

# Near complete remission in a stage IV triple negative breast cancer (TNBC) with low-dose checkpoint inhibitors in combination with high dose interleukin-2 (IL-2) and fever range whole body hyperthermia

Ralf Kleef<sup>a</sup>, Ralph Moss<sup>b\*</sup>, Marcell Szasz<sup>d</sup>, Arthur Bohdjalian<sup>e</sup> and Tibor Bakacs<sup>f</sup>

## Addresses:

<sup>a</sup>Immunology & Integrative Oncology; Auhofstraße 1, A-1130 Vienna, Austria; [ralf.kleef@dr-kleef.at](mailto:ralf.kleef@dr-kleef.at)

<sup>b</sup>Cancer Decisions, PO Box 1076, Lemont, PA 16851; [ralphwmoss@gmail.com](mailto:ralphwmoss@gmail.com);

<sup>d</sup>2nd Department of Pathology, Semmelweis University, Budapest, Hungary, and Division of Oncology and Pathology, Department of Clinical Sciences Lund, Faculty of Medicine, Lund University, Lund, Sweden; [szaszam@gmail.com](mailto:szaszam@gmail.com)

<sup>e</sup>Rudolfinerhaus Hospital, 1190 Vienna, Austria; [a.bohdjalian@rudolfinerhaus.at](mailto:a.bohdjalian@rudolfinerhaus.at)

<sup>f</sup>Department of Probability, Alfred Renyi Institute of Mathematics, Hungarian Academy of Sciences, Reáltanoda utca 13-15, H-1053 Budapest, Hungary; [tiborbakacs@gmail.com](mailto:tiborbakacs@gmail.com)

\*Corresponding author: Ralf Kleef, M.D., [ralf.kleef@dr-kleef.at](mailto:ralf.kleef@dr-kleef.at)

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## Abstract

*Introduction:* Triple-negative breast cancer (TNBC) has a more aggressive course with shorter disease-free survival and overall survival (OS) times than other breast cancers. Due to the lack of specific targeted therapies increasing interest has been generated in novel treatment strategies in the metastatic setting, which would be essential to improve the survival of this high-risk subgroup.

*Material and method:* Diagnosis of the female patient [AW, 06.09.1964.] was TNBC [ICD10: C50.9] with disseminated lung metastasis [ICD10: C78.6] and lymphadenopathy [ICD10: R59.1]. First, a low-dose PD-1 immune checkpoint (IC) inhibitor nivolumab (0.5 mg/kg) with CTLA-4 IC inhibitor ipilimumab (0.3 mg/kg) was administered weekly, over three weeks. This was accompanied by loco regional hyperthermia with radiofrequency fields (13.56 MHz) using the Syncrotherm device 3 times per week (max output 400 w) over the thoracic region in combination with high dose vitamin C (0.5 g/kg) and alpha lipoic acid (600mg) over three weeks. Then, this was followed by long duration fever range whole body hyperthermia (using the Heckel device) in combination with low dose chemotherapy using cyclophosphamide 300 mg/m<sup>2</sup> to down modulate T<sub>reg</sub> cells. Then, a high dose (HD) interleukin 2 (IL-2) (54 Mio/m<sup>2</sup> as decrescendo regime) therapy under Taurolidine protection was administered for five days.

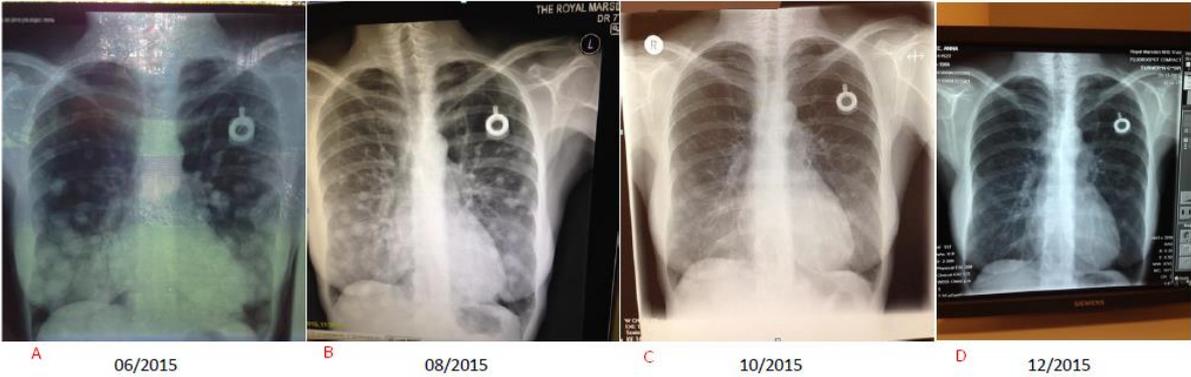
*Results and discussion:* The patient first presented with a Karnofsky score of 80% (ECOG = 1). During inspiration she felt severe pain in the left lateral chest wall, which became extremely painful during sneezing. She complained about severe shortness of breath (SOB) on exertion, lack of appetite, insomnia, and exhaustion. The patient went into remarkable partial remission after five months of her first interim analysis. Importantly, this was associated with an excellent clinical condition with a Karnofsky score of 100%. SOB on exertion or any other cancer related symptoms have vanished.

Based on the concept of using low dose IC blockade in minimal residual disease, we hypothesized that a prolonged low dose IC blockade of two checkpoints, CTLA-4 and PD-1

(using ipilimumab and nivolumab simultaneously), could be safely and effectively administered in patients with high tumor burden provided the CI blockade is complemented with HD IL-2 stimulation treatment. This hypothesis is based on the assumption that a frequently administered low dose CI blockade would prevent T cell exhaustion enabling them to travel to tumor sites without prematurely succumbing to apoptosis. This would make main stream HD IL-2 stimulation treatment safer and more effective.

*Conclusion:* Thus far we have treated seven stage IV patients with disseminated lung metastasis of different origins who responded similarly well to the TNBC case presented here. Clearly, this combination immune treatment warrants further clinical studies.

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**Figure 1:** Chest X-ray taken in June 2015 (A); in August 2015 (B); in October 2015 (C); and in December 2015 (D);

