Abstract C209: Strong Synergistic Activity of NKTR-102 – Pegylated Liposomal Doxorubicin (PLD) Combination Therapy in a Nonclinical Model of Platinum Resistant A2780 Human Ovarian Cancer

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Purpose: NKTR-102, a next generation topoisomerase I inhibitor, has been demonstrated to be superior to etoposide, carboplatin and irinotecan in a mouse model of platinum-resistant A2780 Human Ovarian Cancer (Abstract 805, ECCO 15-ESMO 34; 32-SEP-10). NKTR-102 as a single agent in women with platinum resistant/refractory ovarian cancer who have failed pegylated liposomal doxorubicin (PLD) therapy has demonstrated a confirmed ORR of 17% (RECIST 1.0, n = 20-30) (CISCA 2011 Vol. 25, No. 15, suppl. 1; SEER 2011). As a single agent, NKTR-102 appears highly active in the defined population, however, we hypothesize that the combination of NKTR-102 and PLD could result in synergistic activity through concurrent, long lasting inhibition of topoisomerase I. This report is a presentation of the results of a study of NKTR-102 as a single agent, and a combination of NKTR-102 and PLD in mice bearing A2780 Human Ovarian tumors that are minimally responsive to carboplatin. Methods: NKTR-102 was determined to be 10 mg/kg q7dx2 in a pilot study. NKTR-102 doses were limited to 150 mg/kg due to toxicity and dose volume limitations rather than tolerability. Mice bearing A2780 ovarian tumors (~ 100 mm3) received either vehicle, PLD, NKTR-102, or a combination of NKTR-102 and PLD as follows for 10 mg/kg PLD on days 1 and 8; 100 or 150 mg/kg NKTR-102 on day 1 or 5/100, 10/100, 5/150, or 10/150 mg/kg PLD on days 1/NKTR-102 on day 1 (n = 10/treatment). Anti-tumor efficacy was evaluated based on tumor growth delay (TGD) and regression response rate. To qualify as partial regression (PR), the tumor volume had to be 50% or less of its Day 1 volume for three consecutive measurements. To qualify as complete regression (CR), the tumor volume had to be 0% or less of the Day 1 volume for three consecutive measurements. To qualify as complete remission (CR), the tumor volume had to be less than 1.3 mm3 for three consecutive measurements. TGD was calculated as the time to reach a tumor volume of 2000 mm3. BW: body weight.

Results

- NKTR-102 and PLD in combination showed marked synergism demonstrated by high tumor activity in a range of tumors in Phase I (17% confirmed PRs; EMA 2008, also SLB).
- NKTR-102 showed a 22% confirmed response rate per RECIST in heavily pre-treated women with platinum resistant/refractory ovarian cancer (ASCO 2010, also SLB), and a 39% confirmed response rate in NSCLC (SARC 2010, also SLB).
- The combination of NKTR-102 and PLD did not show any significant toxicity compared to PLD as a single agent in mice bearing A2780 ovarian tumors (~ 100 mm3).
- All treatments were acceptably tolerated.
- Combination of NKTR-102 and PLD did not increase the body weight loss over single agents.
- No remarkable clinical observations.

Conclusions

- NKTR-102 demonstrated high anti-tumor activity in a range of tumors in Phase I (17% confirmed PRs; EMA 2008, also SLB).
- Combination of NKTR-102 and PLD did not show any significant toxicity compared to PLD as a single agent in mice bearing A2780 ovarian tumors (~ 100 mm3).

Background

- Nektar’s proprietary polymer conjugation technology to improve the pharmacokinetics of topoisomerase I inhibitors and its active metabolite SN38.

Objective

To investigate the nonclinical anti-tumor activity of NKTR-102 (topoisomerase I inhibitor) in combination with PLD (topoisomerase II inhibitor) in the platinum resistant A2780 ovarian tumor model.

Study Design

Tumor cells were cultured and implanted subcutaneously in 9-10 week old female athymic nude mice. Animals were randomized into treatment groups (n=10/group) when their tumors reached 75-144 mm3. Tumors were measured until an endpoint (2000 mm3 or Day 76) was met. Efficacy was measured by tumor volume limitations rather than tolerability. Mice bearing A2780 ovarian tumors (~ 100 mm3) received either vehicle, PLD, NKTR-102, or a combination of NKTR-102 and PLD as follows for 10 mg/kg PLD on days 1 and 8; 100 or 150 mg/kg NKTR-102 on day 1 or 5/100, 10/100, 5/150, or 10/150 mg/kg PLD on days 1/NKTR-102 on day 1 (n = 10/treatment). Anti-tumor efficacy was evaluated based on tumor growth delay (TGD) and regression response rate. To qualify as partial regression (PR), the tumor volume had to be 50% or less of its Day 1 volume for three consecutive measurements. To qualify as complete regression (CR), the tumor volume had to be 0% or less of the Day 1 volume for three consecutive measurements. To qualify as complete remission (CR), the tumor volume had to be less than 1.3 mm3 for three consecutive measurements. TGD was calculated as the time to reach a tumor volume of 2000 mm3.

Tolerability/Toxicity

- All treatments were acceptably tolerated.
- Maximum mean body weight losses were minimal or zero for single agent NKTR-102.
- Maximum mean body weight losses were less than 10% for single agent PLD.
- Combination of NKTR-102 and PLD did not increase the body weight loss over single agents.
- No remarkable clinical observations.

Acknowledgment:

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