Persistent prevention of CIPN using calmangafodipir (PledOx®): Results from a placebo-controlled randomized phase II study (PLIANT) in patients with metastatic colorectal cancer (mCRC)

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Introduction and Objective

Chemotherapy-induced peripheral neuropathy (CIPN) is a major problem after oxaliplatin treatment.

Calmangafodipir (PledOx), has shown promising activities in model systems in preventing oxaliplatin-induced adverse effects (Karlsson et al. 2015). In a dose-escalating phase I study including 11 patients, doses up to 10 µmol/kg were well tolerated and had promising preventive effects on CIPN (Glimelius et al. 2015).

A randomized placebo-controlled multicenter phase II study (NCT 01619423) assessed safety and efficacy of PledOx in ameliorating CIPN.

Methods

The PLIANT study included 173 mCRC patients treated with the FOLFOX-6 regimen (oxaliplatin 85 mg/m^2, calciumfolinate 200 mg/m^2, 5FU bolus 400 mg/m^2, 5FU infusion 2400 mg/m^2) every fortnight either in first or second-line. Ten minutes prior to each chemotherapy cycle PledOx 2 and 5 (initially 10) µmol/kg or placebo was given intravenously during 5 minutes.

Primary endpoint was neurotoxicity according to the Oxaliplatin Sanofi Specific Scale , evaluated by the physician prior to each cycle up to cycle 8.
Secondary endpoints included the patient reported outcomes Cold Allodynia Test and the Leonard Scale at each cycle up to cycle 8, end-of -treatment and during follow-up every 3 months (up to 12 months). Disease and tumor evaluations after 4 and 8 cycles and during follow-up every 3 months.

References: Karlsson et al. Drug Discovery Today 2015 , Glimelius et al. MASCC Meeting Copenhagen 2015

Figure 1. Reduction of investigator reported CIPN

(excl. first two cycles)

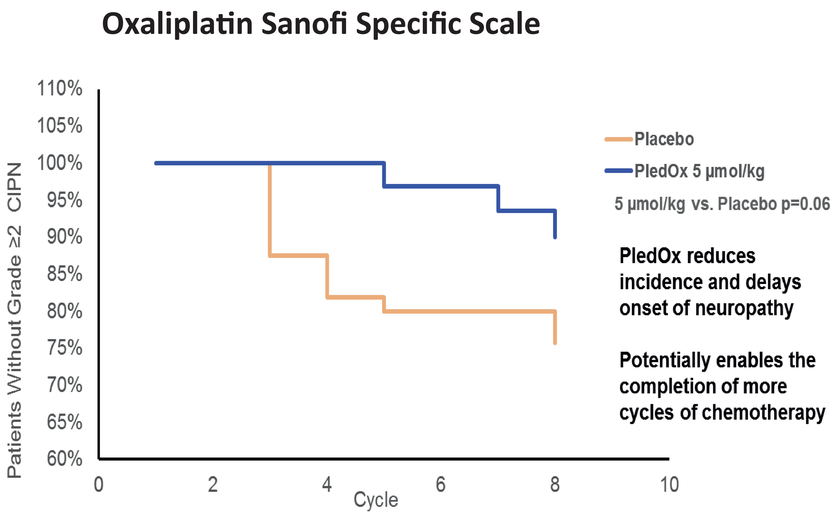
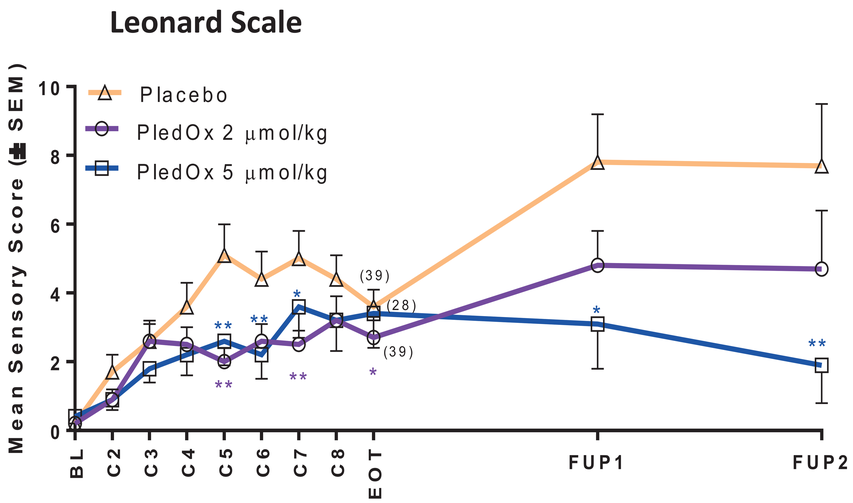
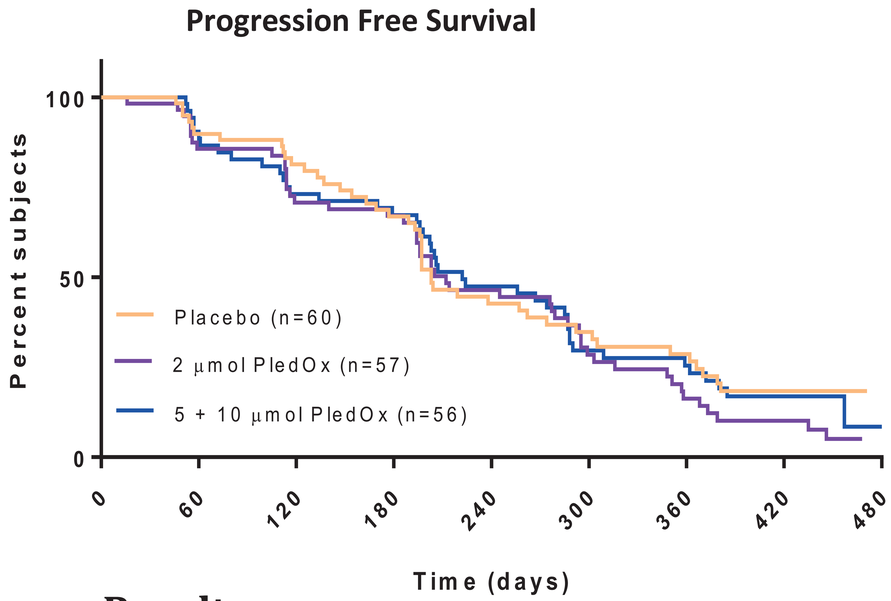


Figure 2. Delayed onset and reduced incidence of patient reported acute and persistent CIPN



Number within brackets indicate number of patients that completed at least 7 cycles of chemotherapy and completed the optional Leonard questionnaire during at least one of the follow-up visits

Figure 3. PledOx does not interfere with the anti-cancer effect of chemotherapy



Results

PledOx was well tolerated. CIPN according to the Oxaliplatin Sanofi Specific scale (Figure 1) was clearly less in patients treated with 5 µmol/kg after the 3rd up to the 8th cycle (p=0.06). PledOx had a dose-dependent and significant effect on persistent CIPN measured as mean sensory score on the 3 and 6 months FU. See Figure 2 for further details (* p<0.05, ** p<0.01 vs. placebo). There were no signs of any negative influence on the antitumor effects from chemotherapy (Figure 3). Furthermore, objective responses (CR+PR) was seen in 30% in the placebo group and 40% in the group treated with PledOx 2 µmol/kg and 30% in the group treated with 5+10 µmol/kg.

Conclusions

The activity of the chemoprotector PledOx is promising in preventing acute and persistent CIPN without any detectable negative influence on the antitumor activity of an oxaliplatin-5FU combination in patients with mCRC. A phase III trial using 5 µmol /kg will be initiated.