

# **Exploiting autoimmunity to treat advanced cancer Using off-label low-dose immune checkpoint blockade in combination with hyperthermia and IL-2**

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# Exploiting autoimmunity unleashed by an off-label-dose immune checkpoint blockade in combination with hyperthermia and interleukin-2

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## Abstract

Checkpoint inhibitors achieved regression of cancer in a minority of patients, while the majority suffered immune-related adverse events (irAEs). irAEs could affect any tissue, their incidence may reach up to 90% of patients and toxicity is dose-dependent. Cancer regression can only be achieved by tolerance breakdown. Since autoimmunity is emerging as the nemesis of immunotherapy, a therapeutic paradigm shift is required. Based on the hypothesis that the anti-CTLA-4 therapy has similar mechanism to that occurring in inherited human CTLA4 haplo-insufficiency, it was predicted that autoimmune T cells can be harnessed by a low-dose combined checkpoint blockade. The proof-of-principle was first demonstrated in a heavily pre-treated triple negative breast cancer (TNBC) patient with far advanced pulmonary metastases and severe shortness of breath, who had exhausted all conventional treatment. The patient was treated with immune checkpoint blockade including ipilimumab (0.3 mg/kg) combined with nivolumab (0.5 mg/kg). This was complemented with interleukin-2 treatment and loco regional- and whole body hyperthermia without classical chemotherapy. The patient went into complete remission of her lung metastases and all cancer related symptoms vanished with transient WHO I-II diarrhea and skin rash. The patient remained alive for 27 months after the start of treatment. Previous NCI director and Nobel laureate Harold Varmus stated that we can really learn from such "exceptional responders". Since this protocol consists only of approved drugs and treatments, our prediction that autoimmune T-cells induced by a low-dose immune checkpoint blockade are powerful therapeutic tools can be confirmed or refuted in prospective controlled clinical trials.



## Exploiting autoimmunity to treat advanced cancer\*

Using off-label low-dose immune checkpoint blockade in combination with hyperthermia and IL-2

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\*Based on: [Bakacs et al, Exploiting autoimmunity unleashed by an off-label low-dose immune checkpoint blockade to treat advanced cancer](#) (under review)

## Checkpoint inhibitors: paradigm shift is required (elevator talk)

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- ✓ Regression in a minority of patients
  - ✓ Majority suffered immune-related adverse events (irAEs)
  - ✓ Regression was achieved by tolerance breakdown
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- ✓ “Autoimmunity is the Achilles' heel of immunotherapy”
  - ✓ Autoimmune T cells can be harnessed by a low-dose checkpoint blockade combined with hyperthermia and IL-2
  - ✓ “We might only be at the tip of the iceberg” of immunotherapy

## “Seismic shift in cancer”

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Improved survival with ipilimumab in patients with metastatic melanoma  
Hodi et al, N Engl J Med, 2010

**“Abrogation of the function of CTLA-4 would permit CD28 to function unopposed and might swing the balance in favor of immune stimulation, tolerance breakdown and tumor eradication...”**

This prediction proved to be entirely correct:

- Response rate of 10.9 % in 676 patients; CR 0.2%; in one patient out of 403
- Tolerance to self was broken in ~70% of the patients
- 38.7% of the patients experienced severe irAEs
- There were 14 deaths related to the study drugs

We have considered the very same published evidence of the NEJM paper

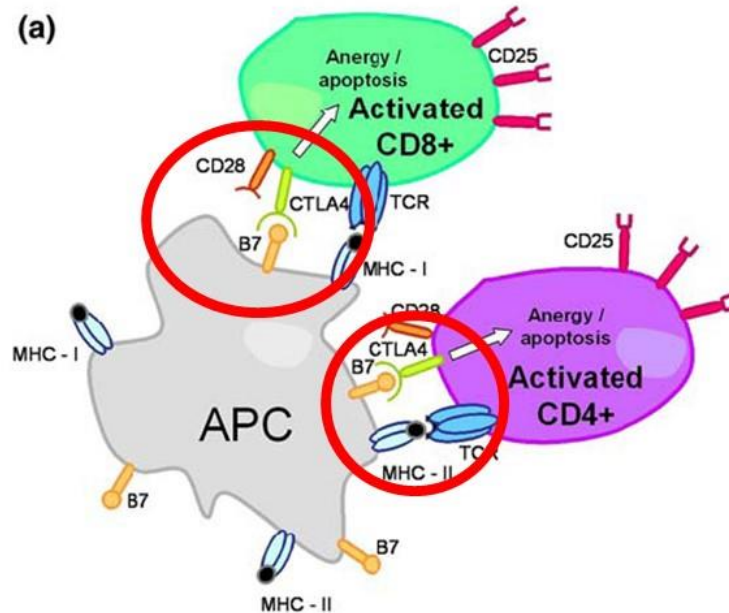
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- Ipilimumab (Yervoy) and the TGN1412 catastrophe, Bakacs et al, Immunobiology, 2012
- As if looking at a painting of Escher: others saw only the white picture, while we saw also the black one



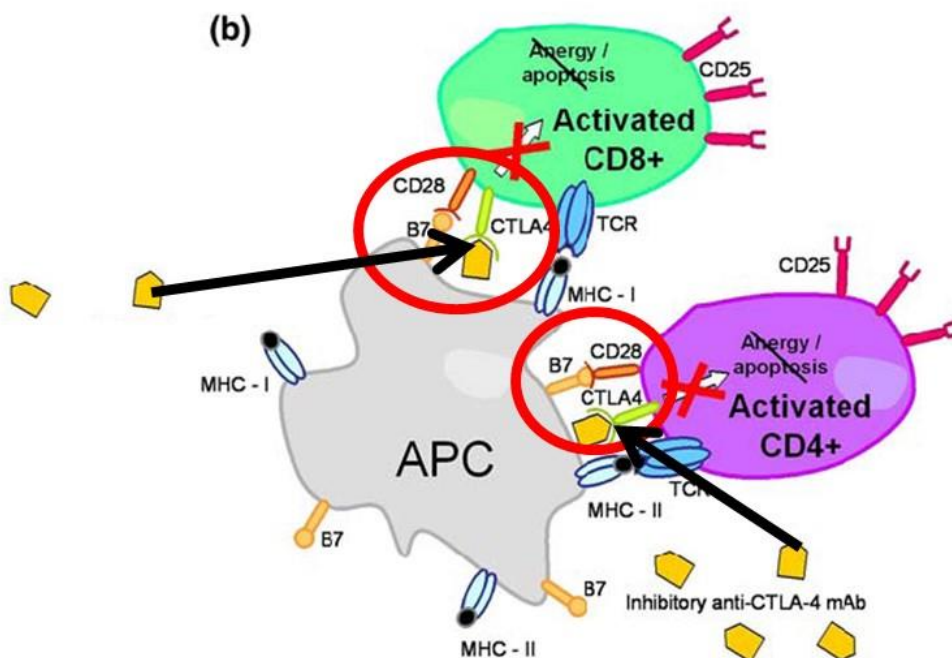
The B7-CD28 co-stimulatory and B7-CTLA-4 co-inhibitory pathways of T cells are pivotal in maintaining health

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“Anti-CTLA-4 selectively extends the functional longevity of activated T-cells”

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## Lessons from the anti-CD28 mAb (TGN1412) trial catastrophe in London

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Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412

Suntharalingam et al, N Engl J Med, 2006

- Cytokine storm: life-threatening organ failures in volunteers
- anti-CD28 (TGN1412) mAb “preferentially” activated Treg but also activated all CD28 positive T cells
- **Common Ags on targeted as well as non-targeted T cells**
- With increasing dose the kinetics shifts from specific toward non-specific T cell expansion

## irAEs of anti-CTLA-4 (ipilimumab) explained by a new theory: all T cells possess self reactivity

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T cells survey the stability of the self: a testable hypothesis on the homeostatic role of TCR-MHC interactions

Bakacs et al, Int Arch Allergy Immunol, 2007

- Short-lasting 'tonic' TCR signal 1 promotes survival of T cells
- T cells temporarily expressing CTLA-4 can be targeted by ipilimumab
- Ipilimumab blockade causes T cell activity to spill over onto healthy cells or tumor cells

## The mechanism of anti-CD28 (TGN1412) and anti-CTLA-4 (ipilimumab) therapies are similar

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- PubMed search in **2011**:  
ipilimumab/ 144; TGN1412/ 120 papers  
**ipilimumab and TGN1412: 0 paper**
- PubMed search in **2018**:  
ipilimumab/ 2483; TGN1412/ 167 papers  
**ipilimumab and TGN1412: 1 paper**

Medical community is still unmindful of the anti-CD28 (TGN1412) trial catastrophe insisting that anti-CTLA-4 (ipilimumab) targets only tumor specific T cells

## Dogma: immunity is as protective against isogeneic cancer as against xenogeneic infections

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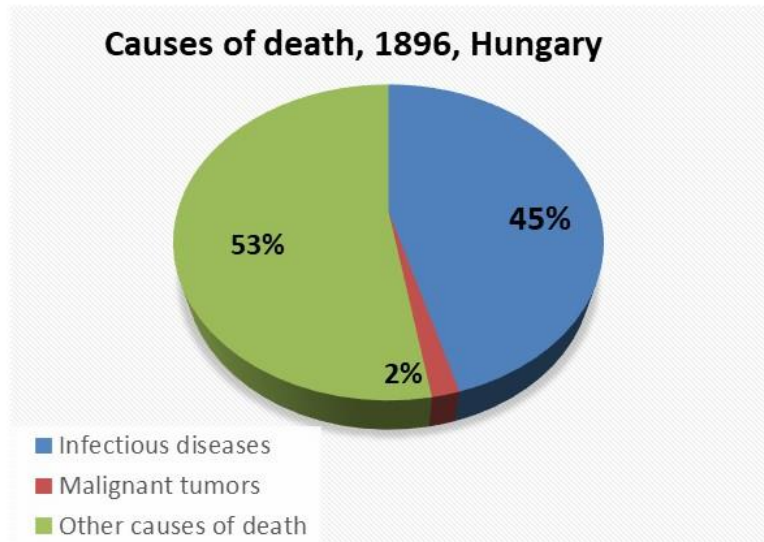
### The Fallacy of Tumor Immunology

Bakacs et al, Arxiv Cornell University Library, 2016

- Cancer immunotherapy trials resulted in anecdotal responses
- Evolutionary origin of adaptive immunity is not related to defense against pathogenic microorganisms (Burnet)
- Why invertebrates (more than two million species; 20 phyla) use only innate immunity?
- Why vertebrates reject any allogeneic or xenogeneic transplanted tissue?

„Prior to modern medicine people were long consumed by tuberculosis, dropsy, cholera, smallpox, leprosy, plague, or pneumonia before cancer developed.”

Mukherjee, *The Emperor of All Maladies; A biography of cancer*, 2011



- The immune system evolved for purging nascent selfish cells
- Defense against pathogens (xenogeneic aliens) appeared later in evolution

Insisting that ipilimumab is tumor specific is ignoring the obvious

Managing toxicities associated with immune checkpoint inhibitors Puzanov et al, *Journal for Immunotherapy of Cancer*, 2017

- irAEs affect any tissue, incidence up to 90%
- Overall incidence <75% with ipilimumab monotherapy; ≤30% anti-PD-1/PD-L1 agents
- IrAEs of ≥ grade 3 up to 43% with ipilimumab and ≤20% with PD-1/PD-L1 agents
- Combination of ipilimumab with nivolumab: 55% of grade 3/4 irAEs; discontinuation rate 30%
- irAEs with ipilimumab and pembrolizumab is dose-dependent
- Death due to irAEs occurred in up to 2% of patients

Patients often deny their symptoms when they fear their treatment will be stopped due to irAEs

**IMMUNOTHERAPY** WALLET CARD

NAME: \_\_\_\_\_

CANCER DX: \_\_\_\_\_

I-O AGENTS RCVD:  CHECKPOINT INHIBITOR(S)

CAR-T  VACCINES  ONCOLYTIC VIRAL THERAPY


MONOCLONAL ANTIBODIES

DRUG NAME(S): \_\_\_\_\_

IMMUNOTHERAPY TX START DATE: \_\_\_\_\_

OTHER CANCER MEDICATIONS: \_\_\_\_\_

NOTE: IMMUNOTHERAPY AGENTS ARE NOT CHEMOTHERAPY AND SIDE EFFECTS MUST BE MANAGED DIFFERENTLY. (SEE BACK)



**IMMUNOTHERAPY CARD**

IMMUNE-RELATED SIDE EFFECTS\*, COMMON WITH CHECKPOINT INHIBITORS VARY IN SEVERITY AND MAY REQUIRE REFERRAL AND STEROIDS. PATIENTS HAVE A LIFETIME RISK OF IMMUNE-RELATED SIDE EFFECTS.

\*MAY PRESENT AS RASH, DIARRHEA, ABDOMINAL PAIN, COUGH, FATIGUE, HEADACHES, VISION CHANGES, ETC. – CONFER WITH ONCOLOGY TEAM BEFORE CHANGING I-O REGIMEN OR STARTING SIDE EFFECT TREATMENT.

ONCOLOGY PROVIDER NAME \_\_\_\_\_

ONCOLOGY PROVIDER NO. \_\_\_\_\_

EMERGENCY CONTACT \_\_\_\_\_

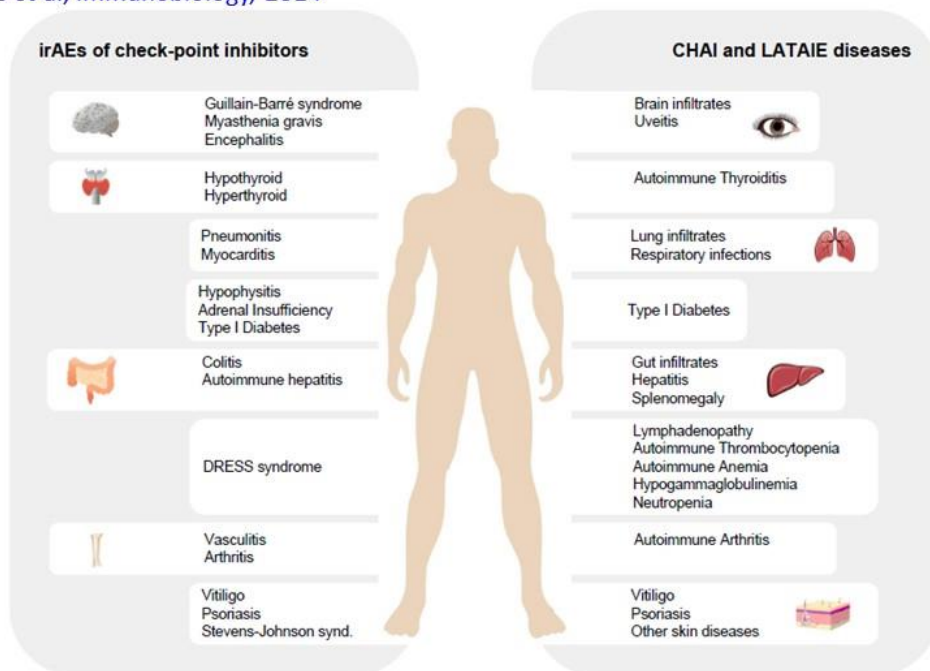
CONTACT PHONE NO. \_\_\_\_\_

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Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy, Brahmer et al, J Clin Oncol, 2018

Anti-CTLA-4 therapy may have mechanisms similar to those occurring in inherited human CTLA4 haploinsufficiency

Bakacs et al, Immunobiology, 2014



## Paradigm shift: exploiting Graft-Versus-Tumor (GVT) effect

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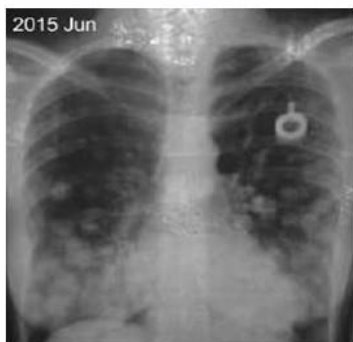
The same GVT effect could be achieved by ipilimumab as by donor lymphocyte infusion but without severe GVHD

- 3 mg/kg ipilimumab reversed relapse without worsening GVHD after allogeneic HSCT ([Bashey et al, Blood, 2009](#))
- Ipilimumab 0.3 mg/kg mild-to-moderate irAEs suggests a biological effect ([Wolchok et al, Lancet Oncol, 2010](#))
- Low-dose adjuvant ipilimumab (0.3 mg/kg) could induce auto-GVHD at the stage of minimal residual disease (MRD) ([Slavin et al, Pharmacol Res, 2013](#))
- High-dose (10 mg/kg) adjuvant ipilimumab gained FDA approval (33.3 times higher dose than that of suggested by Slavin) ([Eggermont et al, N Engl J Med, 2016](#))

## Complete remission of lung metastases in TNBC

Transient WHO I-II diarrhea and skin rash, patient alive for 27 months

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**ipilimumab (0.3 mg/kg) nivolumab (0.5 mg/kg)**  
**interleukin-2 (54 Mio/m<sup>2</sup> as decrescendo regimen)**  
loco regional- and whole body **hyperthermia**

[Kleef et al Integrative Cancer Therapies, 2018](#)  
DOI: 10.1177/1534735418794867

## Autoimmunity is the Achilles' heel of cancer immunotherapy

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- Incidence of irAEs is underestimated
  - ✓ most cancer trials follow patients for only a brief time
  - ✓ patients who died from their cancer are not included
- Incidence of irAEs will rise as these therapies become more widely used
- The risks of the ICIs is „a massively understudied area”

**Since our low-dose ICI protocol consists only of approved drugs and treatments it can be confirmed or refuted in controlled clinical trials**

„As I go around the country, I talk about the tragedy of cancer to remind people that the tragedy is not our inability to prevent the inevitable or to do the impossible; tragedy is when a person, a group or a society fails to achieve the possible.”



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**Cancer, minorities & the medically underserved\***

The role of the National Cancer Institute

Richard D. Klausner M.D.

First published: 09 November 2000

# Thank you for your attention

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