**Percutaneous Hepatic Perfusion (CHEMOSAT® or CS-PHP) of Melphalan in Patients with Hepatic Metastases from Melanoma: Phase III Pharmacokinetic Analysis**

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### Background

- Chemoradiation therapy with percutaneous hepatic perfusions (CS-PHP, CHEMOSAT®) is a minimally invasive, repeatable regional therapy which—allows percutaneous inter-arterial administration of a chemotherapeutic agent to the liver—subsequently filters the regional (hepatic) venous blood by extracorporeal filtration—lowers the concentration of chemotherapeutic agent in the blood before returning it to the systemic venous circulation.

- CS-PHP is available in the EU and Australia, and is currently undergoing FDA review.

### Purpose

- A randomized phase 3 study (n=93) compared CS-PHP using high-dose melphalan with best alternative care (BAC) in patients with ocular or cutaneous melanoma metastatic to the liver—based on an intention-to-treat analysis by the investigators (April 2010, primary data lock), CS-PHP melphalan significantly improved hepatic progression-free survival by 6.4 months at the median, with a hazard ratio of 0.36 (95% CI 0.18–0.64; p=0.001) versus BAC.

### Study Design

- Randomized, open-label, multicenter phase 3 study.
- Patients: Ocular or cutaneous metastatic melanoma predominantly in the liver parenchyma with limited extra-hepatic disease.

### Treatment

- Melphalan CS-PHP:—3.0 mg/kg as a 30-minute hepatic intra-arterial infusion—an additional 30 minutes of extracorporeal filtration at end of infusion (washout)—under general anesthesia—up to 6 treatments, repeated every 4–8 weeks.

### Pharmacokinetic Sampling

- Blood samples were collected during cycle 1 of CS-PHP melphalan.
- Samples (7 mL) were collected from 3 sites at each timepoint:—systemic (arterial line in the arm)—pre-filter (extracorporeal circuit)—post-filter (extracorporeal circuit).

### Sample collection times: baseline, 15 minutes after infusion start, immediate post-infusion; and 5, 10, 15, and 30 minutes post-infusion.

- Plasma concentrations of melphalan were determined by high-pressure liquid chromatography with ultraviolet detection:
  - assay was validated, sensitive and accurate.

### Pharmacokinetic Analysis

- Data were analyzed using a non-compartmental approach with WinNonlin v5.2 (Pharsight Corporation, Mountain View, CA).

### Results

- Mean filter efficiency was 71.2% (range 26.4–86.8%).

### Conclusions

- CS-PHP effectively exposes the liver to high concentrations of melphalan.
- The mean filter extraction efficiency of the first-generation CS-PHP filtration system is 71%.
- Sixty minutes of filtration using the CS-PHP system consistently removes most of the melphalan administered, minimizing systemic exposure.
- The PK and filter extraction efficiency data support the clinical evidence of substantial regional efficacy of CS-PHP in controlling liver-dominant metastases with a manageable safety profile.

### References


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