Sensitivity of SCLC PDX models to talazoparib inhibition

**Abstract #242**

**Talazoparib (BMN-673) as Single Agent and in Combination With Temozolomide or PI3K Pathway Inhibitors in Small Cell Lung Cancer and Gastric Cancer Models**

**Ying Feng¹, Yuqiao (Jerry) Shen¹, Evelyn Wang¹, Karen Yu¹, Robert J. Cardnell², Bing Wang¹, Lauren A. Byers³, and Leonard Post¹**

¹BioMarin Pharmaceutical Inc., Novato, CA; ²MD Anderson Cancer Center, Houston, TX

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**INTRODUCTION**

- Talazoparib (BMN-673) is a novel PARPi inhibitor with strong anticancer activity that is primarily mediated by inhibiting PARP-1 de-O-acetylase. Talazoparib is the most potent PARPi inhibitor reported.

- Recent studies suggest that PARPi inhibitor treatment activates the PI3K/mTOR pathway in SCLC cell lines and animal models (Cardnell et al. EORTC-NCI-AACR 2014). It is predicted that talazoparib combination with PI3K pathway inhibitors may have greater antitumor activity than either agent alone.

**METHODS**

- Single agent and combination cytotoxicity assay: All PDX models were treated from commercial sources. SCLC and gastric cancer (GC) cell lines are from ATCC, JCRB or SNU collections. Cells were treated for 5 days with either talazoparib, antitumor agents (TMZ, PI3K inhibitors) or combination. In vivo studies: Human SCLC patient derived xenograft (PDX) models were performed at various control research organizations (Wang, Apple, Response Lifen, Lee, Boston, Thermo, etc). PDX tumors at different passages were tested on gels in an immune deficient nude and treated daily with either agent alone or 0.5 mg/kg from day 0 to the end of study. Human SCLC NCI-H69 and NCI-H187 tumors used were excised in the flank of SCD or nude mice. When tumors reached ~100 mm³ average volume, animals were dosed with either vehicle, each single agent alone or the combinations as indicated in the graph. SCLC xenograft models were performed by Shengbing Chen/Peidong Piao.

**RESULTS**

**Sensitivity of SCLC PDX models to talazoparib inhibition**

**Table 1. Summary of SCLC PDX Data**

**Combination with TMZ in SCLC models**

**Figure 1. Response of SCLC PDX models to single agent talazoparib treatment.**

**Figure 2. Potentiation of talazoparib by TMZ in vitro.**

**Figure 3. Potentiation of talazoparib by TMZ in vitro.**

**Figure 4. Western blot of p-ATM in GC cell lines.**

**Figure 5. Correlation of ATM, p-ATM levels with talazoparib sensitivity of GC cell lines.**

**Table 2. Summary of Talazoparib IC50s by TMZ Potentiation**

**Table 3. Summary of GI Value of Talazoparib Combination With PI3Ks**

**Figure 6. Western blot of p-ATM in cells treated with BYL-719 and TMZ.**

**Figure 7. Activity of talazoparib, BYL-719 single agent and combination in GC cells.**

**SUMMARY**

- As has been observed in humans (Wang et al. ASCO 2014), we observed responses, stable diseases, and lack of resistance to response in SCLC PDX models. Some SCLC PDX models also showed that talazoparib BRCA mutations are sensitive to talazoparib single agent treatment. Biomarkers that may predict talazoparib response need to be identified.

- We have found some GC cell lines are highly sensitive to talazoparib. Western blot analysis of protein expressions for ATM, p-ATM, PARP1, Akt, p-Akt, etc. in GC cell lines were measured by standard Western blot as described.

**ACKNOWLEDGEMENT**

Author would like to thank Jacy Le, etc. at MD Biosciences, LLC, for assistance with 6 color analysis and evaluation slide analysis.