

**Exogenous and endogenous hyperthermia combining low-dose checkpointinhibitors with interleukin-2 (IL-2) and fever range whole body and local regional hyperthermia in stage IV cancer**

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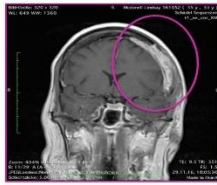
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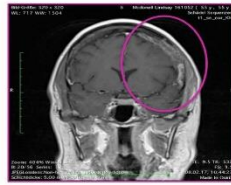


**Exogenous and endogenous hyperthermia combining low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever range whole body and local regional hyperthermia in stage IV cancer. Kleef R et al, Vienna, Austria**

**Case 1.: COMPLETE CLINICAL REMISSION** of stage IV breast cancer with bone, liver and lung metastasis With low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever range hyperthermia



11/2016



02/2017

09/2014 grade 3 invasive ductal adenocarcinoma of the left breast, ER 100% positive, PR neg., Her2-neu neg. Patient underwent initial resection (02/2015) and neoadjuvant chemo radiation ACT, followed by aromatase inhibitor  
07/2016 very large bone metastasis left skull, infiltrating to her dura mater; the patient underwent initial radiation; also new pulmonary metastasis.  
11/2016-02/2017 – immune-thermotherapy two times following each other, and 3 cycles of topotecan chemotherapy.  
08/2017 PET indicates CR

**Case 2.: COMPLETE pathological RESPONSE (pCR)** of stage IIIB oesophageal cancer combining low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever range hyperthermia

The patient was a 56-year-old male newly diagnosed with:  
Advanced uT4, N2, M0 inoperable adenocarcinoma of the distal esophagus [ICD10:C15.9] with disseminated mediastinal, sub/infradiaphragmal lymphadenopathy [ICD10: R59.1].  
MSI-low, Her-2-neu positive. He refused neoadjuvant chemotherapy, radiotherapy and chemoradiotherapy. pCR was documented by 8 biopsies when re-endoscoped in 10/2016 after 8 weeks of primary combined immunotherapy



08/2016



10/2016



**Case 3.: COMPLETE CLINICAL REMISSION** of stage IV breast cancer with bone and lymph node metastasis of stage IV breast cancer with bone and lymph node metastasis combining low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever range hyperthermia

The 65 y female first presented in September 2016 with a massive fungating exulcerating right breast carcinoma deeply infiltrating the anterior right chest wall with metastatic right axillary lymph adenopathy and metastasis to the right iliac bone and vertebral body L5 and T8. She underwent Tru-Cut biopsy which revealed invasive ductal carcinoma of no special type, G3, ct4 N1 M1 (bone), ER 100% and PR 40% positive, KI-67 19%, HER-2/NEU (erbB-2) neg. confirmed by FISH, Score 2+; the cancer was luminal A, EGFR neg., Tp53 neg., AR neg., PD-L1 and CTLA-4 overexpressed, CA 15-3 was elevated at 42 KU/l. When she was seen initially she presented with hemoglobin of 3.3 g/dl.

Patient underwent emergency palliative radiation 4 times (5Gy Per fraction) November, 2016. Additionally to our immunotherapy low-dose metronomic chemotherapy was performed only twice combining gemcitabine (800mg/m2) and vinorelbine (30mg/m2).

Unexpectedly, restaging at the end of January 2017 performed with bone scintigram, and CT thorax/abdomen and full laboratory workup proved complete remission of the primary large fungating breast cancer, complete remission of bone metastasis and massive shrinkage of lymphadenopathy with normal tumour markers. Follow-up in CR 05/2018 1.5 years.



10/2016 before treatment



11/2016



03/2017



05/2017

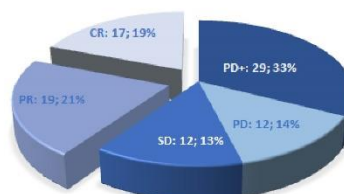


09/2017

**Diagnostic/Treatment**

All patients were tested for expression of PD-1/PDL-1, CTLA-4 with genetic fingerprint (m-RNA). Txt consisted of an off-label low-dose (LD) ICB anti-PD-1 and anti-CTLA-4 antibodies treatment (Ipilimumab/Nivolumab) with low dose interleukin-2 (IL-2) and loco regional (13.56 MHz Synchrotherm/Oncotherm) - and whole body hyperthermia (WBH). WBH was induced using external heating (heckel HT3000) followed by systemic fever induction using IL-2.

**THERAPEUTIC RESULTS OF EVALUABLE PATIENTS**



n= 84 Stage IV  
objective response: 40%  
overall response: 52%