ABSTRACT

Background

HER2 is dysregulated in a wide range of solid tumors, including breast cancer, and is an attractive target for tailored oncologic treatment. GBR 1302 is a HER2xCD3 bispecific antibody that redirects cytotoxic T cells to kill HER2-overexpressing cancer cells. This unique mode of action is anticipated to result in superior antitumor activity in HER2-positive tumors by harnessing the cytotoxic capabilities of patients’ existing T cells.

Methods

This ongoing, phase 1, first-in-human, open-label, multicenter, dose-escalation study is evaluating GBR 1302 in adults with progressive HER2-positive solid tumors for which no standard or curative treatment is available. Subjects receive intravenous GBR 1302 on Day 1 and Day 15 in 28-day treatment cycles at escalating dose levels, starting at 1 ng/kg. The first 4 cohorts consisted of a single subject; subsequent cohorts are being enrolled using a 3+3 design. Blood samples were collected for pharmacokinetic (PK) and anti-drug antibody (ADA) analyses (secondary endpoints). Quantification of GBR 1302 serum concentrations (for PK) and detection/confirmation of anti-GBR 1302 antibodies (for immunogenicity) were performed using validated LC/MS/MS and ELISA methods, respectively. PK parameters were evaluated using standard non-compartmental methods.

Results

As of 21 August 2018, PK data were available from 31 subjects over dose range of 1 ng/kg to 750 ng/kg. Serum concentrations were less than the lower limit of quantification of 50 pg/mL at the first dose (1 ng/kg), and only transient concentrations were observed at 3 and 10 ng/kg dose levels. Evaluable PK profiles were observed from 30 ng/kg onwards. GBR 1302 showed maximum serum concentration ($C_{\text{max}}$) around the end of infusion, after which serum concentrations declined bi-exponentially with a mean terminal half-life of around 4 to 7 days. Both $C_{\text{max}}$ and area under the curve (AUC$_{0-\text{t}}$) showed a near dose-proportional increase up to 750 ng/kg (maximum evaluated dose). None of the samples collected from subjects up to cohort 5 showed positive ADA response.

Conclusions

Per ongoing analysis, GBR 1302 showed a favorable, linear PK. None of the subjects evaluated so far showed positive ADA response.
STUDY DESIGN/STATUS

- A phase 1, multicenter, open-label, first-in-human study of GBR 1302 (NCT02829372) is currently ongoing and designed to evaluate the safety, tolerability, and preliminary efficacy of GBR 1302 in patients with HER2-positive cancers; the study additionally aims to characterize the immunomodulatory (or immunostimulatory) effects triggered by GBR 1302.
- This ongoing study consists of two parts (Figure 1):
  - Part 1 Dose-Finding: currently enrolling up to 70 adult patients with progressive HER2-positive solid tumors (IHC positive), for which no standard or curative treatment is available, to determine the maximum tolerated dose (MTD) of GBR 1302.
  - Part 2 Expansion: plans to enroll multiple patient cohorts to further evaluate the anti-tumor activity and safety profile of GBR 1302 administered at the MTD.
- Pharmacokinetics (PK), pharmacodynamic biomarkers, and immunogenicity assessments are also included in Parts 1 and 2 of the study.

Figure 1. GBR 1302-101 Study Design

Dosing Schedule (Part 1)

- Intravenous GBR 1302 is administered on Day 1 and Day 15 in 28-day treatment cycles at escalating dose levels, starting at 1 ng/kg to planned maximum of 3800 ng/kg.
- Cohorts 1-4 each consist of a single subject; subsequent cohorts enroll using a standard 3+3 design.
- First administration of GBR 1302 is at the safe dose from the previous cohort; second and subsequent doses are at the designated higher dose.
- Cycles may be repeated where clinical benefit is indicated.
Pharmacokinetic Analysis
- Blood samples are collected for PK analyses at pre-infusion and up to 14 days after each dosing occasion in Cycle 1 and Cycle 2; for subsequent treatment cycles, blood samples are collected pre-infusion on days 1 and 15
- A hybrid immunoprecipitation liquid chromatography with tandem mass spectrometry (LC-MS/MS) method is used for quantification of GBR 1302 in human serum; the lower limit of quantification (LLOQ) of the assay is 50 pg/mL (Figure 2)

Figure 2. Hybrid Immunoprecipitation LC-MS/MS Method to Quantify GBR 1302

Immunogenicity Assessment
- Blood samples are collected for immunogenicity assessments at screening and visit 8 for Cycles 1 and 2 and day 28 for subsequent cycles
- Detection and confirmation of anti-GBR 1302 antibodies in serum is performed using validated Electrochemiluminescence (ECL) Assay
- Neutralizing potential and titers will be assessed for any positive anti-drug antibody (ADA) samples

RESULTS
Pharmacokinetics
- As of 21 August 2018, PK data were available from 31 subjects over a dose range of 1 ng/kg to 750 ng/kg
- Serum concentrations were less than LLOQ at the first dose (1 ng/kg), and only transient concentrations were observed at 3 ng/kg and 10 ng/kg dose levels
- Evaluable PK profiles were observed from 30 ng/kg onwards
- GBR 1302 showed $C_{\text{max}}$ around the end of infusion, after which serum concentrations declined bi-exponentially with a mean $t_{1/2}$ of around 4 to 7 days (Figure 3; Table 1)
- Both $C_{\text{max}}$ and $\text{AUC}_{0-1}$ showed a near dose-proportional increase up to 750 ng/kg, the maximum evaluated dose (Figure 4)
Figure 3. Serum Concentration vs Time Profiles of GBR 1302

Figure 4. GBR 1302 Exposure vs Dose

A. Mean $C_{\text{max}}$ vs Dose

$y = 0.0131x$

$R^2 = 0.9497$

B. Mean $\text{AUC}_{0-t}$ vs Dose

$y = 0.784x$

$R^2 = 0.9885$

*Data shown as mean (SD).$

*AUC$_{0-t}$: area under the serum concentration-time curve from zero to last quantifiable concentration; $C_{\text{max}}$: maximum serum concentration; $R^2$: coefficient of determination; SD: standard deviation.*
KEY FINDINGS

Table 1. Summary of Pharmacokinetic Parameters of GBR 1302

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Infusion start, h</th>
<th>GBR 1302 dose, ng/kg</th>
<th>C_{max}, ng/mL</th>
<th>AUC_{0-t}, ng·h/mL</th>
<th>T_{max}, h</th>
<th>t_{1/2}, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 5 (n=8)</td>
<td>0</td>
<td>60</td>
<td>0.53 (0.18)</td>
<td>34.4 (27.8)*</td>
<td>4.0 (4.0 – 4.1)</td>
<td>108\textsuperscript{b} (21.2)</td>
</tr>
<tr>
<td>Cohort 5 (n=6)</td>
<td>336</td>
<td>100</td>
<td>0.96 (0.43)</td>
<td>83.6 (55.5)</td>
<td>4.1 (4.0 – 4.3)</td>
<td>109\textsuperscript{c} (9.70)</td>
</tr>
<tr>
<td>Cohort 5 (n=5)</td>
<td>672</td>
<td>100</td>
<td>1.09 (0.51)</td>
<td>103 (57.5)</td>
<td>2.0 (2.0 – 4.0)</td>
<td>107\textsuperscript{c} (18.5)</td>
</tr>
<tr>
<td>Cohort 5 (n=4)</td>
<td>1008</td>
<td>100</td>
<td>1.53 (0.95)</td>
<td>104 (58.3)</td>
<td>1.0 (1.0 – 1.0)</td>
<td>97.4 (13.7)</td>
</tr>
<tr>
<td>Cohort 6 (n=3)</td>
<td>0</td>
<td>100</td>
<td>0.64 (0.10)</td>
<td>41.6 (15.6)</td>
<td>4.1 (4.1 – 4.2)</td>
<td>125\textsuperscript{d}</td>
</tr>
<tr>
<td>Cohort 6 (n=3)</td>
<td>336</td>
<td>200</td>
<td>1.06 (0.13)</td>
<td>87.9 (16.8)</td>
<td>4.1 (4.1 – 6.8)</td>
<td>108\textsuperscript{b} (16)</td>
</tr>
<tr>
<td>Cohort 6 (n=3)</td>
<td>672</td>
<td>200</td>
<td>1.37 (0.50)</td>
<td>105 (36.6)</td>
<td>3.9 (2.0 – 5.5)</td>
<td>113\textsuperscript{b} (13.8)</td>
</tr>
<tr>
<td>Cohort 6 (n=2)</td>
<td>1008</td>
<td>200</td>
<td>1.54 (0.21)</td>
<td>107 (40.6)</td>
<td>2.7 (1.0 – 4.3)</td>
<td>86.9\textsuperscript{d}</td>
</tr>
<tr>
<td>Cohort 7 (n=3)</td>
<td>0</td>
<td>200</td>
<td>1.91 (0.45)</td>
<td>151 (64.5)</td>
<td>4.7 (4.1 – 5.8)</td>
<td>126\textsuperscript{d}</td>
</tr>
<tr>
<td>Cohort 7 (n=3)</td>
<td>336</td>
<td>300</td>
<td>2.68 (0.33)</td>
<td>272 (76.0)</td>
<td>4.0 (4.0 – 4.7)</td>
<td>106 (9.52)</td>
</tr>
<tr>
<td>Cohort 7 (n=2)</td>
<td>672</td>
<td>300</td>
<td>3.26 (1.19)</td>
<td>224 (114)</td>
<td>3.0 (2.0 – 4.1)</td>
<td>80.2\textsuperscript{d}</td>
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<tr>
<td>Cohort 7 (n=1)</td>
<td>1008</td>
<td>300</td>
<td>3.62</td>
<td>NC</td>
<td>1.0</td>
<td>NC</td>
</tr>
<tr>
<td>Cohort 8 (n=3)</td>
<td>0</td>
<td>300</td>
<td>2.56 (0.60)</td>
<td>197 (69.7)</td>
<td>4.0 (4.0 – 6.2)</td>
<td>108\textsuperscript{d}</td>
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<tr>
<td>Cohort 8 (n=3)</td>
<td>336</td>
<td>500</td>
<td>4.53 (2.03)</td>
<td>347 (140)</td>
<td>4.0 (4.0 – 6.4)</td>
<td>126\textsuperscript{d}</td>
</tr>
<tr>
<td>Cohort 8 (n=3)</td>
<td>672</td>
<td>500</td>
<td>5.54 (0.77)</td>
<td>344 (79.5)</td>
<td>2.0 (2.0 – 2.5)</td>
<td>131\textsuperscript{d}</td>
</tr>
<tr>
<td>Cohort 8 (n=2)</td>
<td>1008</td>
<td>500</td>
<td>6.18 (1.05)</td>
<td>339 (86.8)</td>
<td>1.0 (1.0 – 1.0)</td>
<td>NC</td>
</tr>
<tr>
<td>Cohort 9 (n=10)</td>
<td>0</td>
<td>500</td>
<td>6.04 (1.66)</td>
<td>392 (191)</td>
<td>4.6 (3.9 – 11.2)</td>
<td>124\textsuperscript{e} (22.7)</td>
</tr>
<tr>
<td>Cohort 9 (n=5)</td>
<td>336</td>
<td>750</td>
<td>10.8 (3.54)</td>
<td>646 (314)</td>
<td>4.0 (4.0 – 5.8)</td>
<td>127\textsuperscript{c} (20.6)</td>
</tr>
<tr>
<td>Cohort 9 (n=2)</td>
<td>672</td>
<td>750</td>
<td>12.6 (2.62)</td>
<td>556 (319)</td>
<td>2.6 (2.0 – 3.1)</td>
<td>144\textsuperscript{d}</td>
</tr>
<tr>
<td>Cohort 9 (n=1)</td>
<td>1008</td>
<td>750</td>
<td>10.6</td>
<td>575</td>
<td>1.0</td>
<td>155</td>
</tr>
</tbody>
</table>

Data shown are mean (SD), unless otherwise noted.
Data not shown for Cohorts 1 – 4 (n=1 each).
* Median (min-max); \textsuperscript{a} n=2; \textsuperscript{b} n=3; \textsuperscript{c} n=1; \textsuperscript{d} n=7
AUC_{0-t}, area under the serum concentration-time curve from zero to last quantifiable concentration; C_{max}, maximum serum concentration; NC, not calculable; t_{1/2}, terminal half-life; T_{max}, time from dosing to C_{max}.

Immunogenicity
- As of 19 September 2018, serum samples collected from 31 subjects through cohort 9 were evaluated for ADA response
- One subject (3.2%) from cohort 8 tested positive for ADA at a single time point (Cycle 2, Day 28) with a titer of 32
- Impact of ADA on PK could not be evaluated reliably due to limited data
- An assessment of the neutralizing potential of this ADA-positive sample will be performed

CONCLUSIONS
- Per ongoing analysis, GBR 1302 showed a favorable, linear PK with a half-life of about 4 to 7 days
- The PK and immunogenicity results from this study support the initiation of a phase 1 study in HER2+ breast cancer with a weekly dosing regimen
- A weekly dosing regimen is anticipated to maintain higher minimum serum concentration over the entire treatment duration, thereby potentially maximizing the killing of HER2+ tumor cells