Mechanism of Action of GRN1005

Yamamoto M, Ikeda K, Ohshima K, et al. Increased expression of low density lipoprotein receptor-related protein (LRP) on tumors, high LRP in tumor cells facilitates the transport of the prodrug GRN1005 [Figure 1 and Figure 2].

GRN1005 is a prodrug which is believed to be converted to active drug in tumor cells. GRN1005 has been shown to cross the BBB via LRP mediated transcytosis [Figure 1].

References

Shibata M., Yamada S., Kumar SR et al., Clearance of Alzheimer's amyloid-β(1-40) peptide at therapeutic levels [Breedveld et al., 2006, Gabathuler, 2010].

Study design

Purpose: Investigate effectiveness and tolerability of GRN1005 in patients with brain metastases from breast cancer.

Patients: Patients with measurable brain metastases (with a maximum size of ≤1 cm) will receive 1500 mg/m2 of GRN1005 every 3 weeks.

Endpoints: Response will be assessed with the exception of duration of response for the 550 mg/m2 dose. The primary endpoint will be objective response rate (ORR) in patients with brain metastases from breast cancer.

Analysis Population

The primary analysis will be performed on the patient population with complete response (CR) or partial response (PR) in CNS, by IRF per CNS RECIST v1.1 (Shibata et al., 2000; Shinohara et al., 2010) and on the cells of various tumor types [Yamamoto et al., 1997, 1998; Demeule et al., 2008].

Interim Analysis

The interim analysis will be performed for the first 30 evaluable patients (complex). Data will be used on an investigator's report to complement two phase 1/2 studies (on investigator's report) on enrollment of patients with a central core of study drugs.

Safety: Safety and tolerability will be assessed in all patients who receive study treatment. The interim analysis will be performed to determine optimal doses and determine if GRN1005 will be further evaluated in the clinic.

Total (N=53)

Adverse Events HER2- (N=32) HER2+ (N=21)

Anemia 26 (81%) 1 (3%) 17 (81%) 2 (10%) 43 (81%) 3 (6%)
Leukopenia 22 (69%) 12 (38%) 19 (90%) 15 (71%) 41 (77%) 27 (51%)
Neutropenia 17 (53%) 12 (38%) 18 (86%) 14 (67%) 35 (66%) 26 (49%)

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Most Frequent Non-hematological Adverse Events

Adverse events include spinal cord compression, infection, neutropenia, pulmonary embolism, respiratory failure, fatigue, weakness and leg pain.

Inclusion criteria:

- Adult patients with measurable brain metastases from breast cancer.
- Prior trastuzumab and KPS ≥70%
- Women must have a negative pregnancy test base.
- Men or women of reproductive age must agree to use effective contraception.

Safety results-all patients at starting dose of 550 mg/m2

Efficacy results-first 30 evaluable at starting dose of 550 mg/m2

Intra-Cranial Objective Response Rate by IRF

- Best Percent Change in Sum of Intra-Cranial Target Lesions by IRF

summary of all patients at starting dose of 650 mg/m2

- Drug-related events (≥3 dose levels, dosing intolerance, intercurrent illness, etc.) will be considered at the date of discontinuation of GRN1005 due to any AEs.
- All patients, caregivers and staff who have participated in this study.

References

Shibata M., Yamada S., Kumar SR et al., Clearance of Alzheimer's amyloid-β(1-40) peptide at therapeutic levels [Breedveld et al., 2006, Gabathuler, 2010].

Primary Endpoint Summary

- The interim analysis based on first 30 evaluable patients resulted in no confirmed intracranial responders as assessed by IRF according to modified CNS RECIST.
- The protocol specified efficacy boundary has been crossed for patients with 1500 mg/m2 every 3 weeks starting dose.

Study Status

- As of November 30, 2012, a total of 47 patients have been enrolled with 10 discontinuing treatment due to AEs.
- Five patients have discontinued treatment due to death.
- Due to meeting the futility boundary the study is now closed to further accrual.

GRABM-B, A phase 2, Multi-center, Open Label Study Evaluating GRN1005 Alone or in Combination with Trastuzumab in Breast Cancer Patients with Brain Metastases - Preliminary Results (Interim Analyses)

Introduction

- GRN1005 has been shown to cross the BBB via LRP mediated transcytosis [Figure 1].
- Further, has a low terminal elimination half-life, baselines on the trend of size of the brain and tumor [Figure 2].
- The terminal body weight affects the total body clearance, followed by a linear relationship.

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Conclusion

- The trial the interim analysis for futility based on an OBD of 0.7 for all eligible patients with brain metastases from breast cancer and that will be closed for further accrual.
- Patients that study will continue to be followed for efficacy and safety.
- The interim analysis, GRN1005’s safety profile is acceptable and quality consistent with that of paclitaxel administered early in 3-week cycles (30 cycles).
- Although intracranial activity (≥3.00% per ITT) was observed at 1500 mg/m2, the data did not meet the study’s futility boundary.
- The dose level did not lead to unacceptable toxicity.

Acknowledgments

- All of the patients, caregivers and staff who have participated in this study.

Appendix I: Study Interventions

- GRN1005 (550mg/m2) + trastuzumab
- GRN1005 (550mg/m2)