Pediatric Preclinical Testing Program (PPTP) Evaluation of BMN 673, an Inhibitor of Poly-ADP Ribose Polymerase (PARP), with Temozolomide (TMZ)

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BMN 673
- BMN 673 is a potent inhibitor of PARP-1 and -2 that inhibits intracellular PAR formation at a concentration of 2.5 nM (Shen Y, et al. CCR 2013 19:5003-5015).
- PARP-1 and -2 are activated by DNA damage and play a critical role in the base excision DNA repair (BER) pathway.
- PARP inhibitors selectively kill cancer cells that are deficient in BRCA1 or BRCA-2 function.
- PARP inhibitors enhance the cytotoxicity of DNA damaging agents by preventing cancer cells from repairing DNA damage.
- BMN 673 induces cytotoxicity by tightly trapping PARP at sites of DNA damage.
- Prior reports have documented selective sensitivity of Ewing sarcoma cell lines to PARP inhibitors.
- BMN 673 is in clinical evaluation and has shown substantial single agent anti-tumor activity in deleterious germine BRCA ovarian cancer and breast cancer.

BMN 673 + TMZ COMBINATION TESTING: EWING FOCUS AND TWO DOSING REGIMENS
- Regimen B: single agent TMZ at 30 mg/kg/d x 5d.
- Regimen C: single agent BMN 673 at 0.25 mg/kg BID x 5d.
- For the BMN 673 + TMZ combination, two strategies were tested: one with a higher dose of TMZ (30 mg/kg/d x 5d) and the other with a higher dose of BMN 673 (0.25 mg/kg BID x 5d).
  - For TMZ at 30 mg/kg, the tolerable BMN 673 dose was 0.1 mg/kg BID (Regimen D).
  - For BMN 673 at 0.25 mg/kg BID, the tolerable TMZ dose was only 12 mg/kg, (Regimen F).
- The observation period was 12 weeks following one cycle of therapy.

BMN 673 IN VITRO COMBINATION TESTING AGAINST PPTP CELL LINES
- PARP inhibitors have been shown to act both by inhibition of PARP enzymatic activity and by "trapping" PARP to DNA at sites of single strand breaks creating lesions that induce cytotoxicity during DNA replication. Either method could potentiate the activity of chemotherapy agents administered concurrently.
- The ability of BMN 673 (10 nM) to potentiate the activity of TMZ and topotecan against PPTP cell lines was evaluated.
- BMN 673 potentiation of TMZ activity (median 10-fold lowering of IC50) was far greater than its potentiation of topotecan activity (2.8-fold).
- BMN 673 potentiation of TMZ showed histotype selectivity, with a median 50-fold potentiation for Ewing cell lines (noted by arrows).
- BMN 673 potentiation of topotecan showed no histotype selectivity.

ADDITIONAL BMN 673 + TMZ COMBINATION TESTING
- For other xenografts, Regimen E (higher BMN 673 dose and low TMZ dose) was tested (see table below).
- The only xenografts with regressions (D645 and CHLA-79) expressing low MGMT and were previously shown to be responsive to single agent TMZ.
- The observation period was 6 weeks following one cycle of therapy.

CONCLUSIONS
- BMN 673 markedly potentiates the activity of TMZ in vitro with potentiation being particularly notable for Ewing sarcoma cell lines, some of which showed a level of potentiation exceeding 50-fold.
- BMN 673 potentiates the activity of topotecan in vitro to a much lesser extent than it does TMZ, and the potentiation of topotecan has no histotype-specificity.
- In vivo, BMN 673 plus TMZ was highly effective: maintained CRs (MCRs) were observed both for the regimen with higher dose TMZ and that with the lower dose TMZ, and in general responses to the two schedules were comparable. SK-NK1-1 responded better to the low-dose TMZ regimen, while CHLA-258D responded better to the higher-dose TMZ regimen.
- Highly synergistic activity for the BMN 673 + low-dose TMZ combination was observed for 5 out of 10 Ewing sarcoma models, with maintained CRs noted in vivo at TMZ doses of 12 mg/kg (≈ 20% of the standard TMZ in clinical doses).
- The BMN 673 + low-dose TMZ combination was also highly active against xenografts with low MGMT expression that are also responsive to single agent TMZ, including two MGMT-negative GBM xenografts (GBM2 and D645), a MGMT-negative high-grade sarcoma xenograft (RH28), and a neuroblastoma xenograft (CHLA-79). The combination with low-dose TMZ (12 mg/kg) was as or more effective than single agent TMZ at 30 mg/kg for GBM2 and RH28.
- The BMN 673 + low-dose TMZ combination is also highly active against the Wilms tumor xenograft (KT-10) that is responsive to single agent BMN 673.
- The non-TMZ lines evaluated that were not responsive to single agent BMN 673 or TMZ did not show tumor regressions to the BMN 673 plus TMZ combination.
- A pediatric phase 1 trial evaluating the BMN 673 plus low-dose TMZ strategy (ADVL1411) will activate in Q2 2014.

BMN 673 was provided for testing by BioMarin. Testing was supported by NCI-N01CM42216. This poster will be available at: http://pptp.nchresearch.org/presentations.html