Champions' Patient-Derived Xenograft (PDX) Models for Evaluating Novel Therapeutics Targeting the DNA Damage Response Mechanism

Cells have evolved numerous redundant mechanisms to repair damage to genomic DNA resulting from intracellular processes including replication stress, inappropriate nuclease activity, and metabolic generation of reactive oxygen species, as well as exogenous insults from exposure to genotoxic agents such as ultraviolet light and DNA damaging chemicals[1]. These can all lead to senescence, mitotic catastrophe, and eventually apoptosis.

A number of agents have been approved or are in development targeting DNA repair pathway components. Most prominent among these are the PARP inhibitors, including olaparib (AZ), rucaparib (Clovis), niraparib (Tesaro), and talazoparib (Pfizer), which have been approved for treating BRCA-mutated breast and ovarian tumors. The next generation of therapies is focused on additional molecules in the DNA repair family, such as ATR (e.g. VX-970), ATM (e.g. AZD0156), WEE1 (e.g. Adavosertib), and CHK1 (e.g. MK8776). Of great current interest are inhibitors of DNA-PKc (DNA-dependent serine/threonine protein kinase catalytic subunit). Within this landscape, AstraZeneca has developed a potent and selective inhibitor of DNA-PKc, AZD7648, and tested it in combination with the PARP inhibitor olaparib against a variety of cell line and patient-derived xenografts with different DNA repair deficiency backgrounds[2].

AZD7648 had little to no effect on BRCA-deficient cell lines (data not shown). Nevertheless, PARP inhibitors may also be effective against tumors harboring so-called "BRCA-like aberrations" in other molecules of the homologous recombination repair pathway, such as ATM or ATR1. Treatment of an isogenic head and neck cell line xenograft lacking ATM with AZD7648 and olaparib as monotherapies had no effect, whereas, in contrast, combining the two therapies together induced complete and sustained regression, even following cessation of therapy *(Figure 1).*

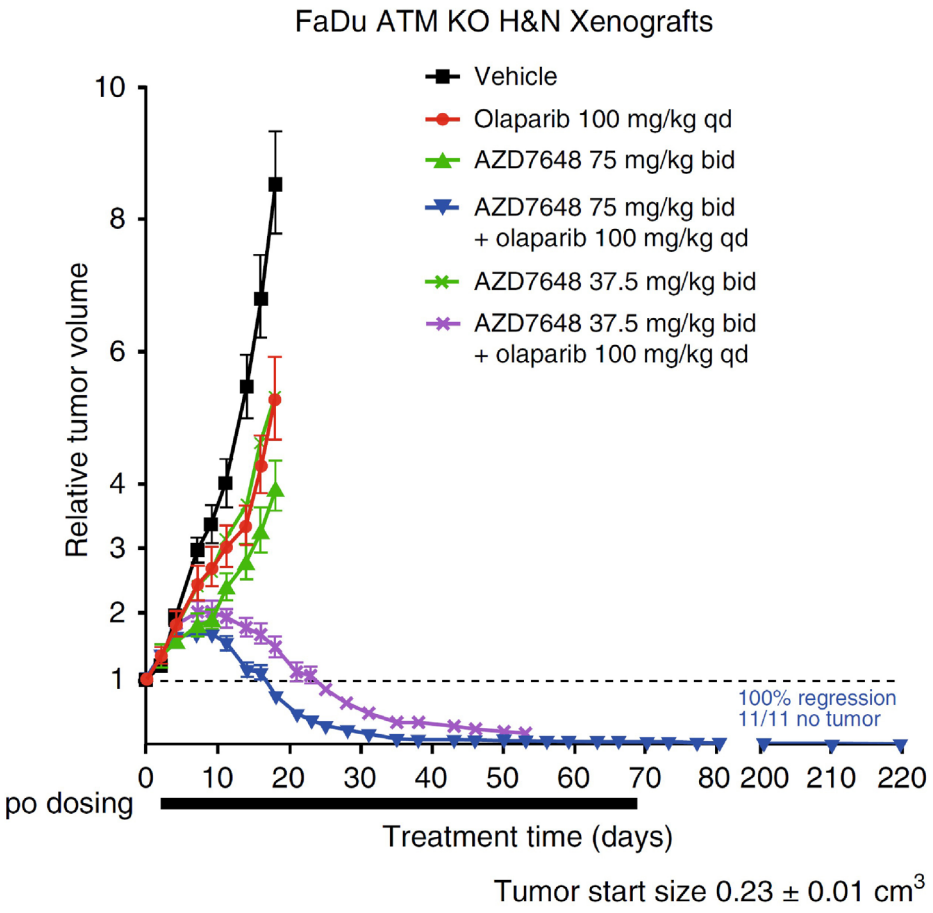

Figure 1. The combination of AZD7648 and olaparib strongly inhibits growth of an ATM-deficient head and neck cell line xenograft

AstraZenca began working with Champions Oncology to select patient-derived TumorGraft models that reflect various DNA repair deficient backgrounds in order to continue developing their DNA-PKc inhibitor. ***They ultimately selected the following models:***

- CTG-0703 (ovarian): BRCA1 LOH; BRCA2 wild type; ATM wild type; ATR gain
- CTG-0828 (NSCLC): FANCA LOH; BLM LOH; ATM mutated; BRCA2 loss; ATR wild type
- CTG-0149 (H&N): RAD51D mutated; BRCA1/2 wild type; ATM wild type; ATR wild type

All models were screened against AZD7648 and olaparib, both as monotherapies and as a combination treatment. The combination of AZD7648 and olaparib was more efficacious than either monotherapy in all models, inducing sustained regression in CTG-0703 and CTG-0828, and strongly inhibiting the normally robust growth of CTG-0149 *(Figure 2)*. Strikingly, the BRCA mutant model CTG-0703 was strongly inhibited by AZD7648 alone, in contrast to the findings in BRCA mutant cell lines where it had little to no effect (data not shown).

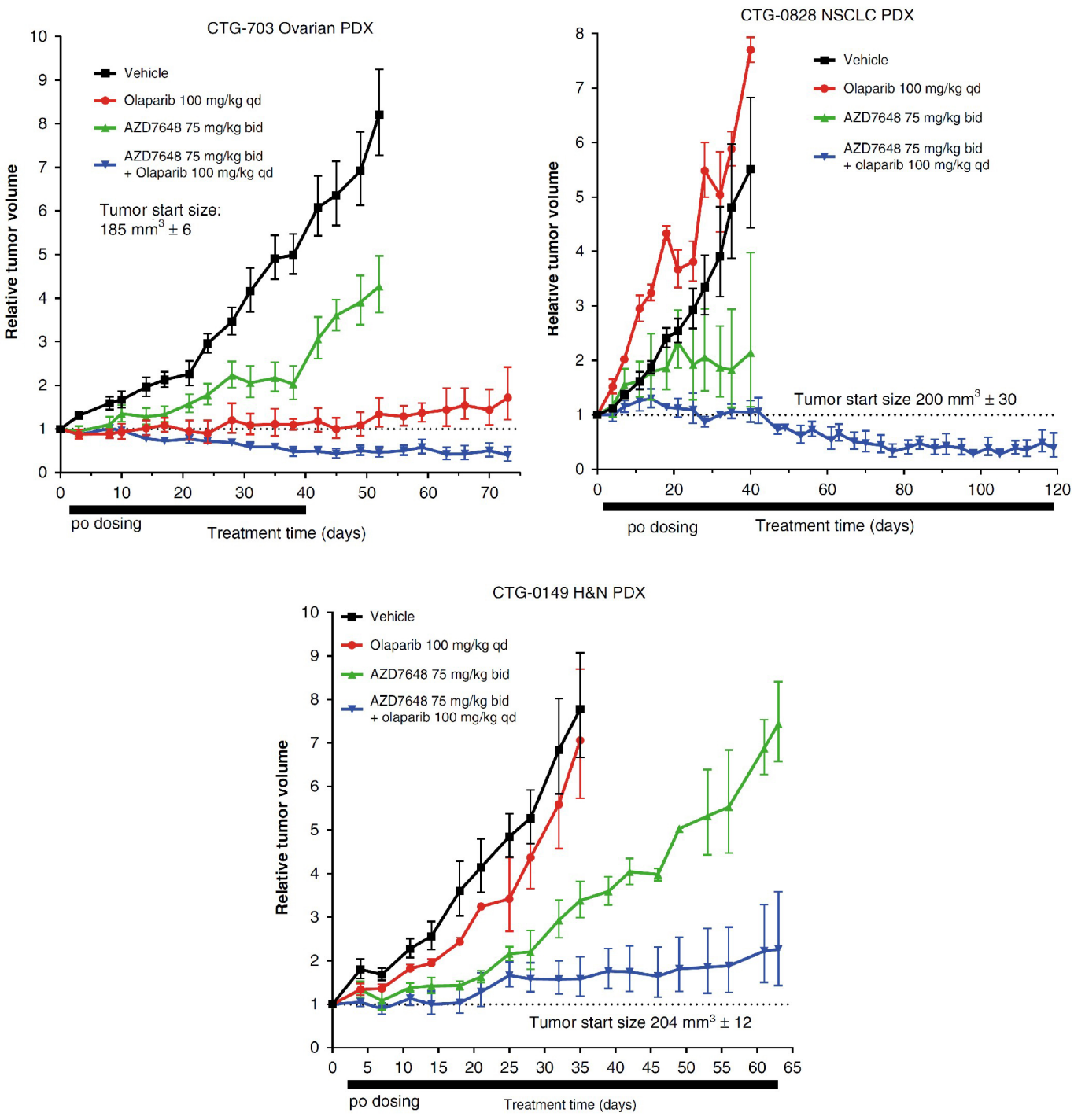

Figure 2. A combination of AZD7648 and the PARP inhibitor olaparib inhibits growth of TumorGraft models with different DNA repair deficiencies

The disparate results in cell lines versus TumorGrafts once more exemplifies the critical need for studies to be conducted in model systems that more closely recapitulate the human tumor environment. Altogether, this study not only highlight the potential of combining therapeutic strategies targeting different DNA repair pathways but once more the utility of leveraging extensively characterized TumorGraft models of cancer to determine preclinical efficacy and help make go/no-go decisions on novel oncology agents.

References

1. Goldstein, M. and Kastan, MB., *Annu. Rev. Med.*, 66: 8.1. 2015.

2. Fok, JHL., et al., *Nat. Commun.*, 10(1): 5065. 2019.