

Meet AZN management: ASCO 2019

Breakout 3: early-stage pipeline

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Rich early to mid-stage pipeline

Tumour drivers and resistance

capivasertib (AKT¹ inhibitor)

- breast, prostate cancers, Phase III to start

AZD9833 (SERD², oral)

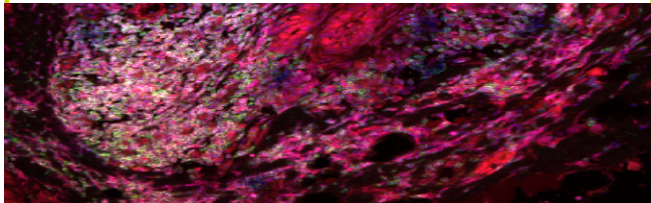
- breast cancer, Phase I

AZD5991 (MCL1³ inhibitor)

- haematologic cancers, Phase I

savolitinib (cMET⁴)

- NSCLC, Phase II



DNA damage response (DDR)

adavosertib (WEE1⁵ inhibitor)

- solid cancers, Phase II

ceralasertib (ATR⁶ inhibitor)

- solid cancers, Phase II

AZD2811 (aurora kinase B inhibitor)

- solid cancers, Phase II

AZD1390 (ATM⁷ inhibitor)

- solid cancers, Phase I

AZD7468 (DNA-PK⁸)

- solid cancers



Immuno-oncology (IO)

monalizumab (NKG2A⁹ mAb¹⁰)

- head & neck, colorectal, Phase II ongoing

MEDI5752 (PD-1/CTLA-4 bispecific mAb)

- solid cancers, Phase I

olecumab (CD73¹¹ mAb)

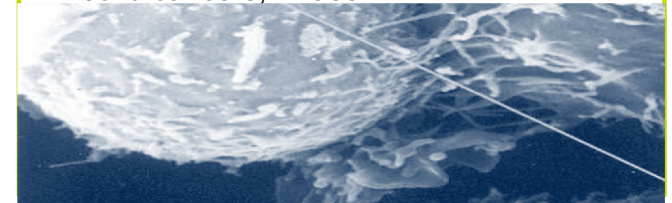
- lung, pancreatic cancers, Phase I/II

AZD4635 (A2aR¹² inhibitor)

- solid cancers, Phase II

AZD9150 (STAT3¹³ inhibitor)

- solid cancers, Phase II



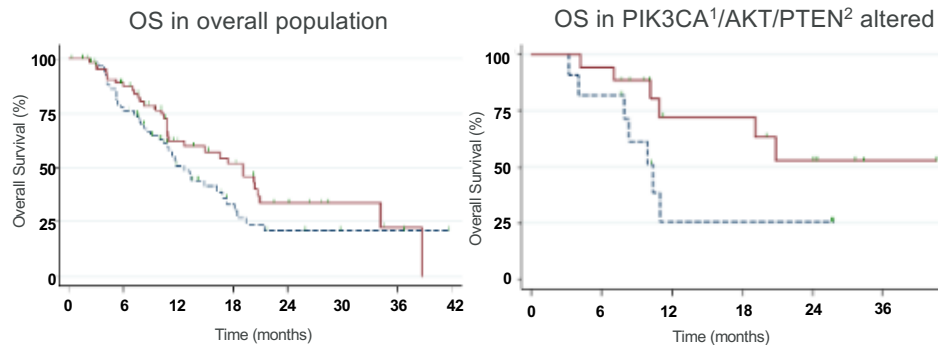
1. Protein kinase B 2. Selective oestrogen receptor degrader 3. Induced myeloid leukaemia cell differentiation protein 4. tyrosine-protein kinase Met 5. Tyrosine kinase WEE1 6. Ataxia telangiectasia and rad3-related kinase 7. Ataxia-telangiectasia mutated protein kinases 8. DNA-dependent protein kinase 9. Inhibitory cell surface receptor covalently bound to CD94 10. Monoclonal antibody 11. 5'-nucleotidase 12. Adenosine A2A receptor 13. Signal transducer and activator of transcription 3.



Tumour drivers and resistance: early breast

Building on an established franchise

Capivasertib (AZD5363): targeting AKT



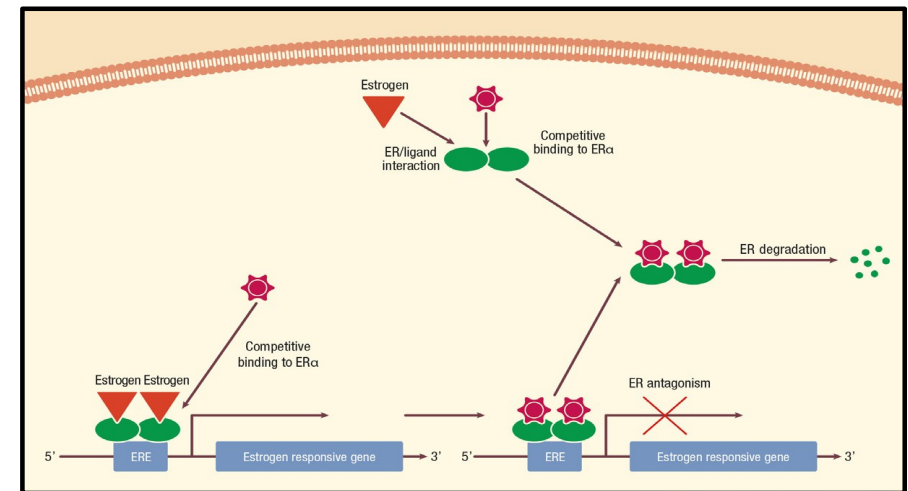
Early evidence of enhanced benefit with capivasertib + paclitaxel in altered metastatic TNBC³

ASCO 2019 data on Tuesday 4 June 2019, abstract #1005:

- OS⁴ HR⁵ 0.57 in the ITT⁶ population

Phase III to initiate

AZD9833 (SERD, oral)



Phase I ongoing
Phase II in planning

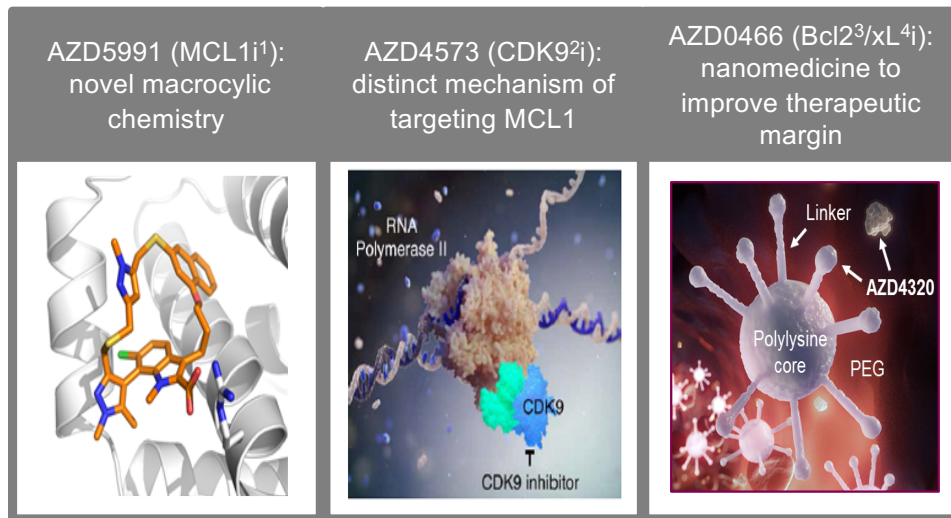
1. Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha 2. Phosphatase and tensin homolog.
3. Triple-negative breast cancer 4. Overall survival 5. Hazard ratio 6. Intention to treat.
Source: ASCO 2018.



Tumour drivers and resistance: cell death

Haematologic cancers the next wave of innovation

Targeting distinct nodes of cell death



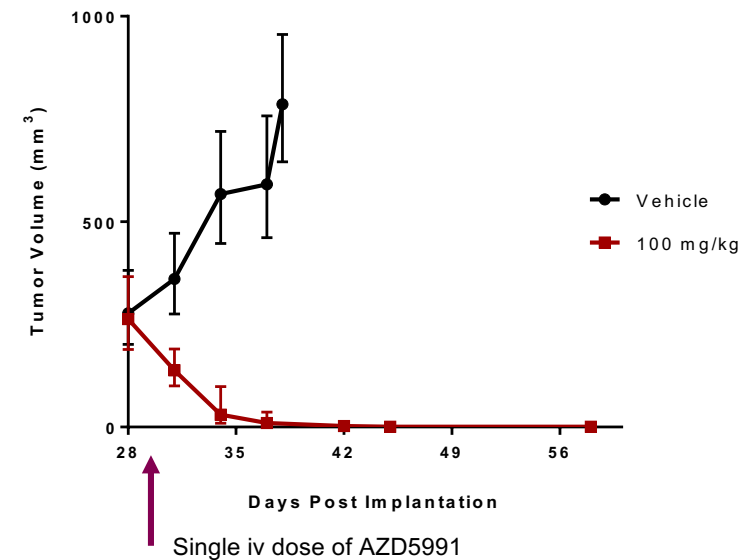
AZD5991 in Phase I

1. Inhibitor.
2. Cyclin-dependent kinase 9.
3. B-cell lymphoma 2.
4. B-cell lymphoma-extra large.

5

AZD5991 (MCL1 inhibitor)

Single dose of AZD5991 achieves tumour regression in haematological cancer preclinical models

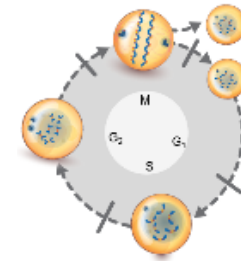


Source: Tron AE et al, *Nature Communications* (9):5341 (2018).



DNA damage response: *Lynparza* and beyond

Developing chemo-free regimens, extending survival



Launch adavosertib (WEE1) /
ceralasertib (ATR) *Lynparza*
combinations

Expand *Lynparza* beyond
BRCA (prostate cancer,
ovarian cancer)

Establish *Lynparza*
leadership as monotherapy

Launch *Lynparza*
combinations (VEGF¹, IO)

Deliver next-generation
DDR medicines:
AZD1390 (ATM inhibitor),
AZD2811 (aurora kinase B
inhibitor)
AZD7648 (DNA-PK)

Scientific leadership in DDR

2016 - 2018

2019 - 2021

2022 - 2025

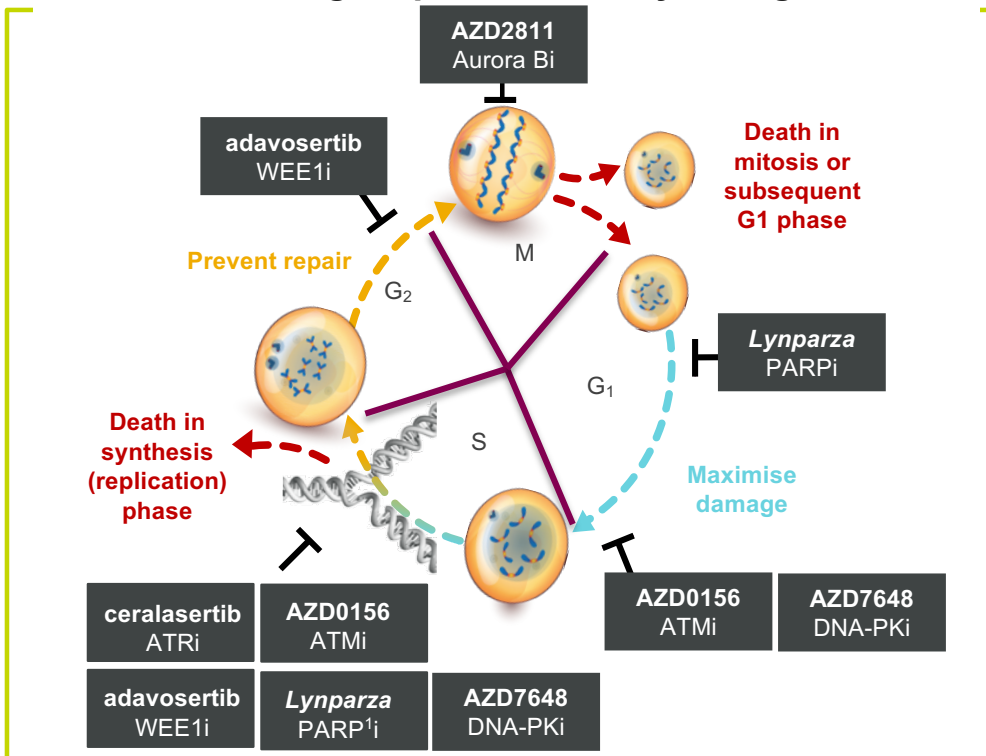
1. Vascular endothelial growth factor.



DNA damage response: pipeline

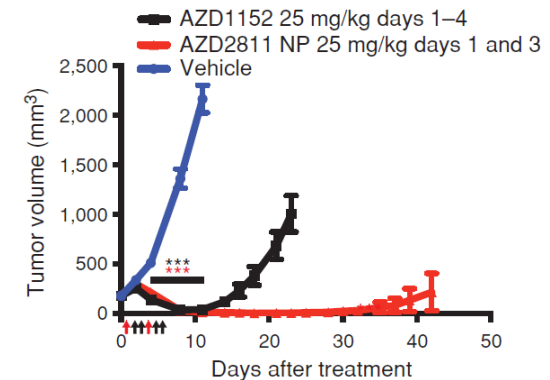
The next wave of potential DDR medicines

A broad pipeline targeting complementary aspects of DNA damage repair and cell cycle regulation



1. Poly (ADP-ribose) polymerase.
G1 – growth, S – DNA synthesis, G2 – Growth and preparation for mitosis M – Mitosis.

AZD2811: targeting Aurora Kinase B



Monotherapy activity in SCLC¹ model *in vivo*

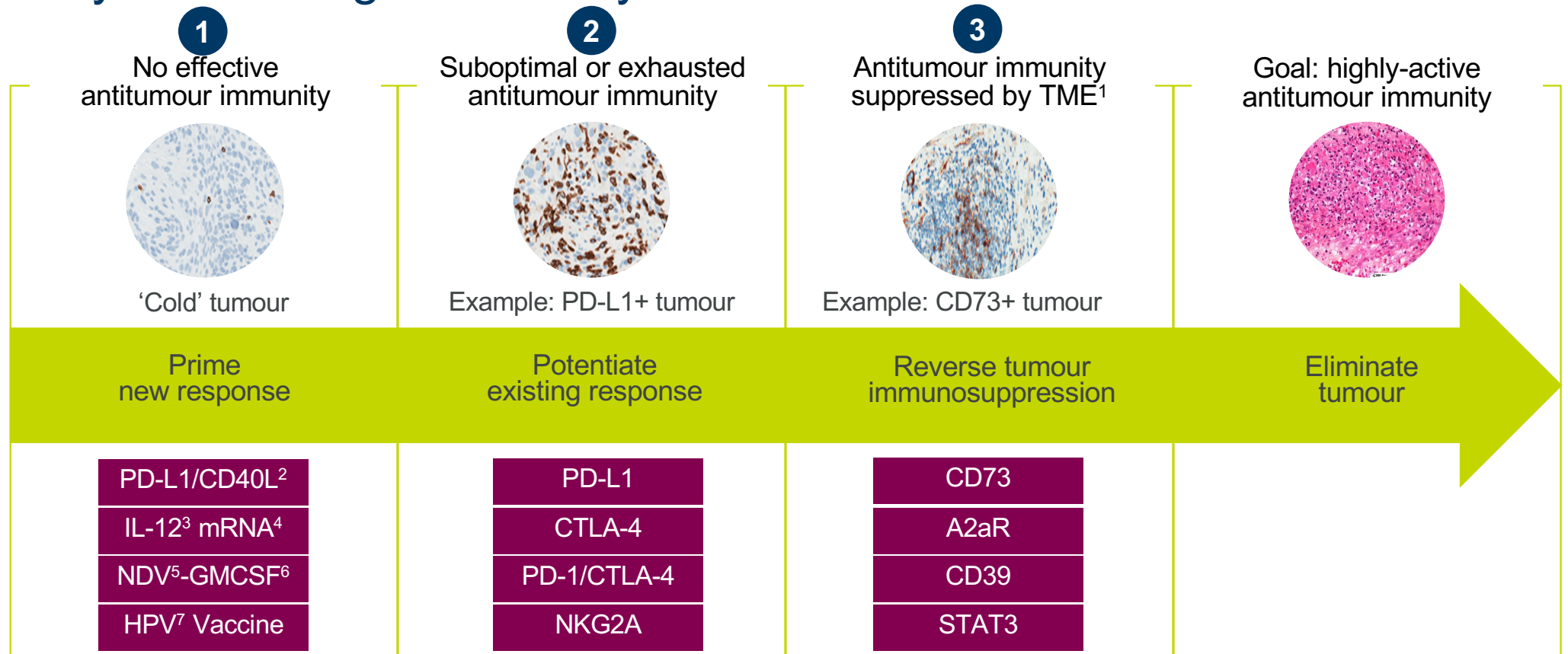
Phase I ongoing
Phase II start in planning

1. Small cell lung cancer.
Source: Ashton et al, AACR, 2017.



Broad IO pipeline: enhancement of antitumour immunity

Fully harnessing immune system to eliminate tumours



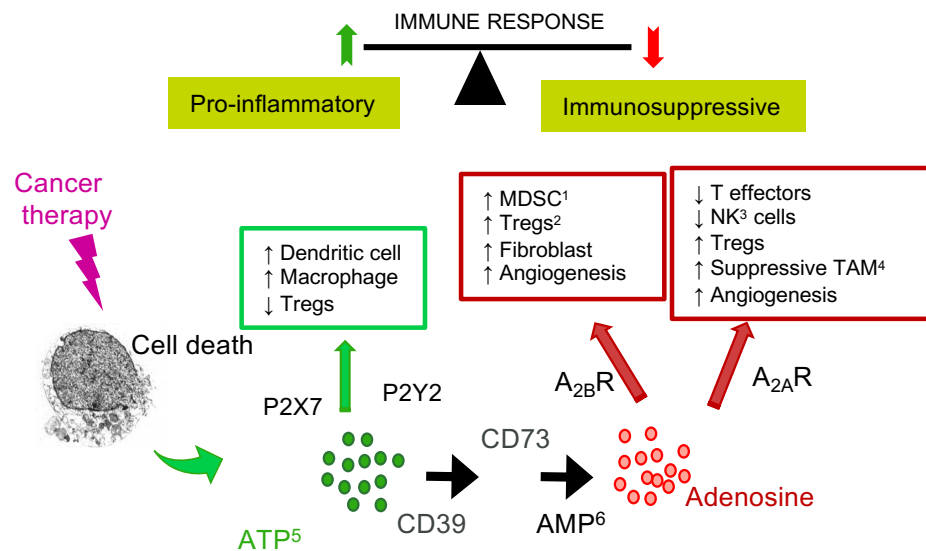
1. Tumour micro environment 2. Cluster of differentiation 40 ligand 3. Interleukin-12 4. Messenger RNA 5. Recombinant Newcastle disease virus 6. granulocyte-macrophage colony-stimulating factor 7. Human papilloma virus.



Developing an adenosine franchise

Reversing tumour immunosuppression

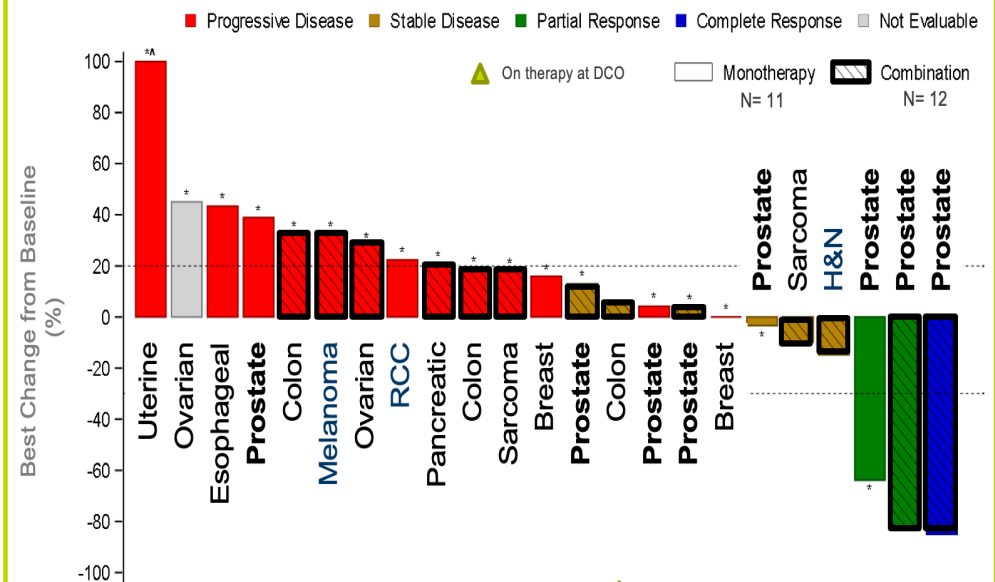
Targeting adenosine pathway



Multiple projects aimed at full suppression

1. Myeloid-derived suppressor cells 2. Regulatory T cells 3. Natural killer cells 4. Tumour-associated macrophages 5. Adenosine triphosphate 6. Adenosine monophosphate.

AZD4635: targeting A2aR



Phase I ongoing
Phase II in planning

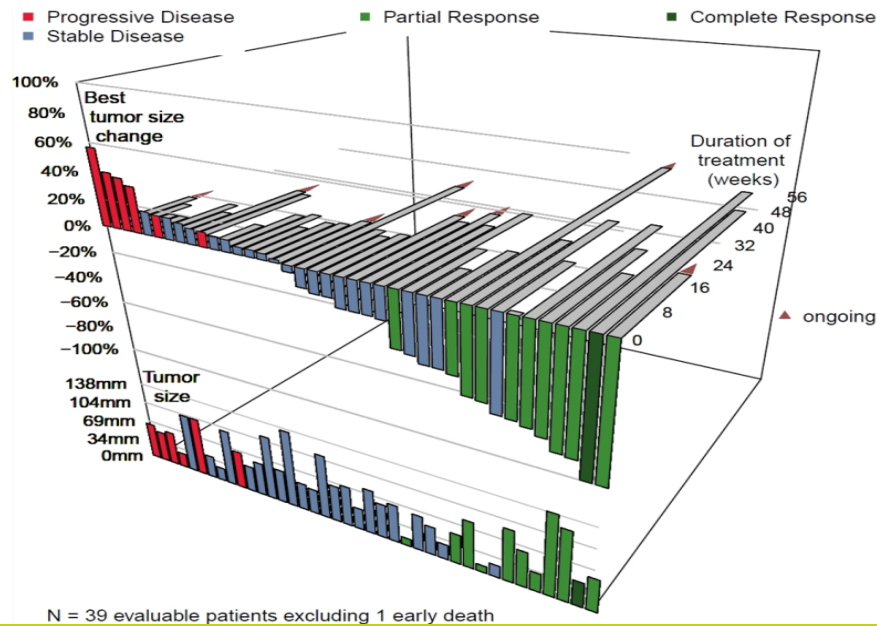
RCC: renal cell carcinoma.
H&N: head and neck cancer.
Source: Merchant et al AACR 2019.



Next-generation checkpoints

Utilising the innate and adaptive immune system

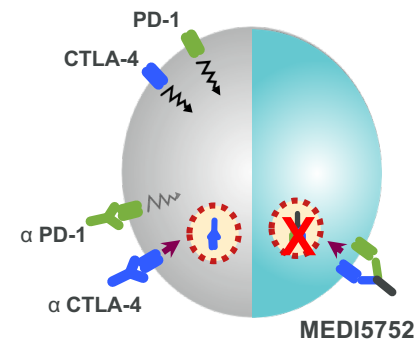
Monalizumab: targeting NKG2A



Phase II ongoing
Phase III in planning

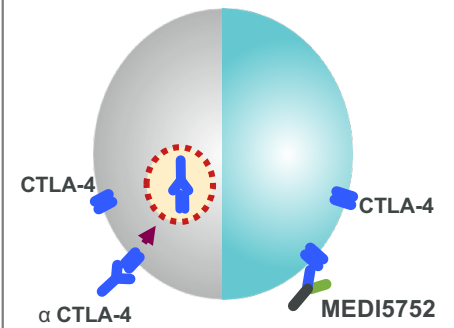
MEDI5752: PD-1/CTLA-4 bispecific

Tumour: increased efficacy



Internalisation and degradation of PD-1 leads to complete and durable blockade of PD-1 and CTLA-4 in the TME

Periphery: increased safety



Mitigated toxicity due to reduced binding to CTLA-4+ peripheral T cells

Phase I ongoing
Phase II in planning

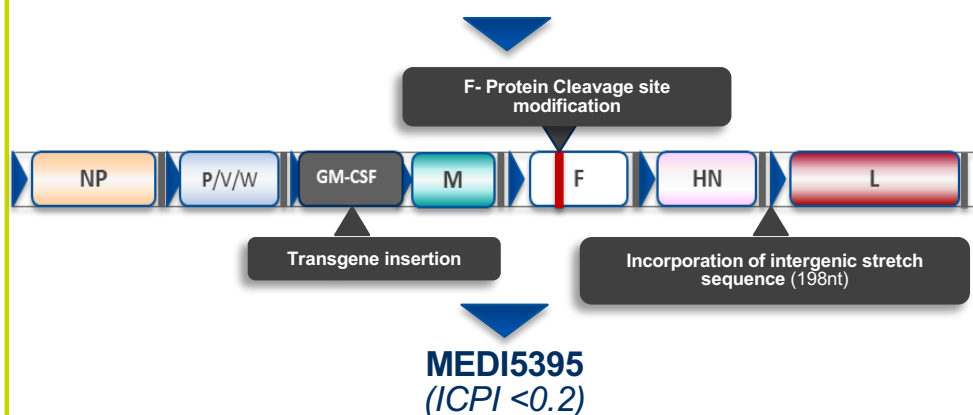


Oncolytic viruses offer multiple mechanisms of action

Leveraging internal and external expertise

MEDI5395: NDV-GMCSF

Not a select agent; suitable for world-wide development



Intracerebral pathogenicity index scale (ICPI): <0.4 is non-pathogenic

Phase I in planning

Collaboration with Transgene

- 1 IFN¹ γ production, Th²1 education
- 2 T cell memory and homeostasis
- 3 Activation of APC³s
- 4 Immune priming and APC activation
- 5 Increase lysis & Type I IFN response

Collaboration of five oncolytic viruses

1. Interferon.
2. T helper.
3. Adenomatosis polyposis coli.

Source: Cheng et al, J.Virol 2016 (11).



Q&A



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