Abstract: CT101-4927- Phase I Clinical Trials

A phase I safety and bioimaging trial of ifabotuzumab (KB004) in patients with glioblastoma

H.K. Gan[1,2,3], L. Cher[1,2], P. Inglis[4], Z. Lwin[4], E. Lau,[2] C. Wichmann[1,3], A. McDonald[1,3], U. Ackermann[1,2], K. Remen[2], K. Fluck[2], G. Bolarnos[4], N. Guo[1,3], S.T. Lee[1,2,3,5], S. Gong[5], J. Palmer[1,3], K. Pathmaraj[5], G. O'Keefe[5], F.E. Scott[1,3], B.W. Day[6], A.W. Boyd[1,4], P. Thomas[4,8], O. Ahmed[7], D. Chappell[7], C. Durrant[7], A.M.Scott[1,2,3,5]

[1] Olivia Newton-John Cancer Research Institute, Heidelberg, VIC, Australia; [2] Austin Health, Heidelberg, VIC, Australia, [3] School of Cancer Medicine, La Trobe University, Heidelberg, VIC, Australia, [4] Royal Brisbane and Womens Hospital, Herston, QLD, Australia; [5] Dept. of Molecular Imaging and Therapy, Austin Health, VIC, Australia; [6] QIMR Berghofer Medical Research Institute, Herston, Qld, Australia.; [7] Humanigen Inc, California, USA; [8]School of Medicine, University of Queensland, Australia.

Background

Glioblastoma multiforme (GBM) is the most frequent and lethal primary brain neoplasm, with only 10% of patients surviving 5 years.[1] EphA3 is a tumor restricted antigen expressed in various solid tumors and the tumor vasculature of 100% of GBM.[2,3] Ifabotuzumab is a non-fucosylated IgG1κ Humaneered® antibody targeting the EphA3 receptor.[4] A Phase I study of ifabotuzumab in haematological malignancies showed it was well tolerated and clinically active.[5] Here we report on a Phase I dose escalation and biodistribution study of ifabotuzumab in recurrent GBM.

Results

12 patients (pts) were enrolled in the study, with 6 pts in each cohort (3.5mg/kg and 5.25mg/kg). Figure 1 outlines the study schema.

Demographics & medical history

Mean patient age at enrolment was 51.6 years (±14.24; age range: 24 – 71 years), with approx. 58% (7/12) male and 42% (5/12) female pts.

Prior anti-cancer treatment history		N (%)
Surgery:	Gross tumor resection	9 (75%)
	Subtotal resection	2 (16%)
	Biopsy only	1 (9%)
Post Operative Radiotherapy:	60Gy, 30 fractions	10 (82%)
	59.4Gy, 33 fractions	2 (18%)
Concurrent chemotherapy:	Temozolomide + Adjuvant Temozolomide	11 (81%)
	Temozolomide	1 (9%)*
Previous anti cancer therapy for recurrent disease:	Subtotal resection and ABT-414 + Temozolomide	1(9%)
	Carboplatin	3(25%)
	Nil	8(66%)

Table 1. Prior treatment history of patients
All pts had received radiotherapy with concurrent chemotherapy. Ten pts were treated at first progression after post-operative chemoradiation therapy. Two pts had received treatment for recurrent disease (Pt: 002 had additional surgery and participated in a clinical trial of ABT-414 + Temozolomide). *1 participant received only concurrent Temozolomide with RT.

Toxicities observed on study

	Total Reported AEs	Treatment Related AEs		Unrelated
	Pts N (%)	Grade 1/2 N	Grade 3/4 N	All grades N
Infusion reactions	4 (33%)	4	0	0
Seizures	3 (25%)	1	0	2(Gr1 & 3)
Cerebral edema	2 (33%)	1	0	1 (Gr1-3)
Rash	1 (16%)	0	1	0
Diarrhea	2 (33%)	1	0	1 (Gr1)
Eye disorder	3 (25%)	0	0	2 (Gr1/2)
Headache	9 (75%)	1	1	7 (Gr1-3)

Table 2. Treatment emergent adverse events
No dose limiting toxicities were observed on trial, all AEs were readily manageable.

Study Design

Primary objective

To determine the safety and recommended Phase II dose of ifabotuzumab in GBM patients (pts).

Primary outcome measures
Number of treatment-related Adverse Events as assessed using CTCAE v4.0 to determine RP2D.

Secondary outcome measures
1. Biodistribution of ^{89}Zr-ifabotuzumab (^{89}Zr-ifab)
2. Response rates following ifabotuzumab infusion
3. Plasma concentration versus time (Serum half-life) of ^{89}Zr-ifab

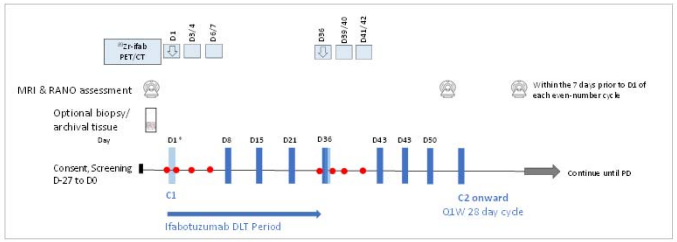

Figure 1 Study Schema.
^{89}Zr-ifab tracer infusion ⇩ is delivered 1-2 hours before imaging □. Ifabotuzumab is administered weekly by IV infusion ▮ over 2 hrs. Trace infusion * 5mg total protein dose ifabotuzumab D1 only, subsequent doses as per cohort.
Serum samples ● for ^{89}Zr-ifab PKs will be obtained pre-infusion, at 5 min, 60 min (+10 min), 2 hrs (±15 min), 4 hrs (±15 min) and 24hrs (±15 min) post infusion, then on days when PET/CT images are acquired.

Biodistribution of ^{89}Zr-ifabotuzumab

^{89}Zr-ifabotuzumab showed rapid, specific targeting of GBM tumor in all patients (arrow) as shown in Figure 2. Whole body biodistribution images showed no specific normal tissue uptake of ^{89}Zr-ifabotuzumab.

Figure 2. Tumor uptake of ^{89}Zr-ifabotuzumab in GBM patient
Post-treatment MRI scans showed predominant T2/FLAIR changes, occasionally marked, which were consistent with treatment effect on tumor vasculature.

Pharmacokinetics of ^{89}Zr-Ifabotuzumab

Pharmacokinetic analysis (n=12) for first infusion ^{89}Zr-ifabotuzumab showed (mean ± SD) $T½\alpha$= 9.03 ± 4.45 hr, $T½\beta$ = 92.50 ± 65.65 hr, V1 = 3.75 ± 0.67 L, CL= 132.11 ± 70.16 mL/hr.

Response to therapy

All patients enrolled have been evaluated by repeat RANO, the **best response** observed was stable disease for 23 weeks as illustrated in Figure 3.

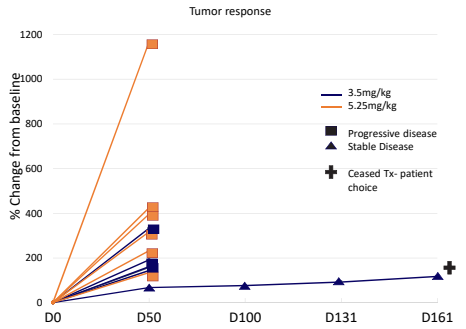

Figure 3. Spider plot of response of patients on ifabotuzumab
Two cohorts (3.5mg/kg and 5.25mg/kg) enrolled 6pts each. All patients were evaluable having at least 1 dose of ifabotuzumab and were assessable by RANO criteria. 11/12 patients progressed by D50, one patient had a durable stable response of >5 months to Ifabotuzumab at 3.5mg/kg.
+ Patient withdrew from study for personal reasons unrelated to study drug

Conclusions

- Ifabotuzumab demonstrated highly sensitive, specific and reproducible targeting of the tumor and tumor microenvironment in all patients in this study.
- The imaging changes suggest direct modulation of the tumor vasculature.
- No objective responses were observed. Additional studies are planned to evaluate ifabotuzumab alone and as an antibody-drug conjugate in solid tumor patients.

References

1. Stupp R, et al, Lancet Oncology 10:459-66, 2009 2. Day BW, et al. Cancer Cell 23:238-48, 2013 3. Vail ME, et al. Cancer Research 74:4470-81, 2014 4. Tomasevic N, et al. Growth Factors 32:223-35, 2014 5. Swords RT, et al. Leukemia Research 50:123-131, 2016

Institutional review board approval: HREC/17/Austin/79; ClinicalTrials.gov registration: NCT03374943.

Acknowledgements

This trial has been generously supported by the Cure Brain Cancer Foundation and Humanigen.