PRELIMINARY PHARMACOKINETIC RESULTS FROM A PHASE 1 STUDY OF GBR 1302 IN PATIENTS WITH HER2-POSITIVE CANCERS

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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_{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_{max} and area under the curve (AUC_{0-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.

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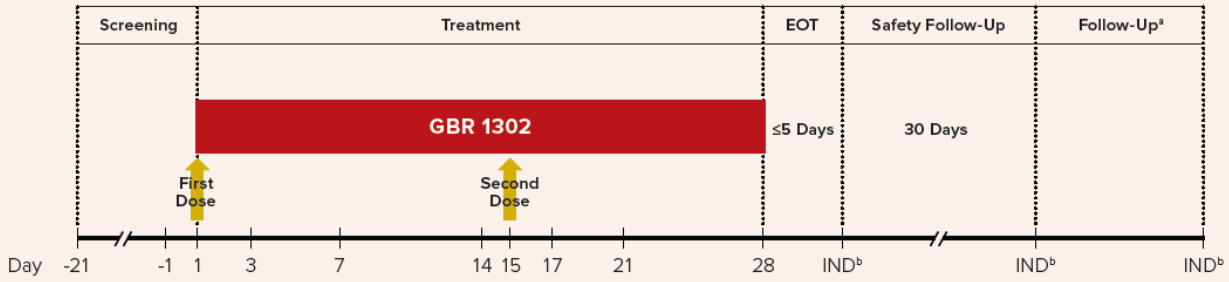
KEY FINDINGS

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



Visit (Cycles 1 and 2)	1	2	3	4	5	6	7	8
Biomarker Sampling[c]	X	X	X		X	X	X	
Pharmacokinetic Sampling[d]	X	X	X	X	X	X	X	X
Immunogenicity Sampling[e]								X

Arrows indicate intravenous dose administration.
[a]Additional follow-up visits until progression, lost to follow-up, treatment with another anti-cancer drug, or up to 4 months after last study dose; [b]As treatment duration is dependent on therapeutic benefit, EOT varies among subjects; as such, the exact study days for EOT, safety follow-up, and follow-up are IND; [c]Biomarkers are assessed in peripheral blood; peripheral blood for biomarker sampling is collected on visits 1-3 and 5-7 of treatment cycles 1 and 2; for subsequent treatment cycles, sampling is collected on visits 1 and 2 (days 1 and 3, respectively) and visits 4 and 5 (days 15 and 17, respectively); [d]Blood for pharmacokinetic sampling is collected on visits 1-8 of treatment cycles 1 and 2; for subsequent treatment cycles, sampling is collected on visits 1 and 4 (days 1 and 15, respectively); [e]Blood for immunogenicity sampling is collected at screening and visit 8 of treatment cycles 1 and 2; for subsequent treatment cycles, sampling is collected on visit 6 (day 28).
EOT, end of treatment; IND, indeterminate.

Dosing Schedule (Part 1)

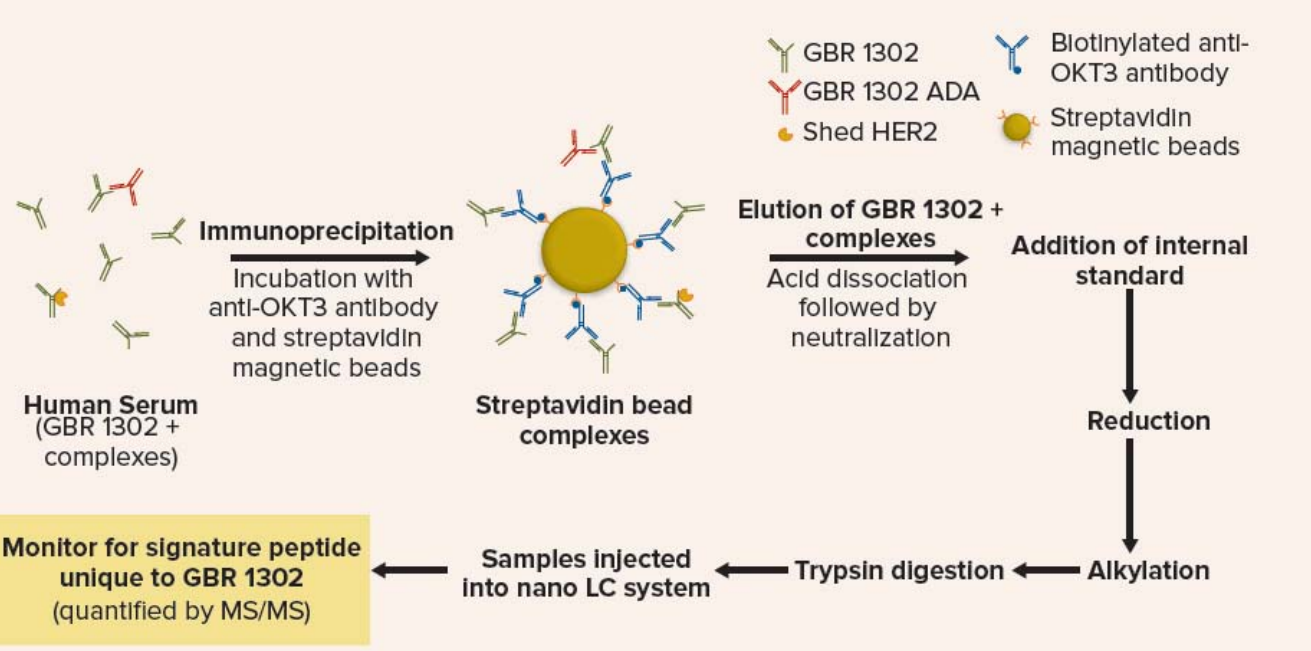
- Intravenous GBR 1302 is administered on Day 1 and Day 15 in 28-day treatment cycles at escalating dose levels, starting at 1 ng/kg to planned maximum of 3800 ng/kg
- Cohorts 1-4 each consist of a single subject; subsequent cohorts enroll using a standard 3+3 design
- First administration of GBR 1302 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

KEY FINDINGS

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



GBR 1302 in serum samples is captured by biotinylated anti-OKT3 antibody on streptavidin magnetic beads. The captured GBR 1302 is separated from the magnetic beads by acid dissociation followed by neutralization. The neutralized solution containing GBR 1302 and its internal standard are subject to reduction and alkylation, followed by trypsin digestion. Finally, the tryptic peptides are injected into a nano LC system and the signature peptide unique to GBR 1302 is quantified by MS/MS.
ADA, anti-drug antibody; LC, liquid chromatography; MS/MS, tandem mass spectrometry; OKT3, anti-CD3 antibody.

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_{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_{max} and $AUC_{0\text{-}t}$ 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

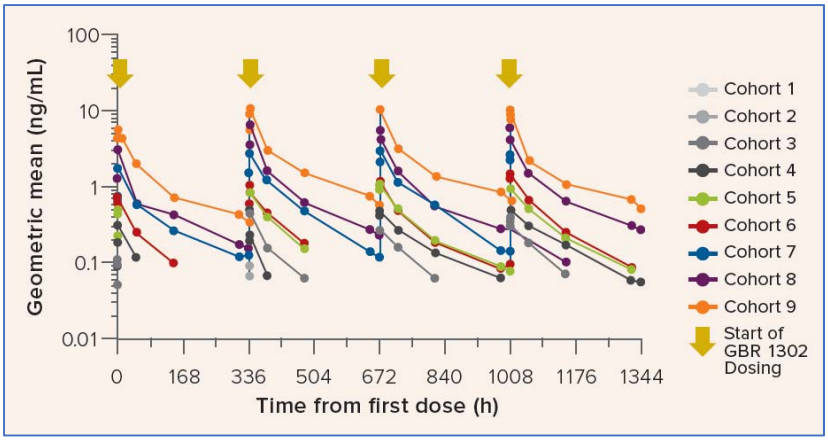
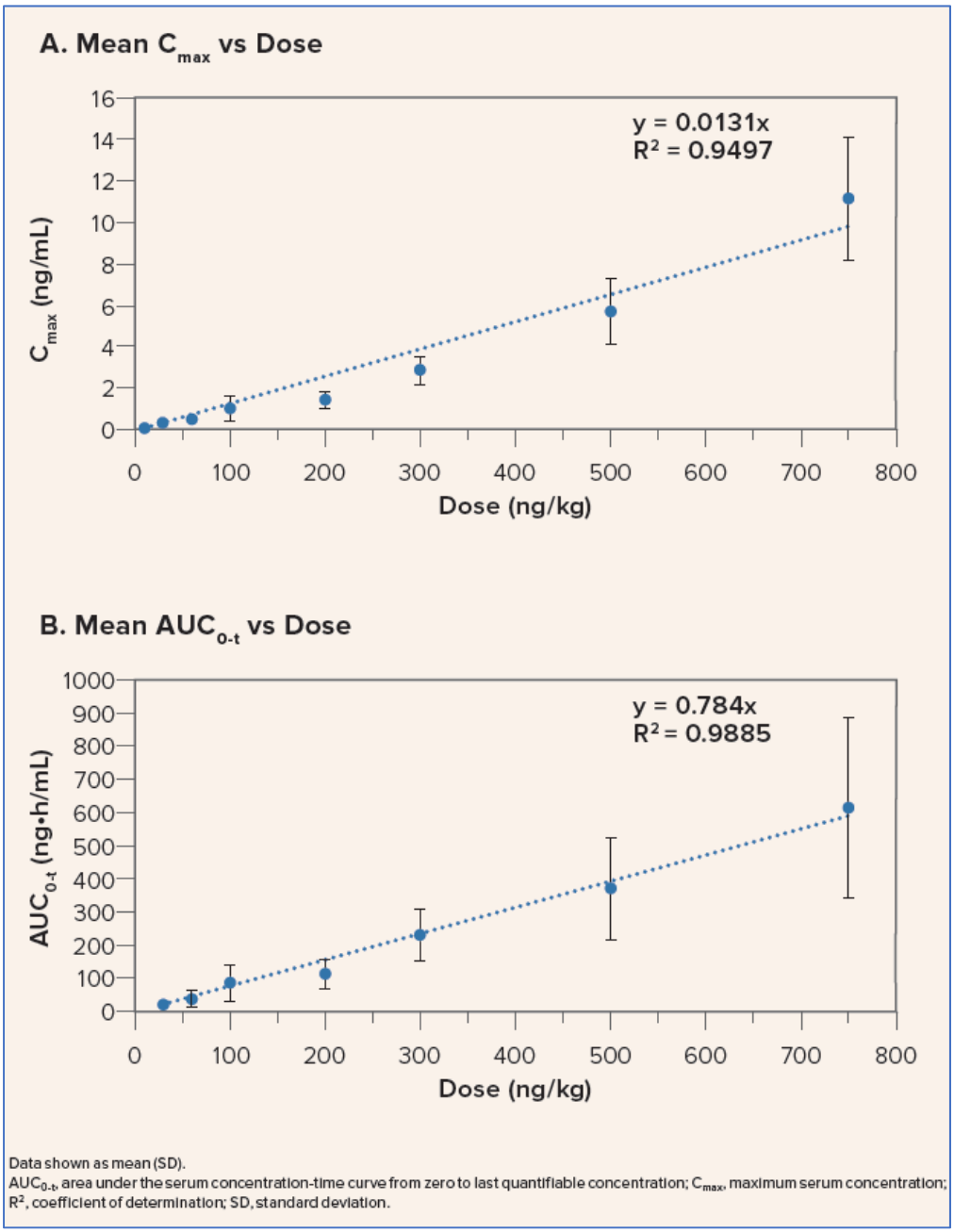


Figure 4. GBR 1302 Exposure vs Dose



Data shown as mean (SD).
AUC_{0-t}, area under the serum concentration-time curve from zero to last quantifiable concentration; C_{max}, maximum serum concentration; R^2, coefficient of determination; SD, standard deviation.

KEY FINDINGS

Table 1. Summary of Pharmacokinetic Parameters of GBR 1302

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

Data shown are mean (SD), unless otherwise noted.
Data not shown for Cohorts 1 – 4 (n=1 each).
[a] Median (min-max); [b] n=2; [c] n=3; [d] n=1, [e] 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