Glutamine Metabolism in the Tumor Microenvironment

- Tumor cells avidly consume glutamine to fuel biosynthesis and proliferation
- Consumption of glutamine by tumors deprives immune cells of this critical nutrient
- CB-839 is a glutaminase inhibitor that blocks tumor glutamine consumption and supports immune cell function
- CB-839 reverses tumor cell-mediated immunosuppression in vitro
- CB-839 raises tumor glutamine in xenograft studies and plasma glutamine in patients
- CB-839 enhances the anti-tumor activity of α-PD-L1 in syngeneic mouse models

Clinical Outcome by Cohorts

- ORR of 19% in melanoma patients and disease control in the other IO refractory cohorts
- ORR of 21% in RCC IO Naive cohort with 74% DCR and 50% of enrolled patients remaining on study treatment

Time on Study for Other RCC Cohorts

- Disease control in heavily pretreated patients in RCC Prior IO cohort
- 50% of RCC IO Naive patients and all responding patients remain on study

Change in Target Lesions

- Deep confirmed responses in melanoma patients progressing on α-PD-L1 at study entry
- In other rescue cohorts, suppression of tumor growth is achieved in the majority of patients
- Target response after initial progression in heavily pretreated IO refractory patient in the RCC Prior IO cohort
- Confirmed and ongoing responses in RCC IO Naive patients with disease control in the majority of patients

Safety: Treatment-Related Adverse Events

- CB-839 + nivolumab is well tolerated
- No mTDT reached
- 1 DLT (3 grade 3 ALT) at 800 mg
- 800 mg CB-839 BID is tolerated
- Two patients discontinued for treatment-related AEs (GRF and G2 pneumonitis)
- No apparent increase in immune-related AE (IRAE) rate and severity compared to nivolumab monotherapy**
  - ** IAE All Grades (13.4%)
  - ** IAE 1-Grade (3.7%)

*Includes dose escalation and expansion patients

**Nivolumab package insert

Conclusions

- The combination of CB-839 + nivolumab is well tolerated
- This ongoing study is designed to stringently test for benefit of adding CB-839 to nivolumab in heavily pretreated and IO refractory patients
- Melanoma responders (ORR 19%) demonstrate clinical activity and suggest that resistance to α-PD-L1 can be overcome by the addition of CB-839
- Disease control seen in the majority of NSCLC and RCC patients progressing on α-PD-L1 therapy at study entry is encouraging
- ORR is 21% in RCC IO Naive cohort with 74% DCR and 50% of enrolled patients remaining on study treatment
- The Melanoma Rescue cohort has been expanded to explore the encouraging signal of this new mechanism of action