Expression of Myeloma Cell BCMA and Soluble BCMA in Relapsed and Refractory Multiple Myeloma Subjects

Treated with GSK2857916 in BMA117159


Aims

To examine the potential utility of BCMA as a biomarker for the BCMA targeted antibody drug conjugate (ADC), GSK2857916.

- BCMA Expression on Myeloma Cells
  - BCMA is an established marker of plasma cells and multiple myeloma cells.
  - Circulating BCMA Expression in Multiple Myeloma
    - BCMA is cleaved by y-secretase and released into circulation as soluble BCMA (sBCMA) in multiple myeloma (Laurent, et al., 2015).
  - BCMA Expression was measured on MM cells and in circulation as sBCMA during the GSK2857916 FTH study and examined relative to patient responses.

Introduction

- B-cell maturation antigen (BCMA) is a cell surface receptor that is widely expressed on multiple myeloma (MM) cells.
- GSK2857916 is a humanized Fc enhanced IgG1 anti-BCMA antibody conjugated to the microtubule inhibitor monomethyl auristatin-F (MMAF).
- Safety and clinical efficacy of a Q3W GSK2857916 dosing schedule were assessed in relapsed/refractory MM subjects in the first in human trial BMA117159 (Trudel, et al., 2017).
- In the dose escalation phase:
  - 38 subjects were treated with doses from 0.03 mg/kg up to 4.60 mg/kg.
  - In the dose expansion cohort:
    - 35 subjects were treated at a dose of 3.40 mg/kg.
    - An overall response rate (ORR) of 60% (21/35; 95% CI: 43.2-76.1) by IWG (2011) criteria was demonstrated.

Results

- Expression of BCMA on plasma cells was measured by two IHC assays (BCMA Single-Plex IHC and BCMA + CD138 IHC).
- Both assays showed expression of BCMA in nearly all MM cells.
- Intensity of BCMA staining showed no obvious relationship with patient responses.
- sBCMA was measured by immunoblot to detect free sBCMA before and after treatment with GSK2857916.
- sBCMA becomes largely bound by GSK2857916 after infusion.
- Clinical responses were observed in patients with low or high BCMA, while the baseline levels of sBCMA were found to be lower overall among responding patients.

BCMA Immunohistochemistry

Figure 2: BCMA Single IHC and Patient Response (Part 2)

Figure 3: BCMA Immunohistochemistry (continued)

- BCMA expression was quantified in all bone marrow mononuclear cells (BMMCs) and in morphological plasma cells (PCs) at baseline and examined relative to best confirmed response in the full dose expansion cohort. All plasma cells were quantified as BCMA+, and no obvious relationship between baseline BCMA levels and clinical responses were identified.

BCMA Immunohistochemistry (continued)

ABCMA Immunohistochemistry (continued)

Figure 4: BCMA IHC Examples

- BCMA expression was quantified in all bone marrow mononuclear cells (BMMCs) and in morphological plasma cells (PCs) at baseline and examined relative to best confirmed response in the full dose expansion cohort. All plasma cells were quantified as BCMA+, and no obvious relationship between baseline BCMA levels and clinical responses were identified.

Biomarker Data Availability

Figure 5: Biomarker Data Availability

- Key: n = total (% with sBCMA+ with single IHC or dual IHC).
- Above table shows the number of patients treated in the dose escalation and dose expansion cohorts. MM117159, with the percentage of subjects in each cohort with sBCMA, single IHC and CD138 + BCMA dual IHC data available at baseline.

BCMA Immunohistochemistry

- BCMA expression was quantified in all bone marrow mononuclear cells (BMMCs) and in morphological plasma cells (PCs) at baseline and examined relative to best confirmed response in the full dose expansion cohort. All plasma cells were quantified as BCMA+, and no obvious relationship between baseline BCMA levels and clinical responses were identified.

Biomarker Data Availability

- Key: n = total (% with sBCMA+ with single IHC or dual IHC).
- Above table shows the number of patients treated in the dose escalation and dose expansion cohorts. MM117159, with the percentage of subjects in each cohort with sBCMA, single IHC and CD138 + BCMA dual IHC data available at baseline.

BCMA Immunohistochemistry (continued)

- BCMA expression was quantified in all bone marrow mononuclear cells (BMMCs) and in morphological plasma cells (PCs) at baseline and examined relative to best confirmed response in the full dose expansion cohort. All plasma cells were quantified as BCMA+, and no obvious relationship between baseline BCMA levels and clinical responses were identified.

Biomarker Data Availability

- Key: n = total (% with sBCMA+ with single IHC or dual IHC).
- Above table shows the number of patients treated in the dose escalation and dose expansion cohorts. MM117159, with the percentage of subjects in each cohort with sBCMA, single IHC and CD138 + BCMA dual IHC data available at baseline.

Aims

To examine the potential utility of BCMA as a biomarker for the BCMA targeted antibody drug conjugate (ADC), GSK2857916.

- BCMA Expression on Myeloma Cells
  - BCMA is an established marker of plasma cells and multiple myeloma cells.
  - Circulating BCMA Expression in Multiple Myeloma
    - BCMA is cleaved by y-secretase and released into circulation as soluble BCMA (sBCMA) in multiple myeloma (Laurent, et al., 2015).
  - BCMA Expression was measured on MM cells and in circulation as sBCMA during the GSK2857916 FTH study and examined relative to patient responses.

Introduction

- B-cell maturation antigen (BCMA) is a cell surface receptor that is widely expressed on multiple myeloma (MM) cells.
- GSK2857916 is a humanized Fc enhanced IgG1 anti-BCMA antibody conjugated to the microtubule inhibitor monomethyl auristatin-F (MMAF).
- Safety and clinical efficacy of a Q3W GSK2857916 dosing schedule were assessed in relapsed/refractory MM subjects in the first in human trial BMA117159 (Trudel, et al., 2017).
- In the dose escalation phase:
  - 38 subjects were treated with doses from 0.03 mg/kg up to 4.60 mg/kg.
  - In the dose expansion cohort:
    - 35 subjects were treated at a dose of 3.40 mg/kg.
    - An overall response rate (ORR) of 60% (21/35; 95% CI: 43.2-76.1) by IWG (2011) criteria was demonstrated.

Results

- Expression of BCMA on plasma cells was measured by two IHC assays (BCMA Single-Plex IHC and BCMA + CD138 IHC).
- Both assays showed expression of BCMA in nearly all MM cells.
- Intensity of BCMA staining showed no obvious relationship with patient responses.
- sBCMA was measured by immunoblot to detect free sBCMA before and after treatment with GSK2857916.
- sBCMA becomes largely bound by GSK2857916 after infusion.
- Clinical responses were observed in patients with low or high BCMA, while the baseline levels of sBCMA were found to be lower overall among responding patients.

BCMA Immunohistochemistry

Figure 2: BCMA Single IHC and Patient Response (Part 2)

Figure 3: BCMA Immunohistochemistry (continued)

- BCMA expression was quantified in all bone marrow mononuclear cells (BMMCs) and in morphological plasma cells (PCs) at baseline and examined relative to best confirmed response in the full dose expansion cohort. All plasma cells were quantified as BCMA+, and no obvious relationship between baseline BCMA levels and clinical responses were identified.

Biomarker Data Availability

Figure 5: Biomarker Data Availability

- Key: n = total (% with sBCMA+ with single IHC or dual IHC).
- Above table shows the number of patients treated in the dose escalation and dose expansion cohorts. MM117159, with the percentage of subjects in each cohort with sBCMA, single IHC and CD138 + BCMA dual IHC data available at baseline.

Aims

To examine the potential utility of BCMA as a biomarker for the BCMA targeted antibody drug conjugate (ADC), GSK2857916.

- BCMA Expression on Myeloma Cells
  - BCMA is an established marker of plasma cells and multiple myeloma cells.
  - Circulating BCMA Expression in Multiple Myeloma
    - BCMA is cleaved by y-secretase and released into circulation as soluble BCMA (sBCMA) in multiple myeloma (Laurent, et al., 2015).
  - BCMA Expression was measured on MM cells and in circulation as sBCMA during the GSK2857916 FTH study and examined relative to patient responses.

Introduction

- B-cell maturation antigen (BCMA) is a cell surface receptor that is widely expressed on multiple myeloma (MM) cells.
- GSK2857916 is a humanized Fc enhanced IgG1 anti-BCMA antibody conjugated to the microtubule inhibitor monomethyl auristatin-F (MMAF).
- Safety and clinical efficacy of a Q3W GSK2857916 dosing schedule were assessed in relapsed/refractory MM subjects in the first in human trial BMA117159 (Trudel, et al., 2017).
- In the dose escalation phase:
  - 38 subjects were treated with doses from 0.03 mg/kg up to 4.60 mg/kg.
  - In the dose expansion cohort:
    - 35 subjects were treated at a dose of 3.40 mg/kg.
    - An overall response rate (ORR) of 60% (21/35; 95% CI: 43.2-76.1) by IWG (2011) criteria was demonstrated.

Results

- Expression of BCMA on plasma cells was measured by two IHC assays (BCMA Single-Plex IHC and BCMA + CD138 IHC).
- Both assays showed expression of BCMA in nearly all MM cells.
- Intensity of BCMA staining showed no obvious relationship with patient responses.
- sBCMA was measured by immunoblot to detect free sBCMA before and after treatment with GSK2857916.
- sBCMA becomes largely bound by GSK2857916 after infusion.
- Clinical responses were observed in patients with low or high BCMA, while the baseline levels of sBCMA were found to be lower overall among responding patients.

BCMA Immunohistochemistry

Figure 2: BCMA Single IHC and Patient Response (Part 2)