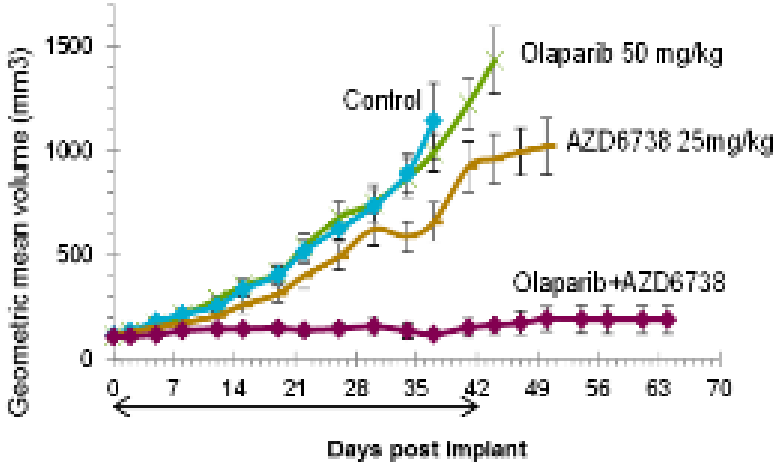
Pre-clinical evidence for activity
Mono-therapy and combinations

Monotherapy – in vivo tumour cell line xenographs



AACR Annual meeting, April 2013

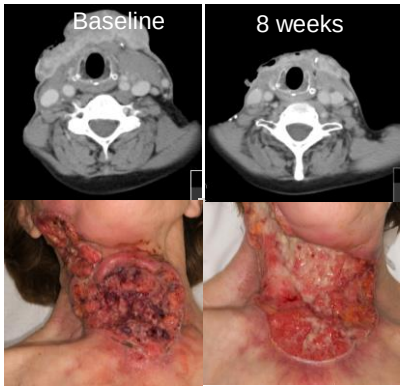
+Olaparib (PARPi) – breast primary explant xenograft



Yap et al., EORTC-NCI-AACR Molecular Targets and Cancer Therapeutics Symposium, 29 Nov-2 Dec, 2016

Evidence for activity in the clinic

AZD6738 mono-therapy 40 mg BD



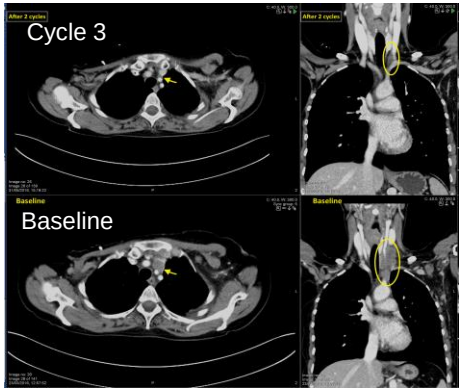
Patient (PATRIOT study)
- 55 yo female, squamous buccal cancer

Treatment
- Wide local excision & radiation
- Cisplatin + 5FU; SD at C2
- Nivolumab 8 weeks; PD at 1st scan
- AZD6738 40 mg BD continuous

Response
- Disease stabilisation (new lesion at 8 week scan)

Dillon et al., AACR Annual Meeting, April 2017

AZD6738 80mg OD d1-d7+ 200mg BD olaparib

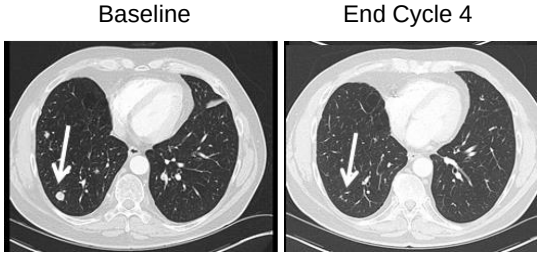


Patient (Study 4, Module 2)
- 42 yr old female, TNBCa BRCA mutant

Treatment
- Bilateral mastectomy; adjuvant FEC-T
- Palliative Carboplatin, Eribulin,
- Paclitaxel + bevacizumab
- AZD6738 80mg d1-d7 + 200mg olaparib BD continuous

Response
- C3 Scan 70% reduction, confirmed

AZD6738 80mg BD d22-28+ 1500 mg durva d1*



*with 14 d 80 mg BD AZD6738 Cycle 0

Patient (Study 4, Module 3)
- 59 yo male, stage IV adeno of right upper lobe
- EGFR dual exon 20 muts (non-sensitizing); Alk negative; KRAS wt

Treatment
- Cisplatin and vinorelibine, pemetrexed

Response
- 59% reduction in tumour size cf baseline at 1st scan
- Scan at end of cycle 6 indicates CR – TBC

Yap et al., EORTC-NCI-AACR Symposium, Dec, 2016

AZD6738 clinical development
Core program

Study 4: modular phase I protocol exploring combinations (ongoing)

- Dose finding: +carboplatin, +olaparib, +durvalumab
- Expansions +olaparib: ATM-def & ATM-prof 2nd line gastric cancer; BRCAm & non-HRRm triple-negative breast cancer (TNBCa)

Study 7: window study in head & neck cancer (ongoing)

Effects of DDR inhibitors on target-related and immune (tumour & peripheral blood) biomarkers

Study 8: randomised Ph2B in TNBCa stratified by BRCAm, HRRm & non-HRRm disease (to begin shortly)

Olaparib vs. Olaparib+AZD6738 vs. Olaparib+AZD1775

ACE-CL-101: AZD6738+acalabrutinib in CLL (to begin shortly)

- AZD6738 monotherapy in R/R CLL
- AZD6738+acalabrutinib in R/R CLL

AZD6738 clinical development
ESR program (inc. baskets)

Ongoing

1. Study 2/PATRIOT (PI: Kevin Harrington, London): monotherapy and RT combination in solid cancers
2. Study 6 (PI: Jeeyun Lee, Seoul): dose escalation with weekly paclitaxel

Planned/committed

- +Olaparib combination in a variety of tumour types
- +Durvalumab combination in a variety of tumour types
- +Paclitaxel combination
- Mono-therapy in a variety of tumour types
- Other: mechanistic studies

AZD6738 clinical development
Opportunities for new concepts

Based on established recommended phase 2 doses

a) +Olaparib combinations
b) +Durvalumab combinations

Other combinations (supported by pre-clinical evidence &/or strong rationale)

c) DDRi-AZD6738 combinations

Mono therapy

d) Exploration of novel patient selection biomarkers

Specific populations/biomarkers

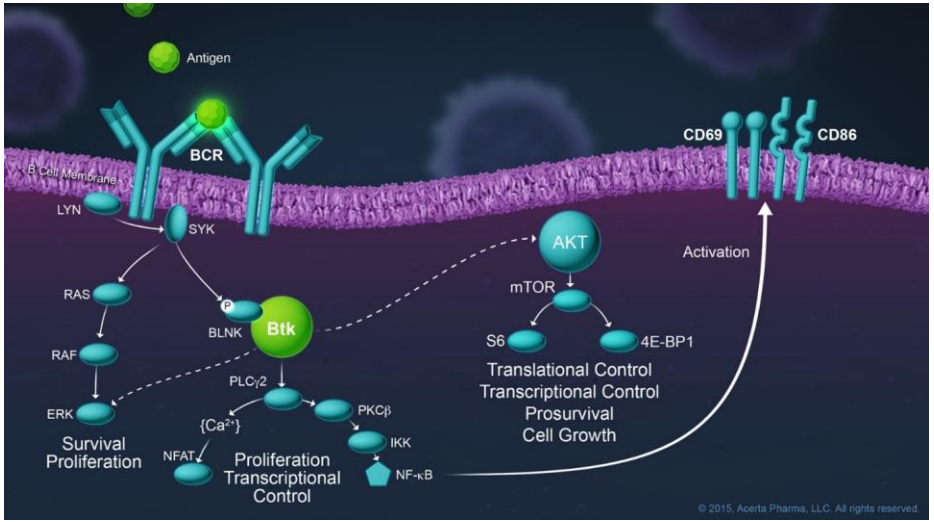
e) Tumours with high replication stress
f) Tumours with high mutation burden

All concepts should be supported by a strong scientific rationale and (ideally) a pre-clinical platform of evidence; feasibility assessment, especially to recruitment timelines; clear pathway to registration; and complementarity to the ongoing and planned clinical development program

Acalabrutinib

Edwin Clark

BTK inhibitor



Acalabrutinib: BTK inhibitor

Background

Mechanism of action

- Acalabrutinib is a potent and highly selective covalent Bruton Tyrosine Kinase (BTK) inhibitor with efficacy reported in CLL patients
- Potency in BCR-mediated activation (CD69) of peripheral B cells in human whole blood assay: EC_{50} = 9.2 nM

Hypotheses

- Core hypothesis: efficacy of acalabrutinib driven direct effects on tumor B cells and integrity of the tumor micro-environment
- Other hypotheses: altered tumor immune response due to direct effects on BTK in myeloid cells. The regimen yields a higher degree of target coverage.

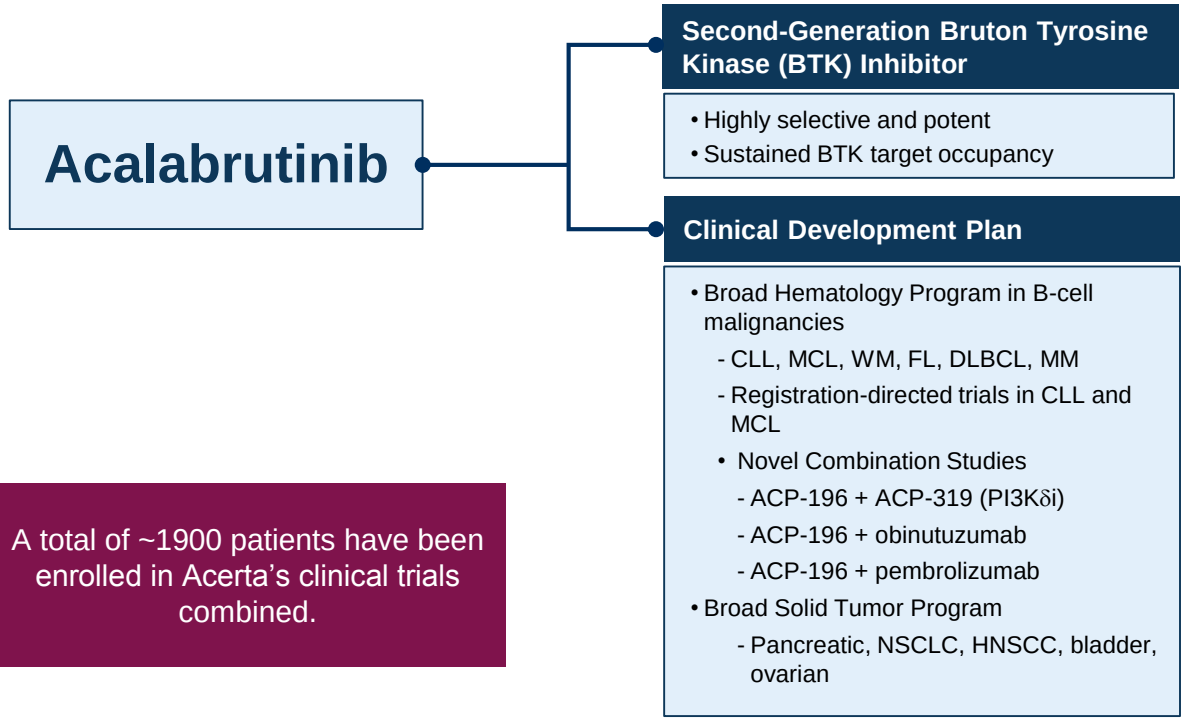
Pre-clinical evidence of anti-tumour activity – reasons to believe

- Monotherapy : Acalabrutinib is active in preclinical models of CLL, DLBCL, MCL
- Combination : Acalabrutinib showed synergistic effects in combination with cell death agents in B-cell malignancy xenograph models

Clinical evidence – reasons to believe

- Reference**:** *Acalabrutinib (ACP-196) in Relapsed Chronic Lymphocytic Leukemia* N Engl J Med 2016; 374:323-332 January 28, 2016 DOI: 10.1056/NEJMoa15099

Acalabrutinib Development Program



A total of ~1900 patients have been enrolled in Acerta's clinical trials combined.

Acalabrutinib: BTK inhibitor

ERCC strategy

Settings available for collaboration

- Combinations with novel agents, including chemo-free combinations, based on scientific hypotheses
- Define molecular signatures and patient subtypes
- New tumor models (hematologic malignancies) for acalabrutinib
- Biomarker/pathway discovery using primary human samples
- Model directed MRD or tumor/microenvironment interactions
- Mechanistic studies of BTK biology
- Address resistance mechanisms

Settings not available for collaboration

- Research questions duplicative of ongoing or planned nonclinical research or previously approved MTAs/SRAs
- Head-to-head studies of acalabrutinib vs ibrutinib (or other BTK inhibitors) where the goal is proof-of-concept
- Studies using samples from acalabrutinib phase 3 studies

Immunotherapy

AstraZeneca
What science can do

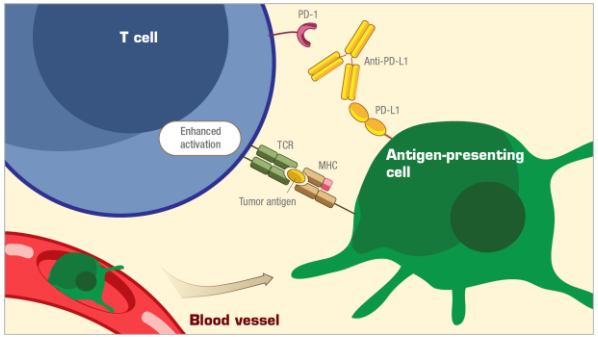
Durvalumab (IMFINZI) – anti-PD-L1

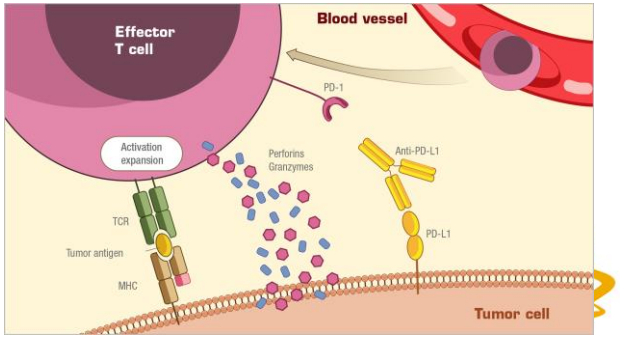
- PD-L1 is a cell-surface protein that binds to the receptors PD-1 and CD80 on activated T cells, B cells, and other myeloid cells. PD-L1 binding to PD-1 on activated T cells has been found to interfere with T-cell proliferation and to inhibit immune responses.[1] Overexpression of PD-L1 on cancer cells and solid tumors may allow these cells to avoid immune detection and elimination[2]

- Durvalumab is an investigational anti-PD-L1 mAb, designed to bind PD-L1 and reduce the interaction between PD-L1 and its receptors. Durvalumab is being evaluated for its potential effects on NSCLC, HNSCC, solid tumors, and various cancers.

Tumor	Setting	Regimen	Phase	Trial identifier
NSCLC	1L (MYSTIC)	Durvalumab ± tremelimumab	III	NCT02453282
	1L (NEPTUNE)	Durvalumab + tremelimumab	III	NCT02542293
	1L advanced	Durvalumab, SoC	III	NCT03003962
	1L (POSEIDON)	Durvalumab ± tremelimumab + platinum-based CT, SoC CT	III	NCT03164616
	1L (PEARL)	Durvalumab, platinum-based CT	III	NCT03003962
	Stage IV	Durvalumab + tremelimumab ± platinum-based CT	II	NCT03057106[a]
	3L+ (ARCTIC)	Durvalumab, tremelimumab, durvalumab + tremelimumab	III	NCT02352948
	2L+ NSCLC (Study 006)	Durvalumab + tremelimumab	Ib	NCT02000947
	Adjuvant±	Durvalumab	III	NCT02273375[a]
	Stage 3 (PACIFIC)	Durvalumab	III	NCT02125461
SCLC	1L Extensive-stage SCLC (CASPIAN)	Durvalumab + platinum-based chemotherapy ± tremelimumab	III	NCT03043872
	Platinum-refractory extensive stage (BALTIC)	Durvalumab + tremelimumab, AZD1775 + carboplatin	II	NCT02937818
HNSCC	1L/2L (Study 11)	Durvalumab + tremelimumab	I	NCT02262741
	2L PD-L1+ (HAWK)	Durvalumab	II	NCT02207530
	2L PD-L1- (CONDOR)	Durvalumab, tremelimumab, durvalumab + tremelimumab	II	NCT02319044
	2L (EAGLE)	Durvalumab ± tremelimumab	III	NCT02369874
	1L (KESTREL)	Durvalumab ± tremelimumab	III	NCT02551159
	1L/2L(SCORES)	AZD9150 ± durvalumab, AZD5069 ± durvalumab	Ib/II	NCT02499328

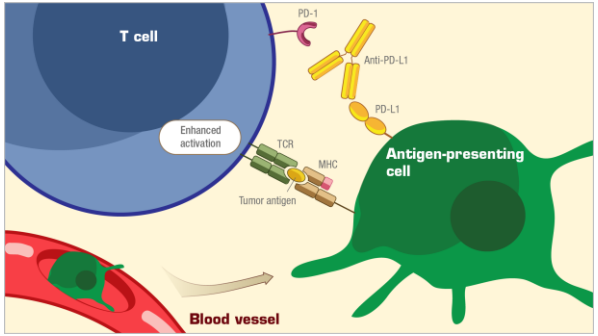
[a] These are Canadian Cancer Trials Group Trials (www.ctg.queensu.ca)

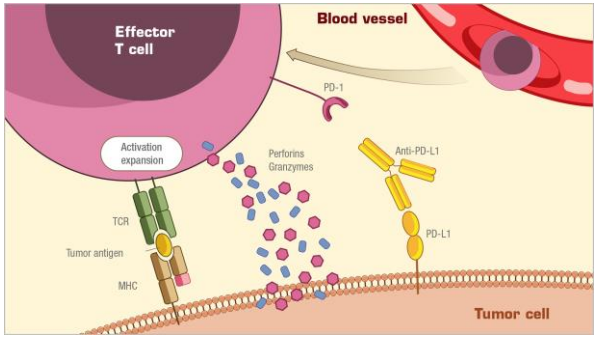




Durvalumab (IMFINZI) – anti-PD-L1 (continued)

Tumor	Setting	Regimen	Phase	Trial identifier
Gastric	2L+	Durvalumab, tremelimumab, durvalumab + tremelimumab	Ib/II	NCT02340975
Advanced solid tumors	(Study 1108)	Durvalumab	I/II	NCT01693562
	(STRONG)	Durvalumab ± tremelimumab	III	NCT03084471
		Durvalumab ± tremelimumab	I	NCT02537418[a]
Bladder	1L (DANUBE)	Durvalumab ± tremelimumab	III	NCT02516241
	DUART	Durvalumab + RT	Ib/II	NCT02891161[b]
		Durvalumab	II	NCT02901548[c]
Pancreatic Ductal Adenocarcinoma	2L (EVERST)	Durvalumab ± tremelimumab	II	NCT02558894
		Durvalumab + AZD5069, durvalumab + chemotherapy	Ib/II	NCT02583477
Diffuse Large B-Cell Lymphoma	2L/3L	Durvalumab, durvalumab + tremelimumab, durvalumab + AZD9150	Ib	NCT02549651
HCC	Unresectable HCC	Durvalumab, tremelimumab, durvalumab + tremelimumab	III	NCT02519348
MDS	2L	Durvalumab + azacitidine, durvalumab + tremelimumab, and durvalumab + tremelimumab + azacitidine	I	NCT02117219





Durvalumab (IMFINZI) – anti-PD-L1: Areas of Interest

Developmental Stage	Phase III
Availability	Open to expressions of interest. Proposals will be prioritised based on scientific merit and fit with the core development program and the Global Medical Affairs strategies for Externally Sponsored Research
Dosing	A recommended fixed dose of 1500mg q4 weekly

Settings of Interest	• NSCLC (early stage and advanced), SCLC, HNSCC (locally advanced and recurrent/metastatic), Urothelial Carcinoma, GI cancers (hepatocellular, pancreatic, oesophageal, gastric, biliary tract, CRC), Triple Negative Breast Cancer (TNBC) and other tumours with credible scientific rationale
	• combinations or sequencing with chemotherapy, radiation, other IO therapies, novel targeted agents
	  • data generation in special populations
	  • evidence in post-IO treatment settings
	  • understanding safety, irAEs and the MOA in depth
	  • understanding mechanisms of resistance
	  • exploration of biomarkers for efficacy

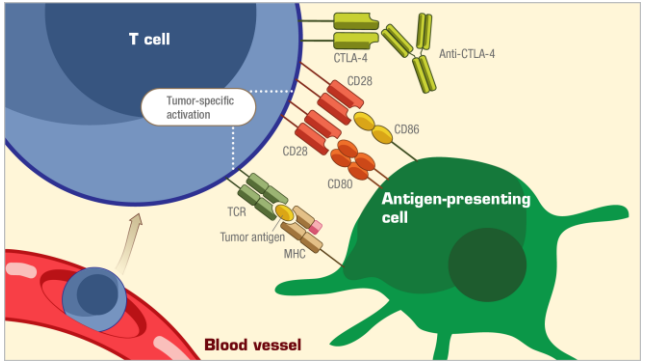
Settings out of Scope	• Proposals that duplicate or contradict AZ pivotal registration programs (past and present) • Proposals that are intending to compare durvalumab-based regimens head to head with other IO-based regimens • Proposals that are seeking to investigate alternative dosages and administration outside of the pivotal registration programs

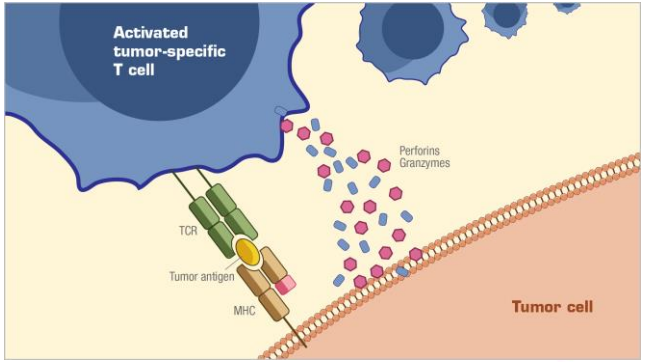
Tremelimumab (anti-CTLA-4)

- CTLA-4 is expressed exclusively on the surface of T cells.[1] CTLA-4 serves to inhibit T-cell activation through delivery of inhibitory signals and through ligand competition with the co-stimulatory receptor, CD28[1,2]
- Inhibition of CTLA-4 can shift the balance of signaling in the immune system in favor of greater T-cell activation, engendering a greater immune response and potentially resulting in the rejection of tumor by the host's immune system[2]
- Tremelimumab is an investigational anti-CTLA-4 mAb that is being clinically evaluated in combination with durvalumab (PD-L1 inhibitor) for the potential treatment of cancer

Tumor	Regimen	Phase	Trial identifier
Advanced solid tumors	Tremelimumab	II	NCT02527434

Developmental Stage	Phase III (only in combination with durvalumab)
Availability	open to expressions of interest for combination studies with durvalumab. Proposals will be prioritised based on scientific merit and fit with the core development program and GMA ESR strategies
Dosing	A recommended fixed dose of 75mg q4 weekly in combination with durvalumab 1500 mg q4 weekly
Settings of Interest	biomarker-driven and translational investigations and studies that provide potential for understanding tremelimumab
Settings out of Scope	• Proposals exploring monotherapy Tremelimumab • Proposals seeking to combine Tremelimumab with other IO therapies other than Durvalumab





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