

**AstraZeneca Webinar**

**Friday 3rd November, 2017 14:00 – 1530**

**Q&A**

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| **AZD9150 – STAT3 antisense oligonucleotide – Esha Gangolli** |
| NB: AZD9150 not available before Q4’2018 This will not pose a problem given the schedule, i.e., February 2018 workshop, May 2018 CRC submission, November 2018 CRC meeting, open trial by November 2019  |
| Q. Do you know the sarcoma sub-type that responded to the combination? (Sandra Strauss) |
| 1. Esha Gangolli to follow up (Post-meeting response: We don’t have pathology yet to subtype the sarcoma. However, we know that it arose in a previously irradiated field. )
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| Q. What are the implications for inhibiting STAT3 directly in haematological malignancies? (Oliver Ottmann) |
| 1. AZ don’t have the data beyond DLBCL to suggest it is not possible. It would be dependent on the trial and would need to investigate the mechanistic aspects.
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| Q. What in-vitro work would need to be done for haematological indications or is it only human studies? (Oliver Ottmann) |
| 1. Preclinical experiments to support mechanistic rationale would be great, if relevant models are available.
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| Q. How do you detect uptake and which cells are targeted? (Martin Dyer) |
| 1. Immunohistochemistry for oligonucleotide was performed in the limited number of paired biopsies from the lymphoma trial. Biopsy showed very little uptake in the tumour cells at the tolerated doses. Uptake was seen in the stroma and endothelium. Lymphoma blood samples also show upregulation of several genes in the IFN signature, previously associated with response to checkpoint inhibition. Similar work is ongoing in the SCCHN trial. . Preclinical experiments show that AZD9150 decreases arginase levels and CD163 macrophages in a number of different tumour types.
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| Q. Do you see much uptake in the reticuloendothelial cells? (Suzy Scholl)  |
| 1. Uptake is seen in endothelium, fibroblasts and infiltrating inflammatory cells of the tumour stroma in DLBCL samples. We have not further typed these cells.
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| **AZD0156 – ATM inhibitor – Andrew Reynolds** |
| Q. Are there any ongoing RT trials at the moment?  |
| 1. No
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| Q. For window of opportunity studies what biomarker would we use to monitor ATM inhibition? (Carlo Palmieri) |
| 1. AZ able to share this information under CDA
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| Q. You mentioned ARID1A as a biomarker, what about ARID1B or 2? (Suzy Scholl) |
| 1. Expected to confer if hypothesis stands up. Defects in pathways involved in DNA repair
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| Q. Ph1 trial has been going for 2 years – have you seen toxicity as a single agent? (Martin Dyer) |
| 1. Olaparib combination is currently in the dose escalation stage currently exploring the dose and schedule. RP2D is expected Q3’2018. The toxicity profile would be available under CDA.
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| **AZD6738 – ATR inhibitor – Simon Smith** |
| Q. Would you expect ATM mutation in these tumours? (Rille Pihlak) |
| 1. This is one of the areas AZ are looking at
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| Q. What is the lowest age of study entry you would consider? (Sandra Strauss) |
| 1. Usually 18+. AZ need to clarify.
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| **Acalabrutinib – BTK inhibitor – Edwin Clark** |
| NB: recently received accelerated approval for MCL(mantle cell lymphoma) |
| **Durvalumab (IMFINZI) – anti-PD-L1 – Asud Khaliq** |
| Q. Do AZ have any interest in Glioma? (Matt Williams) |
| 1. Glioma is not high on the radar; not high but not low priority and therefore would consider a EOI with strong scientific rationale
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| Q. Would AZ consider relapsed Glioma; rear radiation + X? (Matt Williams) |
| 1. Very much of interest. RT plays a fundamental role in changing the tumour microenvironment and would be worth considering
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| Q. Would AZ consider cancers of unknown primary with chemo +/- Durva? |
| 1. AZ have an ongoing ESR trial but would consider a proposal if scientifically sound
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