

## **Hyperthermic Immunotherapy**

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# Complete clinical remission 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

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Advanced stage inoperable breast cancer has a poor prognosis and patients rarely enjoy durable complete response to treatment; progression free survival often is limited.

## Methods

We previously reported complete remission of far advanced lung metastasis in triple negative breast cancer at ITOC3 (Munich) 2016 and complete remission of inoperable esophageal Cancer ITOC4 (Prague) 2017; here we report a similar successful treatment concept.

FD: 09/2016 in our clinic; the 65-y female patient noticed the tumor about 10 years ago. She had always refused treatment. When she first presented in September 2016 she was diagnosed 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 (c- cerbB-2) neg. confirmed by FISH score 2+; the cancer was luminal A, EGFR neg., Tp53 neg., AR neg., PD-L1 and CTLA-4 overexpressed, TM CA 15-3 was elevated at 42 kU/L.

Additionally, soft tissue nodule upper lobe right lung suspicious for lung metastasis. Atelectasis changes in the lingula and lower lobes of the left lung, bilateral pulmonary embolism. Patient was on anticoagulants Tinzaparin 10.000 IE. When she was seen initially she presented with hemoglobin of

3.3 (!) and received 4 units of packed red blood cells. Karnofsky Index was 80%, moderate pain right chest, stable weight of 60 kg.

Social history: married, mother of 5 children; negative family history for cancer.

The patient initially presented with a very far advanced massive right sided breast cancer cT4 N1 M1 (bone) which was bleeding heavily upon slightest touch. The patient therefore underwent emergency palliative radiation 5 times between November 10 and November 17, 2016 with 25 Gy TD at 5 Gy single dose; additionally, she underwent immunotherapy as described previously combining low-dose checkpoint inhibitor ipilimumab–nivolumab in combination with low dose interleukin (IL-2) treatment parallel to local regional and whole-body hyperthermia. Additionally, low-dose metronomic chemotherapy was performed only twice combining gemcitabine (800mg/m<sup>2</sup>) and vinorelbine (30mg/m<sup>2</sup>).

## Results

Unexpectedly, restaging at the end of January 2017 performed with clinical examination, 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. Telephone up in 07/2018 confirms Karnofsky score of 100%, pain or any other cancer related symptoms have vanished. Current (08/2018) follow-up time 22 months.

**Conclusion**

The unexpected remission of far advanced inoperable and metastatic breast cancer following a complex immunotherapy treatment including low-dose checkpoint inhibitors, hyperthermia and metronomic chemo-radiation therapy warrants further clinical studies. The presentation would include description of more cases and an overview of all treated patients.



# Hyperthermic Immunotherapy

**Ralf Kleef, Vienna, Austria**



**36. Conference of the International Clinical Hyperthermia Society  
28th- 29th September 2018, Budapest, Hungary**

## Hyperthermic Immunotherapy Learning objectives

- **Fever and cancer**
- **Loco-regional versus whole-body hyperthermia**
- **Hyperthermic Immunotherapy in oncology**

Epidemiology

**In clear words:**

**Fever protects!**

Fever– Harmful or beneficial?

4 Hypotheses

# Fever– Harmful or beneficial?

## 1. Hypothesis: Evolution Studies [1].

**Even cold-blooded animals can get fever, as a result they are looking for warmer waters or areas**

[1] Kluger et al 2001. Fever and Immunity. In: Ader R et al (eds) Psychoneuroimmunology, 3rd edn. Academic Press, San Diego, pp 687-701

# Fever– Harmful or beneficial?

- 2. Hypothesis: Correlational Studies[2].
- **Comparing the extent of the reaction fever temperature relative to morbidity and mortality.**

**All "fever"-Studies in humans and animals demonstrate the protective function of the fever**

[2] Kluger et al 2001. Fever and Immunity. In: Ader R et al (eds) Psychoneuroimmunology, 3rd edn. Academic Press, San Diego, pp 687-701

## Fever– Harmful or beneficial?

- 3. Hypothesis: Antipyresis [3,4].
- **Reduction of fever increases morbidity and mortality.**

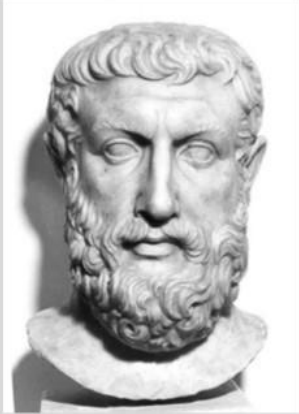
[3] Bernheim et al 1977. Fever: effect of drug-induced antipyresis on survival. Science 193: 237-239  
[4] Covert et Reynolds 1976. Survival value of fever in fish. Nature. 1977 May 5;267(5606):43-5

## Fever– Harmful or beneficial?

- 4. Hypothesis: Hyperthermia [5-8].

**Hyperthermia reduces morbidity and mortality and improves immunological functions**

[5] Kluger et al 1975. Fever and survival. Science 188: 166-168  
[6] Reynolds et al 1976. Behavioral fever in teleost fish. Nature. 259: 41-42  
[7] Jiang et al 2000. Febrile core temperature is essential for optimal host defense in bacterial peritonitis. Infect Immun 68: 1265-1270  
[8] Zellner et al 2002. Human monocyte stimulation by experimental whole body hyperthermia. Wien Klin Wochenschr 114: 102-107



***" I would cure all diseases if only I could produce fever***

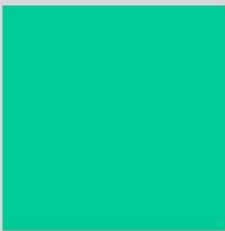
Parmenides, Grec physician , 4. century BC



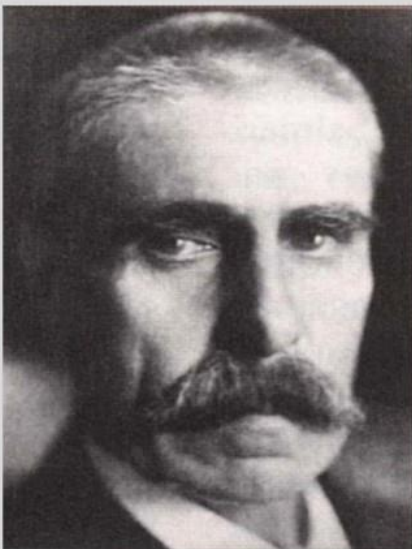
***" Fever is „Body-Buildung“ for the Immune systeme,,***

Kleef, German physician, 21 century AC

## William B. Coley (um 1888)



## Julius Wagner-Jauregg



- 1927 the Austrian Julius Wagner-Jauregg was awarded the Nobel Prize for his fever therapy until then hardly curable syphilis in the final stage. He infected patients with malaria control to trigger the healing fevers.
- Hyperthermia by the means of the 19. century



**Were the ancient physicians better?**



**Fever and cancer are inversley related**

**Kleef R et al. Fever, cancer incidence and spontaneous remissions.  
Neuroimmunomodulation 2001;9(2):55-64.**



**Spontaneous remissions were frequently associated with concurrent febrile infections**

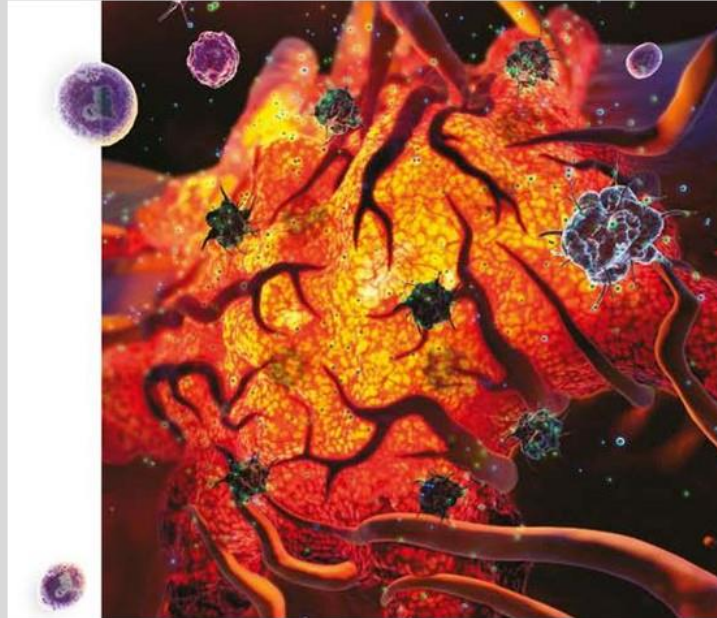
**Kleef R et al. Fever, cancer incidence and spontaneous remissions. Neuroimmunomodulation 2001;9(2):55-64.**

## Chronic Infection or Inflammation and Cancer

- Chronic infection/inflammation engages leukocytes' pro-inflammatory 'tissue repair' mode, resulting in 'vicious cycle' that:
  - (1) Promotes cancer initiation and development
  - (2) Suppresses immune function, including suppression of immune function of:
    - Macrophages
    - Neutrophils
    - Cytotoxic T cells
    - Natural Killer cells
    - B cells

## Malignant inflammation

G. Stix



Following this brief introduction into fever and immunology we will now jump into clinical hyperthermia

# Loco-regional hyperthermia



Issels R et al.



JAMA Oncology

[View Article ▶](#)

JAMA Oncol. 2018 Apr; 4(4): 483–492.

Published online 2018 Feb 15. doi: [10.1001/jamaoncol.2017.4996](https://doi.org/10.1001/jamaoncol.2017.4996)

PMCID: PMC5885262

PMID: [29450452](https://pubmed.ncbi.nlm.nih.gov/29450452/)

## Effect of Neoadjuvant Chemotherapy Plus Regional Hyperthermia on Long-term Outcomes Among Patients With Localized High-Risk Soft Tissue Sarcoma

The EORTC 62961-ESHO 95 Randomized Clinical Trial

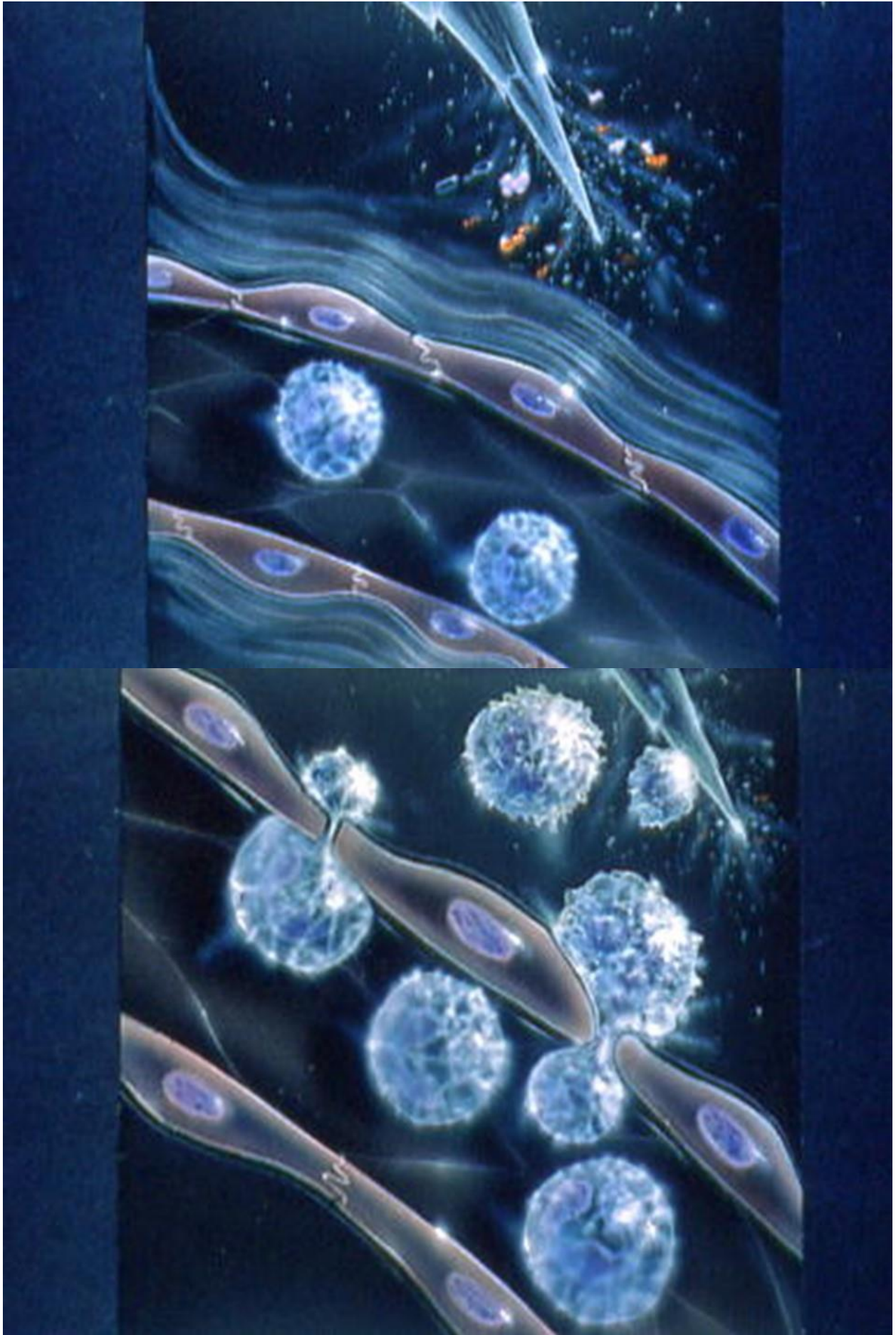
[Rolf D. Issels](#), MD, PhD,<sup>1</sup> [Lars H. Lindner](#), MD,<sup>1</sup> [Jaap Verweij](#), MD,<sup>2</sup> [Rüdiger Wessalowski](#), MD,<sup>3</sup> [Peter Reichardt](#), MD,<sup>4</sup> [Peter Wust](#), MD,<sup>5</sup> [Pirus Ghadjari](#), MD,<sup>5</sup> [Peter Hohenberger](#), MD,<sup>6</sup> [Martin Angele](#), MD,<sup>7</sup> [Christoph Salat](#), MD,<sup>1</sup> [Zeljko Vujaskovic](#), MD,<sup>8</sup> [Soeren Daugaard](#), MD,<sup>9</sup> [Olav Mella](#), MD,<sup>10</sup> [Ulrich Mansmann](#), MD,<sup>11</sup> [Hans Roland Dürr](#), MD,<sup>12</sup> [Thomas Knösel](#), MD,<sup>13</sup> [Sultan Abdel-Rahman](#), PhSc,<sup>1</sup> [Michael Schmidt](#), MD,<sup>14</sup> [Wolfgang Hiddemann](#), MD,<sup>1</sup> [Karl-Walter Jauch](#), MD,<sup>7</sup> [Claus Belka](#), MD,<sup>15</sup> and [Alessandro Gronchi](#), MD<sup>16</sup>, for the European Organization for the Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group and the European Society for Hyperthermic Oncology

## WBH – Heckel HT 3000

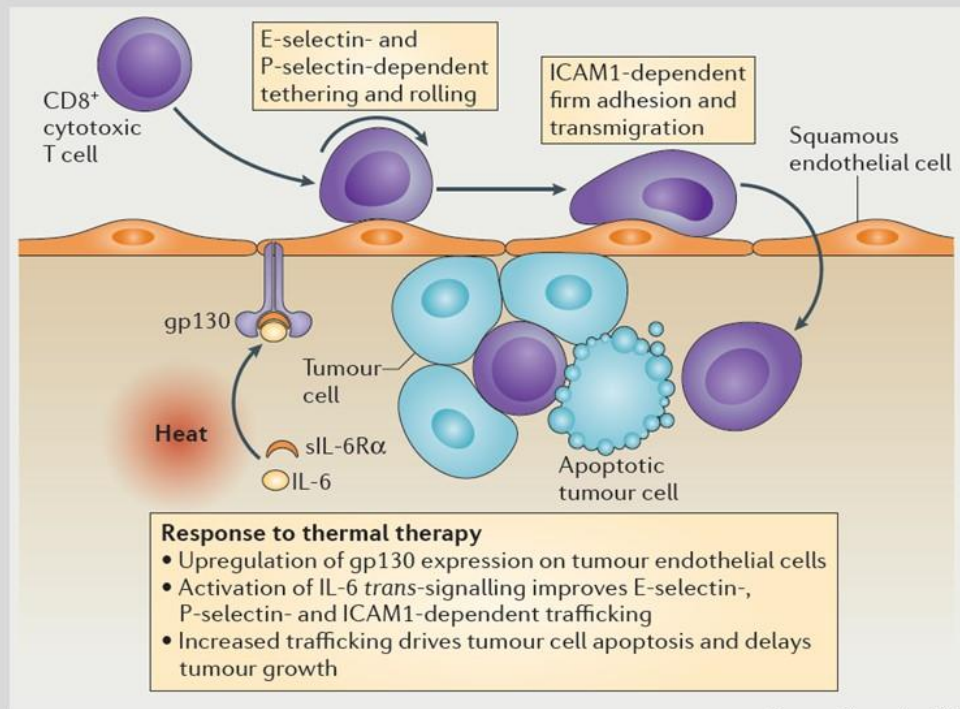


## WBH – Ardenne Iratherm 1000





## Cell adhesion molecule mediated extravasation of immune cells following hyperthermia



Evans, Repasky, Fisher (2015)

Proposed mechanism of action:

## ICD – Immunogenic Cell Death induced by chemotherapy

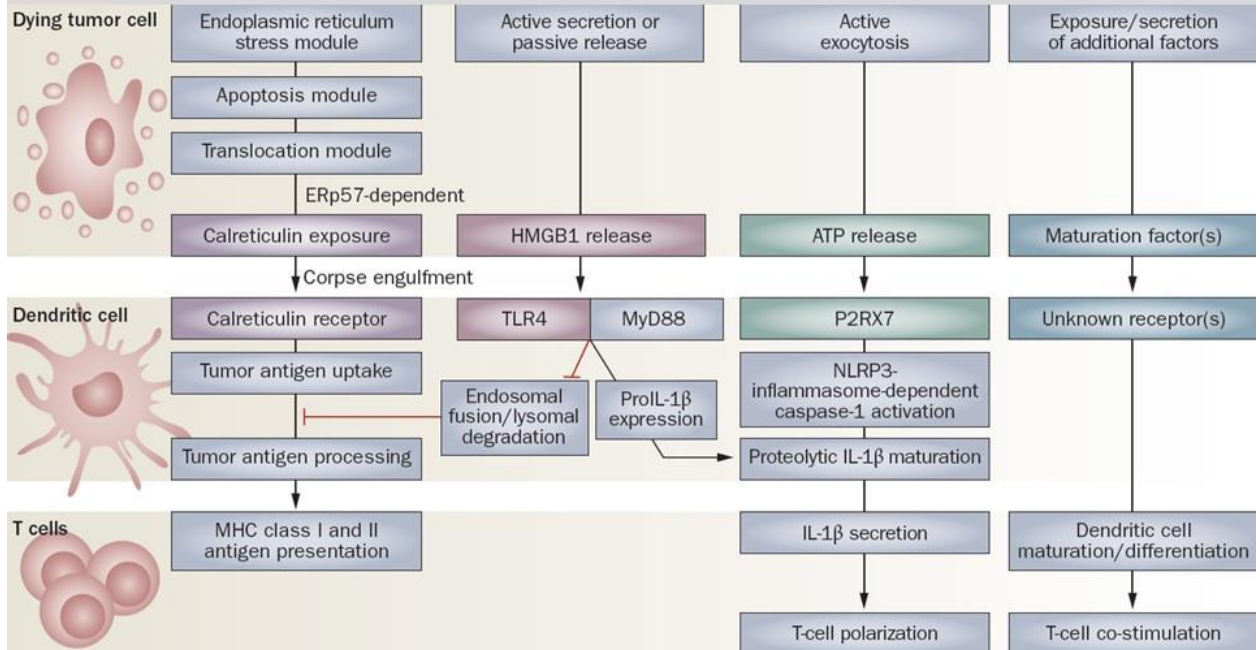
A series of immunogenic signals delivered by tumor cells undergoing ICD stimulates DCs to take up antigens from dying tumor cells.

“Cancer cells succumbing to ICD are de facto converted into an anticancer vaccine and as such elicit an adaptive immune response.”

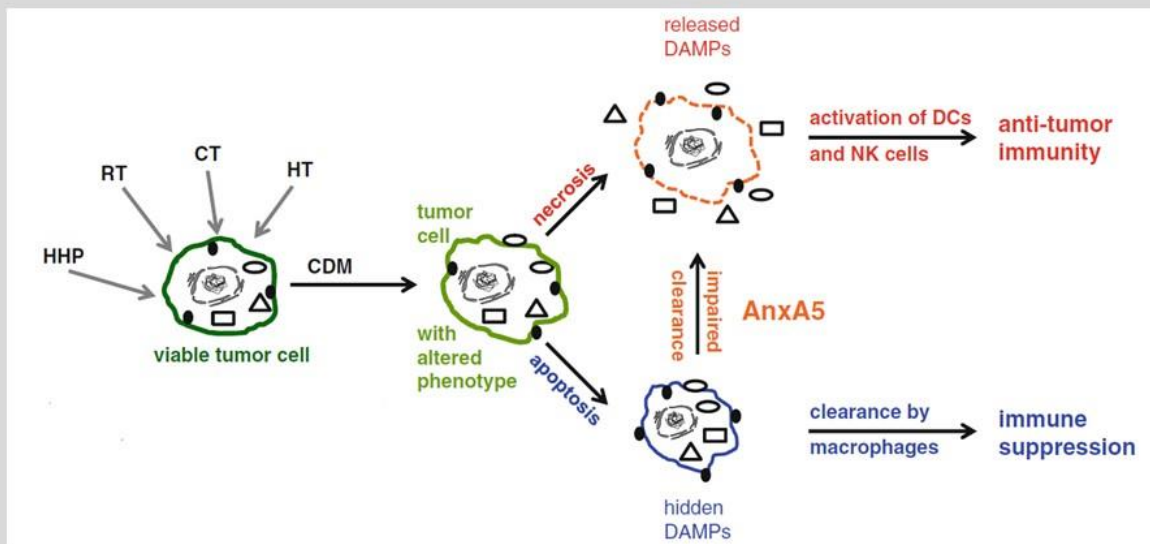
But:

This specific immune effect is considerably counteracted by the general immune-suppressive effect of chemotherapy.

# ICD – Immunogenic cell death

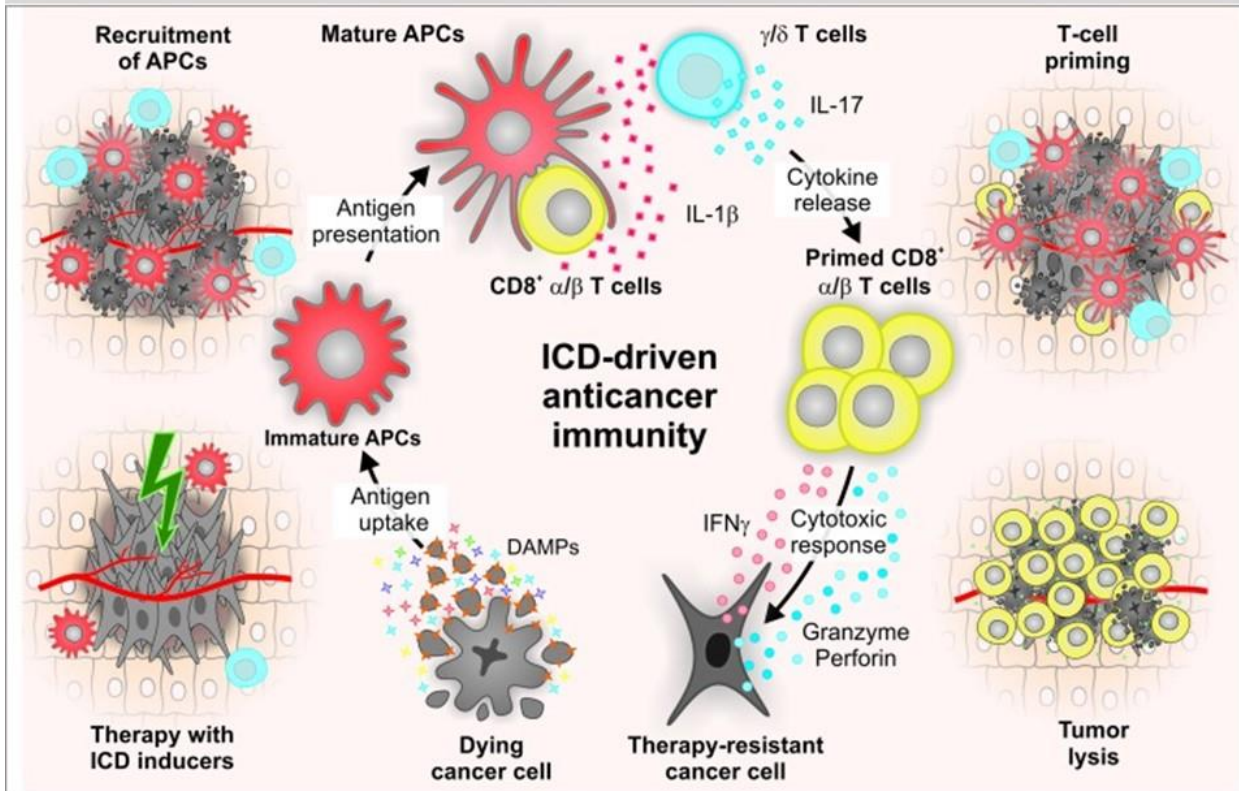


## Hyperthermia releases Damage Associated Molecular patterns (DAMPs)



Gaipl (2011)

## Hyperthermia releases Damage Associated Molecular patterns (DAMPs)



## Rational for Immune therapy in Cancer Patients

- **Disturbed immune system**
- **Inadequate immune reactions**
- **Immune cells are unable to detect tumor cells**

## Disclosures

RK has European and International patent pending



Low-dose checkpoint inhibitor therapy with interleukin-2 (IL-2) and fever range hyperthermia in stage IV cancer: a retrospective analysis with single case presentations

**Ralf Kleef, Vienna, Austria**



**Presentation to 36. Conference of the International Clinical Hyperthermia Society  
28th- 29th September 2018, Budapest, Hungary**

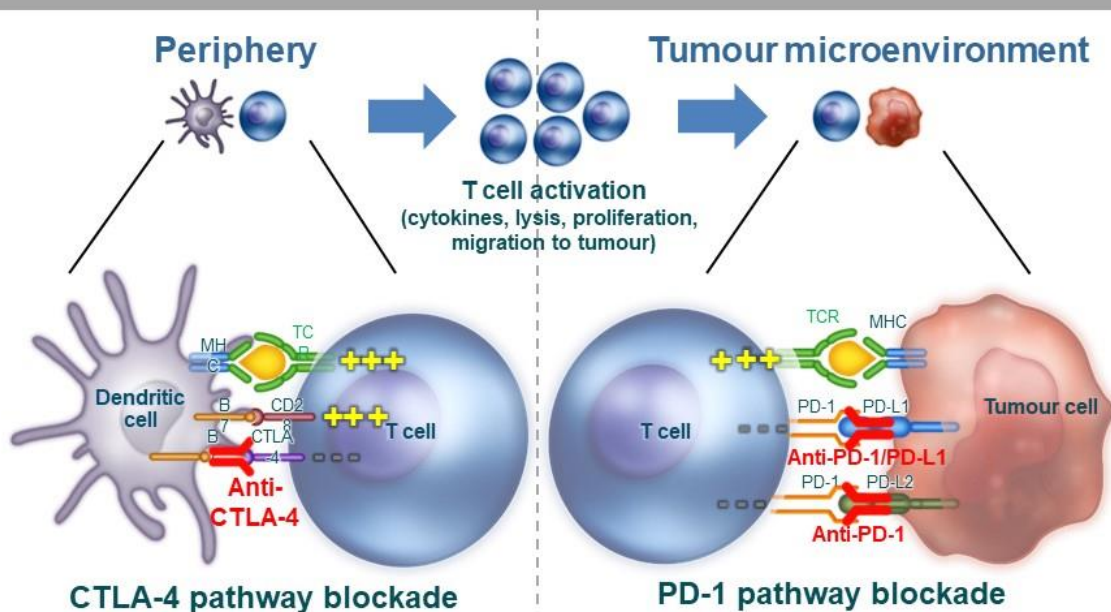
# OUR TREATMENT CONCEPT

- ❖ Every year 8.2 million deaths occur due to metastatic (**stage IV**) cancer worldwide
- ❖ Management of metastatic cancer is palliative by intent; even combination therapies with checkpoint inhibitors results in only a small minority (with the exception of metastatic melanoma) of durable responses, often at the cost of long lasting grade 3 and 4 autoimmune side effects.
- ❖ Our team combines the following immunotherapies (with 52% clinical benefit rate in 98/119 evaluable patients; 38% Objective response rate):

- 1) Low-dose immune checkpoint blockade (LD-IC; ipilimumab plus nivolumab)
- 2) Individually titrated interleukin 2 (IL-2) treatment under Taurolidine protection
- 3) Loco regional – and whole body hyperthermia without classical chemotherapy
- 4) If Chemotherapy: only after Chemo sensitivity testing and metronomic low dose chemotherapy

## IMMUNO-ONCOLOGY:

Blocking CTLA-4 and PD-1 pathways with monoclonal antibodies



CTLA-4 = cytotoxic T-lymphocyte antigen-4; PD-1 = programmed cell death 1; PD-L1/2 = PD ligand 1/2; TCR = T cell receptor.

Adapted from Wolchock J, et al. Oral presentation at ASCO 2013 (Abstract 9012).

## IMMUNE-CHECKPOINT BLOCKADE

**Immune-checkpoint blockade:** antibodies targeting the negative regulatory molecules CTLA-4 and PD-1 to release the brakes on natural T cells responsive to tumor

Disadvantages

- ❖ **Tolerance breakdown** resulting in a high incidence of immune-related adverse events (irAEs)
- ❖ A meta-analysis in 1265 patients from 22 clinical trials found a respective incidence of **72 % for all-grade immune-related adverse effects irAEs and 24 % for high-grade irAEs** leading to hospitalization or intravenous treatment.
- ❖ The risk of developing irAEs in many clinical trials was **dependent of dosage**, with incidence of all-grade irAEs of 61 % for ipilimumab 3 mg/kg and 79 % for ipilimumab 10 mg/kg. Death due to irAEs occurred in 0.86 % of patients.
- ❖ **Tumor regression is frequently associated with the development of autoimmunity**

## THERAPEUTIC PARADIGM SHIFT:

The autoimmune effect of T cells should be exploited for the treatment of advanced cancer

- ❖ Breakthrough concept since irAEs associated with checkpoint inhibitors are considered primarily as severe safety issue (1, 2)
- ❖ *low-dose* immune checkpoint inhibitor (LD-IC) combination immune therapy demonstrated partial to complete remission in stage IV cancer patients (triple negative and hormone rec. pos. breast cancer, melanoma, bladder cancer and prostate cancer, (among others))
- ❖ LD-IC needs the Synergy of hyperthermia and fever

1 June CG et al. Is autoimmunity the Achilles' heel of cancer immunotherapy. Nature Medicine 23; 540-548, 2017

2 Boutros C, et al. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. Nature Reviews Clinical Oncology. 13, 473-486, 2016.

## Proof-of-Principle retrospective analysis

Five best cases out of 119 intend-to-treat patients

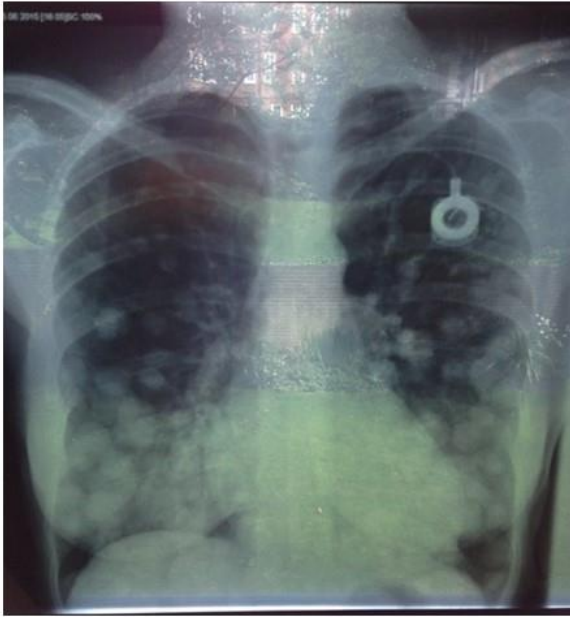
- ❖ We report five cases of stage IV patients with solid carcinomas with far advanced metastases
- ❖ They had exhausted all conventional treatments
- ❖ They went into complete remission with *low-dose* IC (LD-IC) blockade in combination with individualized doses of IL-2 (ID-IL-2) treatment under Taurolidine protection and loco-regional and whole body hyperthermia but without classical chemotherapy.

### Case 1.: COMPLETE CLINICAL REMISSION

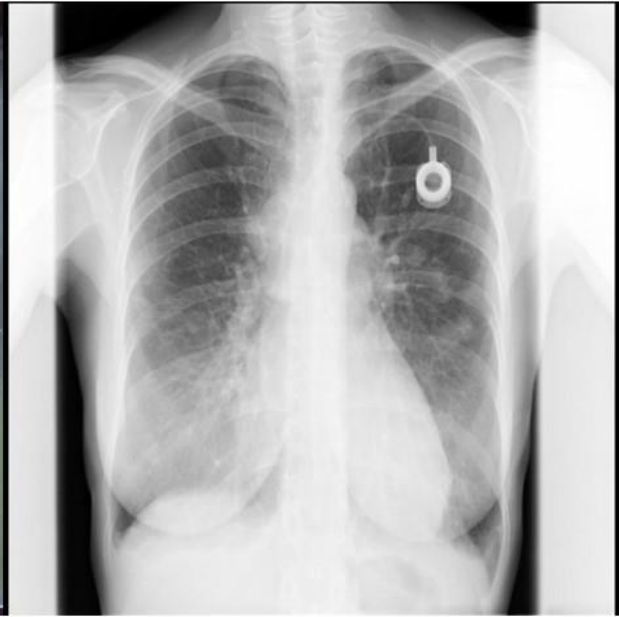
of Lung Metastases of Stage IV Triple Negative Breast Cancer  
Administering Low-Dose Immune Checkpoint Blockade in  
Combination with Hyperthermia and Interleukin-2

- 51 y.o. female with TNBC [ICD10: C50.9]
- Disseminated lung metastases [ICD10: C78.6]
- Malignant Lymphadenopathy [ICD10: R59.1]
  
- Karnofsky score of 70% (ECOG = 1)
- During inspiration severe pain in the left lateral chest wall
- Extreme Pain during sneezing
- Severe dyspnoea on exertion (DOE)
- Lack of appetite, insomnia, and exhaustion
- No more conventional treatments offered

## Case 1.: RESULTS



**06/2015**

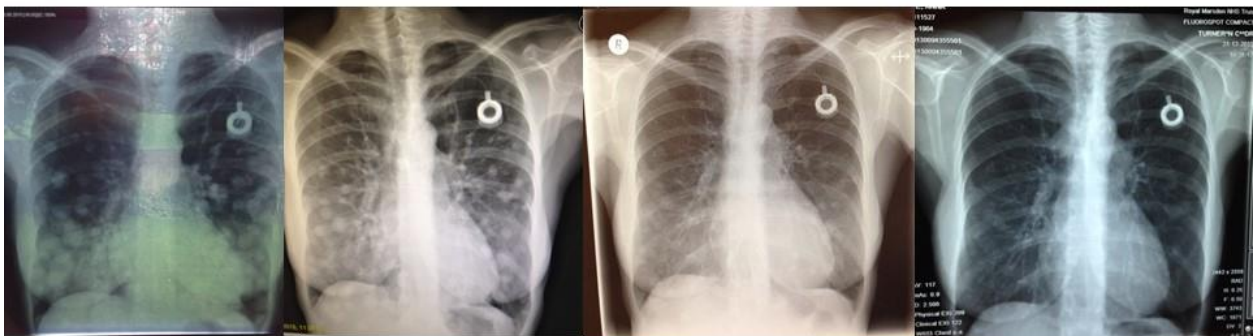


**08/2016**

Accepted for Publication: J. Integrative Cancer Therapies 08/2017;  
presented at ASCO Chicago 2016 and ITOC3 Munich, 2016

### TNBC Pulmonary metastasis

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**06/2015**

**08/2015**

**10/2015**

**12/2015**

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 chemo-radiotherapy

Presented at ITOC4, Prague, March 2017

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



08/2016



10/2016



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

pCR was documented by 8 biopsies when re-endoscoped in 10/2016 after 8 weeks of primary combined immunotherapy

Case 3.: COMPLETE CLINICAL REMISSION  
of stage IV breast cancer chest wall recurrence combining low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever range hyperthermia

51y female, Local (chest wall) recurrence of her-2 neu pos.  
Breast cancer [C50.9]

- FD 11/2015 neoadjuvant chemotherapy Taxotere/Cytosan with Herceptin and Perjeta followed by right-sided mastectomy in May 2015.
- 08/2016 Chest wall recurrence, biopsied and proven to be recurrence of Her2-neu+ breast cancer, unresectable.
- Histology of recurrence was invasive ductal carcinoma grade 3 extending to the anterior inferior margin; also DCIS solid type nuclear grade 3 with microcalcification.
- Unfavorable high Ki-67 expression, p53 75% positive.
- Second opinion of radiation department: no radiation possible

Case 3.: COMPLETE CLINICAL REMISSION  
of stage IV breast cancer chest wall recurrence combining low-dose  
checkpoint inhibitors with interleukin-2 (IL-2) and fever range  
hyperthermia



02.12.2016



08.03.2017

Case 4.: COMPLETE CLINICAL REMISSION  
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) between November 10 and November 18, 2016. Additionally to our immunotherapy low-dose metronomic chemotherapy was performed only twice combining gemcitabine (800mg/m<sup>2</sup>) and vinorelbine (30mg/m<sup>2</sup>).
- ❖ 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

Case 4.: COMPLETE CLINICAL REMISSION  
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



21.10.2016



22.09.2017

Late breaking abstract accepted for ESGO Vienna Nov. 2017

Case 4.: COMPLETE CLINICAL REMISSION  
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



10/2016 before  
treatment



11/2016



03/2017



05/2017



09/2017

Late breaking abstract accepted for ESGO Vienna Nov. 2017

Case 5.: 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

09/2014 grade 3 invasive ductal adenocarcinoma of the left breast, ER 100% percent 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.

08/2016 patient was started on Ibrance and aromatase inhibitor: PD.

09/2016 radiation of the cervical spine and T2.

10/2016 restaging with CT of the thorax and abdomen: stable lung metastasis but increasing pleural nodules; disseminated liver metastasis with index lesions between 2.1, 3.1 and 1.3 cm; new lytic osseous lesions are present; restaging of the skull with MRI indicated PD of the previously radiated left sphenoid lesion as well as PD of further lesions in the skull base and mandible. Bone scan indicates PD of all innumerable bony lesions.

11/2016-02/2017 – immune-thermotherapy two times following each other, and 3 cycles of topotecan chemotherapy.

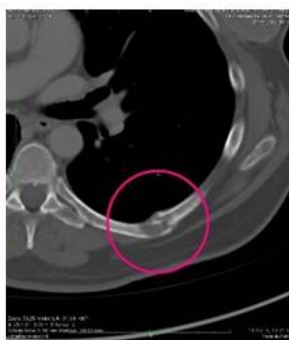
03/2017 restaging with CT of Abdomen, pelvis and thorax demonstrated overall PR

06/2017 tumor markers decreased to the normal range.

05/2017 Restaging, MRI: overall stabilization and PR of the previously demonstrated disseminated metastasis in the skull and head.

08/2017 PET indicates CR

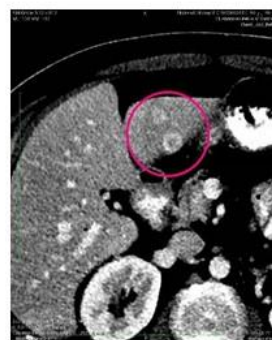
Case 5.: COMPLETE CLINICAL REMISSION  
of stage IV Breast cancer with bone, liver and lung metastasis  
With low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever  
range hyperthermia



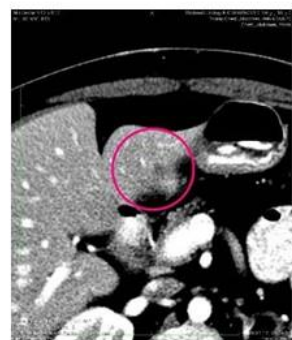
10/2016



08/2017

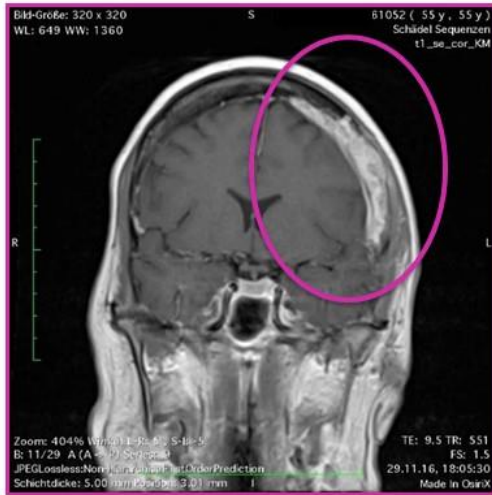


10/2016



08/2017

Case 5.: 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**

Side effect profile  
Low-dose checkpoint inhibitors with interleukin-2 (IL-2) and  
fever range hyperthermia in advanced cancer

Number of patients treated: n=119

**WHO I: 30%**      diarrhea, skin rash, nausea, headache

**WHO II: 15%**     diarrhea, skin rash, pneumonitis, elevated liver enzymes

**WHO III: 7%**

2 patients developed ulcerative colitis after 2 months controlled with corticosteroids

2 patients developed autoimmune thyroiditis controlled with hormone suppl.

2 patients developed autoimmune hepatitis controlled with corticosteroids

2 patients with pre-existing atrial fibrillation developed heart rhythm disturbances  
controlled with standard medical treatment (SMT)

**WHO IV: 3 %**

2 patients developed Diabetes mell. I treated with Insulin

1 patient developed AKI after 1 week and had to be transferred to dialysis

SUMMARY

Low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever range hyperthermia in advanced cancer

**Staging with iRECIST**

**Objective response rate - ORR      38%**

**Overall response – OR      52%**

**n=                      98 of 119 evaluable**

SUMMARY

Low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever range hyperthermia in advanced cancer

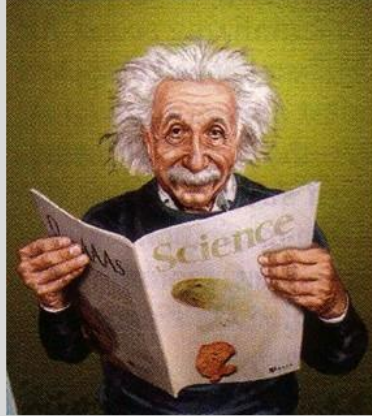
**Staging with iRECIST**

**Objective response number pat.    n=37**

**TTP: not calculated                      n=4**

**Median Follow up:                      14 month (3-33)**

**Great potential but...  
more experience is needed**



***“The only way to increase the success rate is to double the rate of failures”***





Thank you for your attention



[www.dr-kleef.at](http://www.dr-kleef.at)