Safety and effectiveness of plasmapheresis-based elimination of soluble TNFα receptors combined with chemotherapy in advanced, chemorefractory triple-negative breast cancer patients - a phase I/II study (CP7-005) ***NCT04004910***

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INTRODUCTION

Tumor necrosis factor-alpha (TNFα) is a pleiotropic cytokine with known antitumor activity, produced mainly by activated immune cells. Cancer cells neutralize TNFα by shedding soluble TNF receptors 1&2 (sTNF-Rs), which act as TNFα-binding decoys, promoting cancer cell proliferation, survival, and chemoresistance (Fig 1., Tabl. 1). Immunopheresis® employs therapeutic apheresis with the selective immunoadsorption LW-02 column (LW-02) for treating solid malignancies. LW-02-based Immunopheresis® (granted FDA Breakthrough Device Designation and a CE Mark for mTNBC) selectively removes sTNF-Rs from plasma, permitting TNFα to bind to membrane-bound TNF-Rs, activating intracellular death pathways, and also modulate T-cell-mediated immune activity. Part A data of our phase I/II clinical trial in metastatic, chemorefractory, triple-negative breast cancer (mTNBC) patients (NCT04004910) confirmed that LW-02-based Immunopheresis monotherapy is safe and well-tolerated, with signs of disease stabilization (SD) in patients treated >4 weeks. Here we present interim data on the safety and preliminary efficacy of LW-02 Immunopheresis combined with chemotherapy.

CONTACT

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RATIONALE

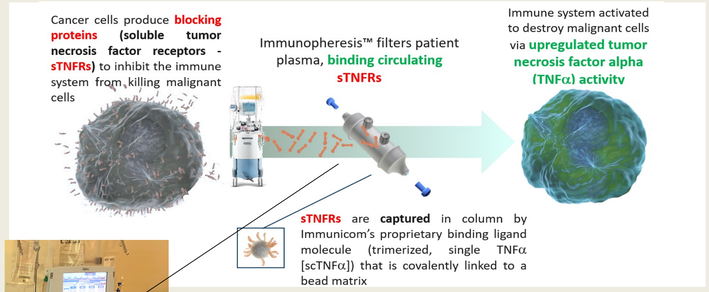


Figure 1. General concept

Figure 2. Spectra Optia

LW-02 – MECHANISMS OF ACTION

TNFα – related

- tumor cell apoptosis
- microvascular collapse
- stimulation of M1 macrophages
- inhibition of Tregs

sTNFR-depletion related

- unleashing of sTNF in tumor microenvironment
- inhibition of tmTNF retrograde signaling
  - decreased survival
  - decreased chemoresistance

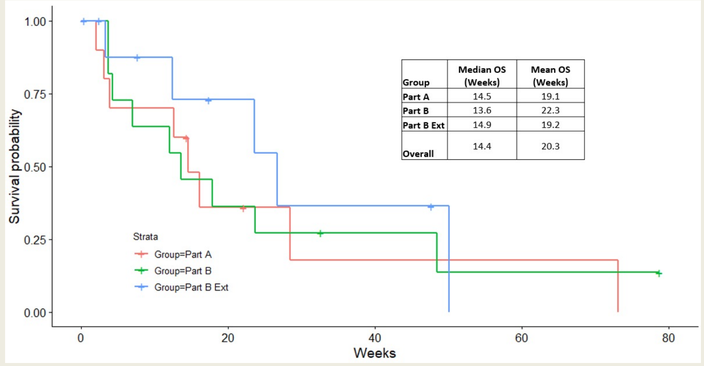
Table 1. Serum concentrations of sTNFR1&2 in various tumors

Values (pg/ml)		Melanoma N=45	Sarcoma N=43	NSCLC N=40	RCC N=31	Ovarian N=42	Breast N=30	Normal N=20
sTNF-R1 (expressed on tumor cells)	Mean	**1,964** ±462	**1,502** ±356	**1,554** ±311	**1,865** ±437	**1,549** ±355	**1,478** ±349	**670** ±232
	Range	934 - 2,886	723 - 2,136	908 - 2,212	554 - 2661	866 - 2,420	1,030 - 2,665	75 - 1,285
sTNF-R2 (expressed on immune cells)	Mean	**1,537** ±312	**1,259** ±315	**1,351** ±291	**1,490** ±282	**1,359** ±345	**1,446** ±231	**568** ±204
	Range	1,054 - 2,146	476 - 1,767	610 - 1,775	1,030 - 1,989	509 - 1,872	852 - 2,108	74 - 1,094

TREATMENT

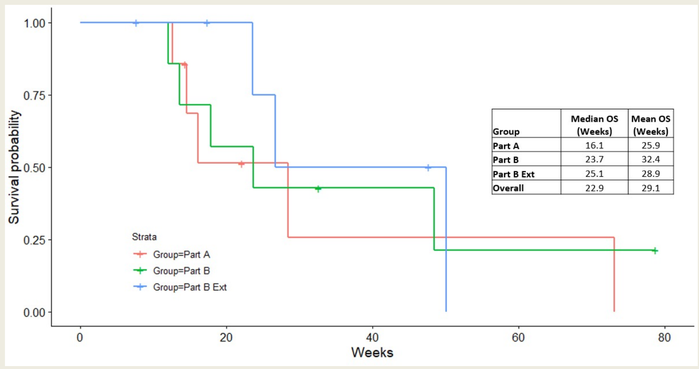
LW-02 Immunopheresis® (3x/week for 16 weeks) using a Spectra Optia device (fig. 2) is combined with paclitaxel (80 mg/m2) + carboplatin (AUC 2) d 1,8 q3w [part B] or irinotecan(125 mg/m2)+gemcitabine(750 mg/m2) d1,8 q3w [Part B-ext] in patients with mTNBC. Treatment lasts 16 weeks in clinical and/or objective responders. Primary endpoints are safety and tolerability. Secondary endpoints assessed in patients treated >4 weeks include overall survival, tumor response according to RECIST, rate of CNS progression and quality-of-life.

Of 11 patients enrolled in Part B of the study, 7 patients were treated for >4 weeks. The ORR was 18% (1CR, 1PR) with one additional patient experiencing SD; the ORR and CBR in patients treated >4 weeks were 29% and 43%, respectively. The median OS, to date, is 18.6 weeks and 26.7 weeks in the group treated >4 weeks. The rate of CNS progression (new or preexisting lesions) appears lower than expected. The most common adverse events (AEs) were chemotherapy-induced myelotoxicity (anemia, neutropenia, thrombocytopenia) and transient electrolyte abnormalities. Thirty-one serious AEs (SAEs) were reported for all 11 patients, 15 (48.4%) were transfusion requiring anemias. Of the SAEs, 3 (9.6%) were judged to have a potential causal relationship to LW-02 column Immunopheresis ®.



Group	Median OS (Weeks)	Mean OS (Weeks)
Part A	14.5	19.1
Part B	13.6	22.3
Part B Ext	14.9	19.2
Overall	14.4	20.3

Figure 3. Overall survival of all patients in CP7-005 study. Part A: LW-02-based Immunopheresis alone, Part B: LW-02 + chemotherapy (paclitaxel + carboplatin), Part B-ext: LW-02 + chemotherapy (irinotecan + gemcitabine)



Group	Median OS (Weeks)	Mean OS (Weeks)
Part A	16.1	25.9
Part B	23.7	32.4
Part B Ext	25.1	28.9
Overall	22.9	29.1

Figure 4. Overall survival of patients in CP7-005 study treated >4 weeks. Part A: LW-02-based Immunopheresis alone, Part B: LW-02 + chemotherapy (paclitaxel + carboplatin), Part B-ext: LW-02 + chemotherapy (irinotecan + gemcitabine)

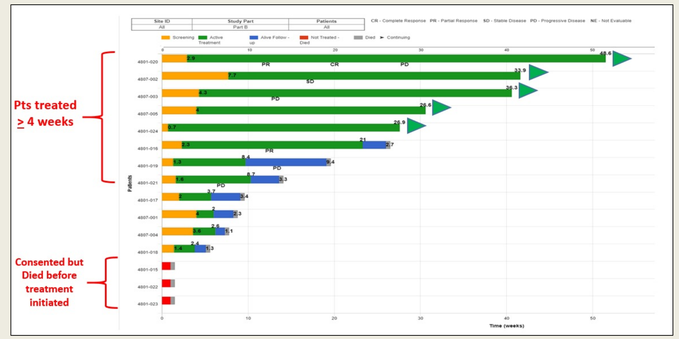


Figure 5. Swimmer plot of patients treated with LW-02-based Immunopheresis + chemotherapy

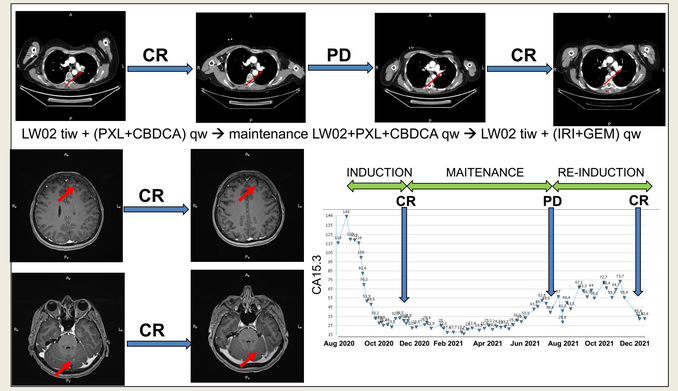


Figure 6. Presentation of a patient (after 3 lines of previous chemotherapy) with complete response (CR) to LW-02 + carboplatin + paclitaxel after 4 months of treatment, with progression (PD) after 9 months of maintenance, and subsequent CR (after 5 months) to LW-02 + irinotecan + gemcitabine

CONCLUSIONS

LW-02-based Immunopheresis® combined with weekly chemotherapy is generally safe, well-tolerated and highly effective in specific sTNFR subtraction on a longer-term basis, with promising signals of clinical benefit in heavily pretreated mTNBC patients (median 3.3 [2-5] prior lines of systemic therapy). Further clinical evaluation of the antitumor activity of LW-02-based Immunopheresis combined with low-dose chemotherapy is ongoing with a focus on quality-of-life and prevention of CNS disease progression, the latter especially important in chemorefractory mTNBC, given the high prevalence of CNS involvement.