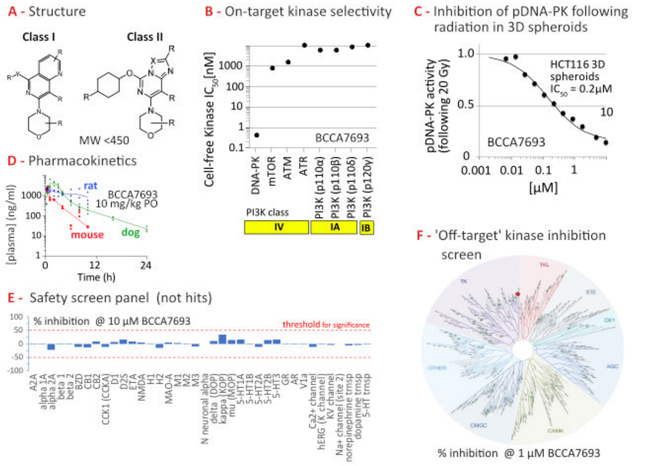
LB459

BCCA7693 - A novel, orally bioavailable DNA-PK inhibitor demonstrates efficacy with targeted MAPK and PARP therapeutics slowing the development of acquired resistance

Alastair Kyle[1,4]; Jennifer Baker[1]; Judit Banath[1]; Sevin Teymori[1]; Kaylee Bains[1]; Claudio Sturino[2]; Joseph Mancini[2]; Simon Osborne[3]; Ela Smiljanic-Hurley[3]; Steve Arns[2]; Jay Paquette[2] & **Andrew Minchinton**[1,4]
BC Cancer Research Institute, Vancouver, Canada[1]; adMare BioInnovations[2]; LifeArc[3]; c7bio[4]

Overview

BCCA7693 emerged as the lead molecule from a rational, structure-based drug development program after synthesis of over 1000 novel structures in two distinct chemical classes. *In vivo*, biochemical and cellular screening assays were used to identify compounds having high potency, selectivity and desirable ADME characteristics in three species.



BCCA7693 a potent and selective DNA-PK inhibitor with a demonstrated safety profile. BCCA7693 chemical class (**A**) displays <nM potency in cell-free kinase assay (**B**) and >1000-fold selectivity over related PI3K class members. Dose response for BCCA7693 inhibition of DNA-PK activity following 20 Gy radiation in HCT-116 3D spheroids (**C**). **D** shows a comparison of mouse, rat & dog plasma pharmacokinetics following 10 mg/kg PO. Oral bioavailability was 0.44 for BCCA7693 compared with 0.53 for AZD7648. **E** *In vitro* pharmacology safety screen (Eurofins) using radio-ligand binding assay for a panel of 38 targets, changes greater than 50% are considered significant and worthy of further study (no hits for BCCA7693 @ 10 μM). **F** Kinase off-target inhibition screen (from Eurofins), 97 kinase panel testing shows low off-target inhibition at 1μM BCCA7693 (C-met is single hit).

Current landscape of DNA-PKi strategies

A - *existing strategies (DSB inducers)*

Primary Therapeutic	Mechanism of action	Impact of DNA-PKi
Radiotherapy	DSB	synergistic in x-ray field
Radio-ligands	DSB	synergistic
Doxorubicin Etoposide	DSB	synergistic

DNA-PK → cell survival, repair, mutation; DNA DSBs → cell death; DNA-PK inhibitor → synergy also in normal tissues!

B - *current proposal (targeting acquired/adaptive resistance)*

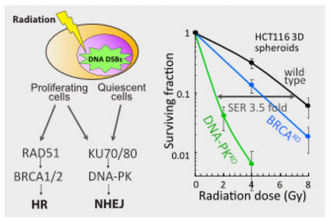
KRASi$^{G12C\ mut}$ BRAFi$^{V600E\ mut}$	pathway suppression	death following chromothripsis
PARPi	synthetic lethal HRD	enhanced synthetic lethality
Immunotherapy	immune modulation	stimulatory
ARi / ERi	pathway suppression	altered transcription

DNA-PK → cell survival, accumulation of mutations; chromosomal instability, replicative stress, HRD → cell death / stasis; DNA-PK inhibitor → tumour selective?

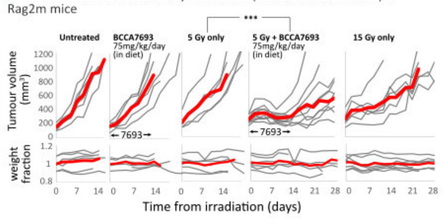
A Current DNA-PKi clinical trials have focused on enhancing primary therapeutic induced DSB cell death. Studies have all been limited by normal tissue sensitization. **B** Novel combination of DNA-PKi with non-DSB inducing tumour selective therapeutics.

BCCA7693 administered via diet sensitizes tumour xenografts to DSB inducing radiation

A - Comparison of NHEJ vs HR status and radio-response



B - *In vivo* radiosensitization by BCCA7693 (>3-fold enhancement) in Rag2m mice



Validation of BCCA7693 efficacy *in vivo* in combination with radiotherapy. **A** Impact of loss of NHEJ vs HR on radiation response in HCT-116 3D spheroids: DNA-PK^{KO} cells yield a 3.5-fold sensitization enhancement factor vs ~1.5 for BRCA2^{KO}. **B** *In vivo* BCCA7693 induces greater than a **3-fold enhancement factor**. FaDu head-and-neck xenografts. BCCA7693 was formulated in mouse diet and treatment began 1 day prior to radiation and continued for 2 weeks. 5 or 15 Gy radiation selectively delivered to the tumour bearing leg. BCCA7693 @ 75 mg/kg/day (diet) maintained plasma levels at 0.5-2 μM.

Long-term efficacy of DNA-PKi vs PolΘi in combination with PARP inhibitors

DNA-PKi drives lethality via micronuclei accumulation following PARPi in a BRCA^{mut} cancer. Impact of DNA-PKi vs PolΘi (ART558) in HDR cells treated with olaparib (HCC1937^{BRCAmut}). **A** Long-term impact of treatment on cell growth/survival. **B** Micronuclei analysis time-course over treatment duration.

BCCA7693 exhibits durable suppression of drug resistance in combination with a variety of non-DSB inducing targeted therapies.

- **DNA-PK KO cells display durable suppression of acquired resistance to Trametinib**

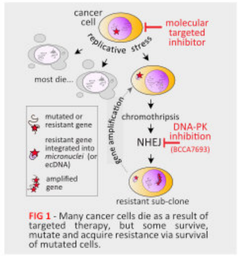
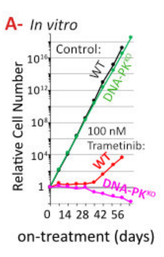
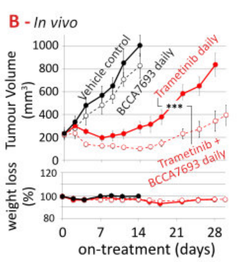


FIG 1 - Many cancer cells die as a result of targeted therapy, but some survive, mutate and acquire resistance via survival of mutated cells.

A- *In vitro*



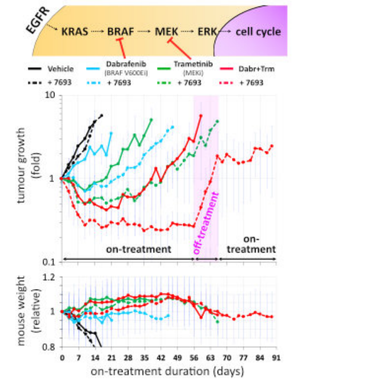
B - *In vivo*



Demonstration of the impact of long-term DNA-PKi on the development of therapeutic resistance to the MEKi trametinib. **A** HCT116 WT cells develop resistance to the MEKi trametinib following continuous exposure at 100 nM. DNA-PK KO cells show no development of resistance under similar conditions, confirming involvement of DNA-PK. **B** Tumour growth - BCCA7693 (100 mpk/day by oral gavage) delays the development of resistance to trametinib (0.75 mpk/day by oral gavage).

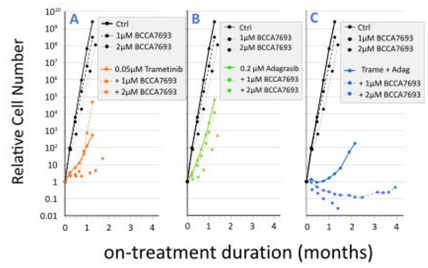
BCCA7693 blocks resistance in BRAF V600E mutant Colo-205 xenografts treated with BRAFi+MEKi

Impact of long-term DNA-PKi on the development of therapeutic resistance in BRAF V600E mut xenografts. Impact of BCCA-7693 on response to dabrafenib and/or trametinib in Colo-205 xenografts (BRAF V600E mut). BCCA7693 (75 mpk/day in diet) delays dabrafenib (10 mpk/day in diet) or trametinib (0.1 mpk/day in diet) and completely abrogates dabra+trame on-treatment resistance for 8-weeks with no increase in weight loss. Off-treatment tumours resume growth but resumption of treatment again halts growth indicating maintenance of sensitivity.



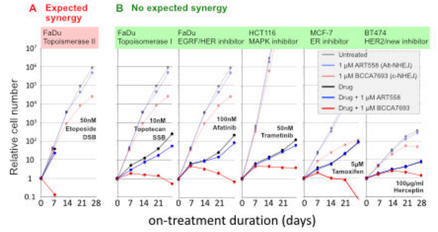
MAPK inhibition via Trametinib (MEKi) or Adagrasib (KRASi G12C mutant) shows reduced onset of resistance or cure when combined with BCCA7693 (DNA-PKi)

DNA-PKi (BCCA7693) inhibits the development of resistance to (A) Trametinib & (**B**) Adagrasib in Mia-Paca-2 (KRAS G12C mut) cells. The combination of all three modalities (**C**) results in significant inhibition of resistance. [Continuous drug exposures performed using Mia-Paca-2 KRAS G12C mutant cells, re-plated weekly at 5x10^5 cells in T175 flasks.]



DNA-PKi treatment (BCCA7693) beneficially increases cell death rate for a panel of non-DSB inducing therapies when incubation periods are extended beyond 7 days.

Comparison of long term cell monolayer response to continuous exposure to DSB inducing etoposide (**A**) vs. a panel of non-DSB inducing therapies (**B**). 28 day treatment duration with weekly passaging and re-plating at 30K cells in 6-well plates. Also shown, inhibition of Alt-NHEJ via ART558 has little effect.



Conclusion

The DNA-PK inhibitor BCCA7693 displays efficacy in a range of models where NHEJ is required for tumour cell survival, suggesting the potential for clinical application of this DSB repair inhibitor in increasing cell death and reducing the development of acquired resistance to a range of targeted anti-cancer therapies.

AACR 2026 - San Diego - Contact/Partnering opportunities: Andrew Minchinton +1 (778)-881-6690, aim@bccrc.ca