Glembatumum Vedotin, an Anti-gpNMB Antibody-Drug Conjugate (ADC), in Combination with Varilumab in Patients with Advanced Melanoma


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Abstract # P260

BACKGROUND

**Glembatumum vedotin (GV)**
- Glycoprotein NMB (gpNMB): internal transmembrane glycoprotein overexpressed in multiple tumor types including ~80% of melanomas1
- High tumor gpNMB expression associated with shorter metastasis-free and overall survival2-4
- Upregulated in BRAFV600E mutant melanoma following BRAF/MEK inhibition5

**Varilumab**
- CD27: Member of the TNF-receptor superfamily
- Constitutively expressed on most T cells and a subset of B and NK cells
- CD27 signaling:
  - Activation of the NF-kB pathway
  - Cell survival, activation, proliferation
  - Role in generation and long-term maintenance of T cell immunity
  - Role in NK cell differentiation and activation
- Varilumab is a fully human IgG, CD27 agonist monoclonal antibody that
  - Induces activation and proliferation of human T cells when combined with T cell receptor stimulation
  - Strong preclinical data demonstrating single agent and combination activity in tumor models
- Safety, biological and clinical activity demonstrated in Ph 1 study6
- Safety and tumor infiltrating lymphocytes increase demonstrated in combination with nivolumab in Ph 1 study6

**CDX011-05 STUDY DESIGN**

**Study Design**
- Single arm, open-label, Ph 2 trial
- Sequential cohorts evaluating GV (1.9 mg/kg IV q3w) as monotherapy or in combination with immunotherapy
- Tumor assessments every 6 weeks for 6 months, then every 9 weeks

**Patient (Pt) Population**
- Unresectable Stage III or IV melanoma
- Refractory to checkpoint inhibition (anti-CTLA-4, PD-1 or PD-L1)
- Refractory to BRAF/MEK inhibition (if BRAFV600E mutant)
- s1 prior cytotoxic regimen

**Endpoints / Statistical Design**
- Preclinical data suggest synergistic anti-tumor activity when ADC- MME is combined with checkpoint inhibitors (CPI)
- Microtubule-depolymerizing cytotoxic agents (e.g., MMEAs) have been shown to convert tumor-resident tolerogenic dendritic cells into active antigen-presenting cells1,7

**Clinical Efficacy**
- **Primary Endpoints:**
  - Confirmed Complete Responses (CR)
  - Any Response Including Those Not Confirmed at Subsequent Assessment
- **Secondary Endpoints:**
  - Refractory to checkpoint inhibition (anti-CTLA-4, -PD-1 or -PD-L1)
  - Objective response rate (RECIST 1.1)
- **Cohort 2: GV with Varilumab**
- Single arm, open-label, Ph 2 trial
- Duration of Advanced Disease, months (median [min, max])
- Braf Mutation (n [%])
- Duration of Advanced Disease, months (median [min, max])
- Gvbraf Mutations (n=19)
- Duration of Advanced Disease, months (median [min, max])
- Gvbraf Mutations (n=19)
- GV Serum Concentrations (n=19)
- Methods:
  - Serum baseline, Cycles 1-2, end of treatment
  - Pre-treatment fresh skin biopsies were collected to elucidate any possible differentially expressed genes (DEGs), data from the 4 best responders (tumor shrinkage > 20% and PFS > 3 months; GI) was compared with the 4 worst responders (tumor growth >10% and PFS < 2 months; GI).
  - Fold change >2 & p <0.05: 198 DEGs
  - Fold change >2 & p <0.01: 76 DEGs
  - Heatmap (left): 53 DEGs
  - Fold change >2 & p <0.005: 53 DEGs
  - Fold change >2 & p <0.005: 198 DEGs
  - Fold change >2 & p <0.01: 76 DEGs
  - Fold change >2 & p <0.005: 53 DEGs

**MAXIMUM TUMOR SHRINKAGE**
- Median OS (months [95% CI]) = 6.4 (3.2, 8.3)

**TRANSLATIONAL RESEARCH**

**Flow Cytometry Analysis of Immune Cell Subsets**
- Effects of varilumab on peripheral lymphocytes are consistent with prior studies of varilumab
- Activation of T cells: evidenced by up-regulation of HLA-DR (P=0.08)
- Decrease in circulating regulatory T cells (Treg) (P=0.003)

**TOLERABILITY**

**Adverse Events Considered Related to GV and/or Varilumab (n=34)**

**References**

1. Tse et al. CCR 2006
2. Rose et al. CCR 2010
3. Liu et al. APMS 2013
4. Kuan et al. CCR 2006
5. Rose et al. CCR 2016
6. Muller et al. CIR 2014
7. Muller et al. MT 2015
8. Burrus et al. JCO 2017
9. Santarom G. CDR 2017
10. Ott et al. CJO 2017

**CONCLUSIONS**

- Building upon the positive monotherapy results, this additional cohort evaluating GV in combination with CPI is enrolling (NCT#02302339)
- Additional, PI3K is a growth factor for dendritic cells, CDX-301, a recombinant human PI3K, has been tested in clinical trials in the oncology setting
- A subsequent cohort is planned to evaluate combination of GV with CDX-301 to assess the safety, tolerability, and biologic activity of the combination
- Future correlative analyses will include molecular profiling with NextGen sequencing on tumor tissues to investigate possible impact of genetic makeup on clinical outcome
- Following completion of this cohort and evaluation of available data, the protocol amendment also allows for the exploration of additional cohorts