Development of Glutathione PEGylated Liposomal Doxorubicin (2B3-101) for the Treatment of Brain Cancer

Pieter Gaillard¹, Werner Gladdines¹, Chantal Appeldoorn¹, Jaap Rip¹, Willem Boogerd², Jos Beijnen², Dieta Brandsma² and Olaf van Tellingen²
¹To-BBB technologies BV, Leiden, the Netherlands; ²The Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital (NKI-AvL), Amsterdam, the Netherlands

Summary
The G-Technology®, using glutathione as targeting ligand, is able to safely enhance drug delivery across the blood-brain barrier, and we have applied this on already marketed pegylated liposomal doxorubicin (Doxil/Caelyx).

• The therapeutic benefit and predictable safety profile of clinical-scale 2B3-101 (glutathione pegylated liposomal doxorubicin) was successfully demonstrated in translational preclinical studies.

• A clinical trial to determine the safety, tolerability and pharmacokinetics of 2B3-101 in patients with solid tumors and brain metastases or recurrent malignant glioma is currently ongoing.

Clinical Scale Production of 2B3-101
• 2B3-101 was prepared using a pre-insertion method, in which GSH-PEG micelles were added to the lipids (HSPC and cholesterol) before extrusion and active loading of doxorubicin.

• 3 batches (each 2L) have been prepared by TTY Biopharm (Taiwan) and were tested for stability: at 5°C 2B3-101 was stable for at least 18 months.

Safety of 2B3-101
No major differences were observed between 2B3-101 and Doxil/Caelyx:
• Body weight
• Inflammatory lesions of the skin or the mucosa
• Myelosuppression
• No cardiotoxicity
• Absence of neurotoxicity
• No neurobehavior findings in EEGs and a GLP-modified Irwin test
• No relevant toxicity findings were observed with empty GSH-PEG liposomes

Efficacy of 2B3-101
• Mice with experimental brain tumors (U87 glioblastoma model; n=10/group) received 2B3-101 at 2 maximum tolerated dosing regimens.

• 10 mg/kg q4dx4 and 18 mg/kg q8dx2 showed a survival benefit of 57% and 60% respectively when compared to saline, where 18 mg/kg q8dx2 seemed superior.

• Mice with experimental brain tumors (U87 glioblastoma model; n=9/group) received 2B3-101 or Doxil/Caelyx (5 mg/kg twice weekly). 2B3-101 inhibited brain tumor growth and prolonged survival.

• Mice with subcutaneous MDA-MB-231 human breast carcinoma xenografts received 2B3-101 and Doxil/Caelyx (10 mg/kg q4dx3, n=10/group). Both treatments produced significant anti-tumor activity and were well tolerated, confirming that 2B3-101 has remained its systemic activity.