Exploiting autoimmunity unleashed by an off-label low-dose immune checkpoint blockade to treat advanced cancer

Tibor Bakacs[1*], M.D., Ph.D., D.Sc., Ralph W. Moss[2], Ph.D., Ralf Kleef[3] M.D., A. Marcell Szasz[4], M.D., Ph.D., Colin C. Anderson[5], Ph.D.

[1]PRET Therapeutics Ltd., Hungary
[2]Moss Reports, USA
[3]Dr. Kleef Hyperthermie, Immunology & Integrative Oncology, Austria
[4]Cancer Center, Semmelweis University, Hungary
[5]Departments of Surgery and Medical Microbiology & Immunology, Alberta Diabetes Institute, Alberta Transplant Institute, University of Alberta, Edmonton, USA

E-mail: tiborbakacs@gmail.com

To the memory of Melvin Cohn, founding fellow and professor emeritus of the Salk Institute for Biological Studies

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www.oncotherm.com/sites/oncotherm/files/2019-10/Exploiting_autoimmunity.pdf

Introduction

As a result of the cancer immunotherapy revolution more than 2,000 immuno-oncology agents are currently being tested or in use to improve responses. Not unexpectedly, the 2018 Nobel Prize in Physiology or Medicine was awarded to James P. Allison and Tasuku Honjo for their development of cancer therapy by blockade of co-inhibitory signals. While success stories of terminal cancer patients achieving complete remissions are accumulating, not enough research has been done into the risks of the new therapies. Since the use of immunotherapy is becoming more common and is beginning to develop into first- and second-line treatments, autoimmunity is emerging as the nemesis of immunotherapy. Immune-related adverse events (irAEs) could affect any tissue; their incidence may reach up to 96% of patients; and toxicity is dose-dependent. While the combination of two immune checkpoint inhibitors (ICIs) increases efficacy, the incidence of severe adverse events is also increased. Apparently, ICIs cannot be restricted to the targeted anti-tumour T cell population. The long-lasting objective of cancer regression can only be achieved by paying a price: tolerance to healthy self-tissues is compromised.

Objectives, Material/Methods

In the face of an ipilimumab-induced pan-lymphocytic activation, a therapeutic paradigm shift is required. The task is not to desperately put the genie back in the bottle by immune suppressive treatments, but instead harnessing the autoimmune forces by an off label low-dose combined anti-CTLA-4 and anti-PD1 antibody blockade, which is supplemented with conventional interleukin-2 (IL-2) stimulation and hyperthermia.

Results

The proof-of-principle of the low-dose-combination therapy was 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. Her pulmonary metastases went into complete remission with transient WHO I-II diarrhoea and skin rash. She lived for 27 months after starting the low-dose-combination therapy. Since then, 111 stage IV cancer patients with a variety of cancer types have been treated. A retrospective analysis of these single cases demonstrated that the overall response (OR) rate was 48% with an objective response (ORR) of 33%, while irAEs of WHO grade I, II, III and IV were observed in 21%, 14%, 7% and 2% of patients, respectively.

Conclusion

Since the low-dose-combination protocol consists only of approved drugs and treatments, these single patient responses can be confirmed or refuted in prospective controlled clinical trials.

Exploiting autoimmunity unleashed by an off-label low-dose immune checkpoint blockade to treat advanced cancer
(Scand. J. Immunol. 2019 in press)

Tibor Bakacs, M.D., Ph.D., D.Sc, Ralph W. Moss, Ph.D., Ralf Kleef M.D.,
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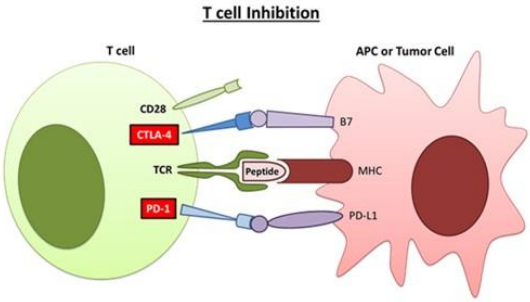
Highlights

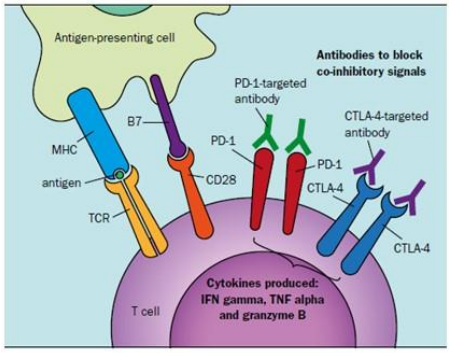
- Autoimmunity emerging as the nemesis of immunotherapy;
- Immune-related adverse events (irAEs) can affect any tissue; their incidence may reach up to 96% of patients;
- Nobel committee: improve understanding of irAEs
- Therapeutic paradigm shift: autoimmune T cells can be harnessed for a graft-versus-tumour (GVT) reaction by an off-label low-dose combined checkpoint blockade, complemented with interleukin 2 (IL-2) and hyperthermia;
- Overall response rate 48% with irAEs of WHO grade III and IV in 7% and 2% of 111 stage IV cancer patients

For survival T cells require regular stimulation from self-peptides



- Self-antigens activate T cells by "tonic" TCR signals
- **Physiologic autoimmunity regulated by checkpoint inhibitors**
- Following short activation T cells express CTLA-4 that terminates activation

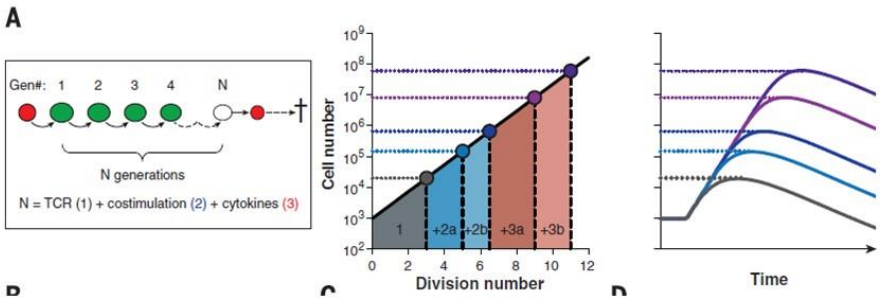
Immune checkpoint blockade turns physiologic autoimmunity into a pan-lymphocytic activation



- CTLA-4 is blocked not only on tumor-specific but on all activated T cells
- This results in immune stimulation, tolerance breakdown and tumor eradication
- **Cancer regressions cannot be achieved without breaking the tolerance**

Rationale for low-dose ICI combination therapy: individual (sub-threshold) effects add up

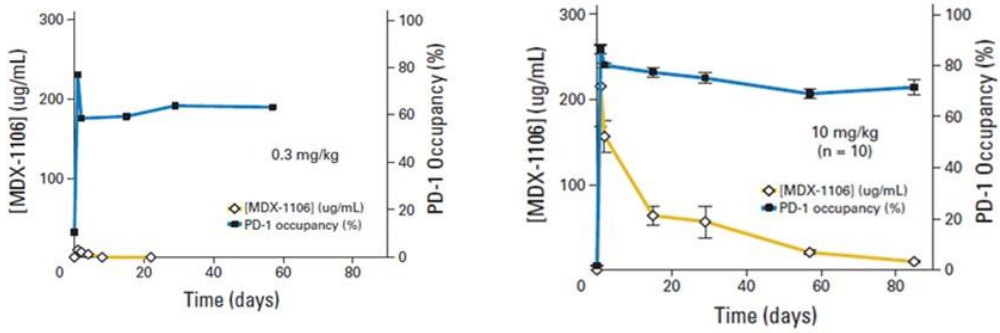
The quantitative paradigm of T cell activation: signals from the TCR, co-stimulatory/co-inhibitory receptors and cytokines are added together



Marchingo et al. Science. 2014 Nov 28;346:1123-7

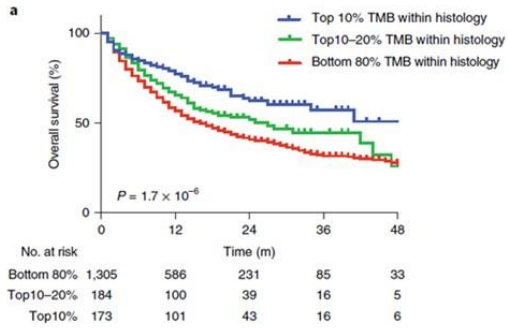
Off-label, low-dose ICI therapy administers the lowest doses (0.3 mg/kg ipilimumab and 0.5 mg/kg nivolumab)

PD-1 occupancy was comparable at **0.3 mg/kg and 10.0 mg/kg**



No patient had an antitumor response but had Gr 2/3 irAEs

Checkpoint inhibitors were more likely to halt tumor growth with higher number of mutations

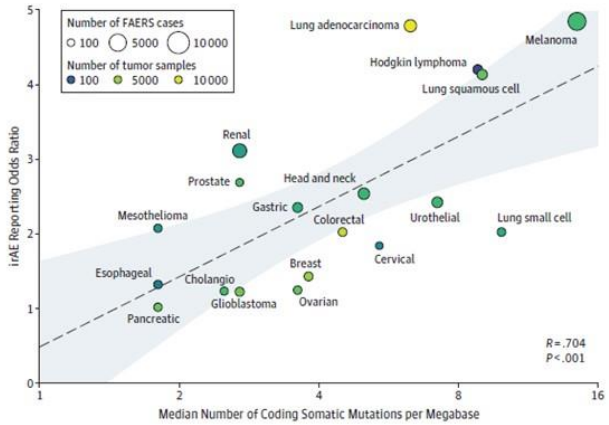


- ❑ Nature: neoantigens generate an immune reaction
- ❑ We suggest: this is a transplantation reaction against new antigens
- ❑ Without ICI blockade too weak to provoke T cell attack
- ❑ **With ICI blockade T cells attack semi-allogeneic tumors resulting in better overall survival**

Samstein, R.M., et al. Nat. Genet. 51:202–6, 2019.

Significant positive correlation between irAEs during anti–PD-1 therapy and TMB across multiple cancer types

Figure. Association of Tumor Mutational Burden With Immune-Related Adverse Events During Anti–PD-1 Therapy Across Multiple Cancers



Bomze, D., Hasan Ali, O., Bate, A., Flatz, L. 2019. Association Between Immune-Related Adverse Events During Anti–PD-1 Therapy and Tumor Mutational Burden. JAMA Oncology.

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

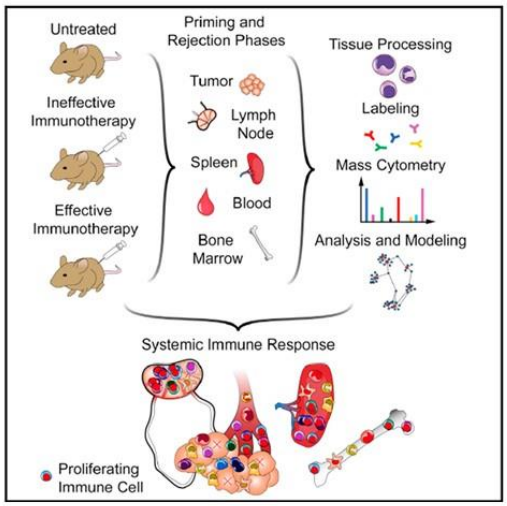
- ❑ irAEs affect any tissue, incidence up to 96%
- ❑ Overall incidence <75% with ipilimumab monotherapy; ≤30% anti-PD-1/PD-L1 agents
- ❑ IrAEs of ≥ grade 3 up to 43% with ipilimumab and ≤20% with PD-1/PD-L1 agents
- ❑ Combination of ipilimumab with nivolumab: 55% of grade 3/4 irAEs; discontinuation rate 30%
- ❑ irAEs with ipilimumab and pembrolizumab is dose-dependent
- ❑ Death due to irAEs occurred in up to 2% of patients

Autoimmunity is the Achilles' heel of cancer immunotherapy

- ❑ **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”

Systemic immunity is critical to tumor rejection following immunotherapy

Spitzer et al. Cell; 2017 Jan 26;168:487-502 e15



- High-throughput and high-dimensional single-cell technologies (mass cytometry, assessing all immune cells simultaneously)
- Supports therapeutic paradigm shift to exploit systemic autoimmunity for the treatment of advanced cancer

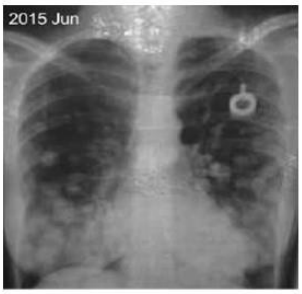
ICI antibodies generate Graft-Versus-Tumor (GVT) effect without allogeneic hematopoietic stem cell transplantation

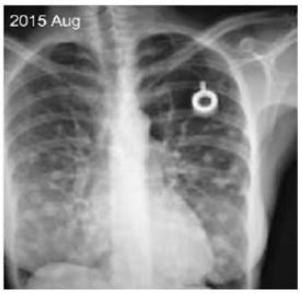
The same GVT effect could be achieved by ipilimumab as by donor lymphocyte infusion but without severe GVHD

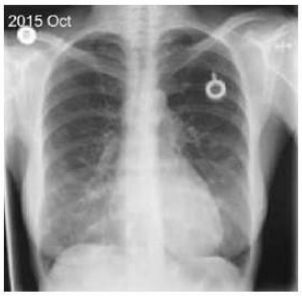
- While a low-dose adjuvant ipilimumab (0.3 mg/kg) could induce auto-GVHD… (Slavin et al, Pharmacol Res, 2013)
- …a high-dose (10 mg/kg) adjuvant ipilimumab gained FDA approval (33.3 times higher dose than that of suggested by Slavin) (Eggermont et al, N Engl J Med, 2016) with 41.6% of a grade 3 or 4 irAEs in the ipilimumab group, but only in 2.7% in the placebo group; 5 patients (1.1%) died due to irAEs of ipilimumab
- Since our low-dose ICI protocol consists only of approved drugs and treatments it can be confirmed or refuted in controlled clinical trials

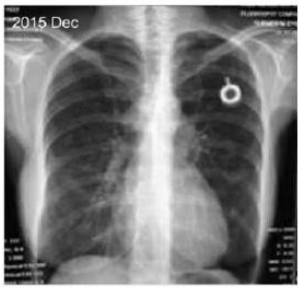
Complete remission of lung metastases in TNBC

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









ipilimumab (0.3 mg/kg) **nivolumab** (0.5 mg/kg)
interleukin-2 (54 Mio/m2 as decrescendo regimen)
loco regional- and whole body **hyperthermia**

Kleef et al Integrative Cancer Therapies, 2018
DOI: 10.1177/1534735418794867

Since the treatment of the first TNBC patient, 111 stage IV cancer patients were treated with a variety of cancer types

- ❑ Efficacy: **OR was 48%** with an ORR of 33%; the median follow-up 22 months
- ❑ Excellent safety: irAEs of WHO grade I in 21% of patients, grade II in 14%, **grade III in 7%, while grade IV in only 2% of patients**.
- ❑ With registered doses of ipilimumab (3 mg/kg) and nivolumab (3 mg/kg): irAEs in 96%, grade 3 or 4 irAEs in 55%, including events in the central nervous system in 7%; one patient died from immune-related myocarditis

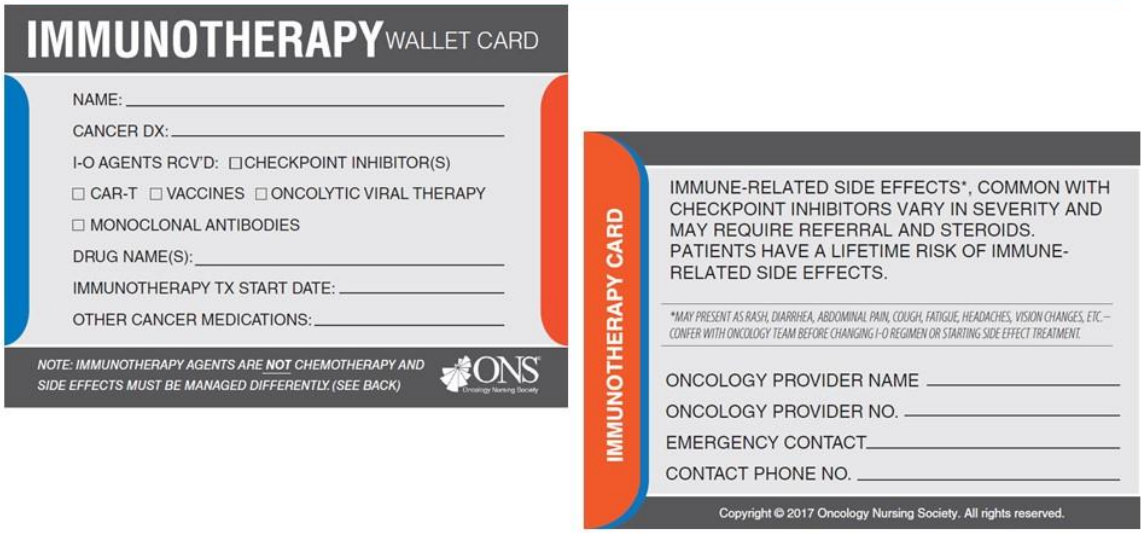
A retrospective analysis of single cases presented at the 8th-annual Oncology Association of Naturopathic Physicians in San Diego, CA, 2019.

Management of irAEs in Patients Treated With ICI Therapy: ASCO Clinical Practice Guideline.

J Clin Oncol. 2018

- ❑ Higher doses produce higher rates of irAEs
- ❑ Combination anti–CTLA-4 and anti–PD-1 significantly increased the risk of grade 3 and 4 irAEs
- ❑ The potential for life-disabling irAEs that are severe and/or irreversible exists
- ❑ **Dose reductions of immune checkpoint therapy should be avoided**

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 RCV'D: ☐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)

ONS Oncology Nursing Society

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. _____

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

University of Texas M.D. Anderson Cancer Centre confirmed the rationale for our low-dose immune checkpoint blockade protocol

- Despite dose-dependent increase in irAEs, no improvement in PFS, OS, or DCR with escalating doses of ICIs.
- Lower doses may reduce toxicity and cost without compromising disease control or survival.

Financial toxicity of newer oncology drugs is an issue for patients and health systems

Less than 5% of the population has coverage for PD-1 in Peru and less than 10% in Chile

TABLE 3. Dose and Cost Estimations for Nivolumab

Nivolumab	0.1 mg/kg Once Every 2 Weeks	0.3 mg/kg Once Every 2 Weeks	1 mg/kg Once Every 2 Weeks	3 mg/kg Once Every 2 Weeks	240 mg Once Every 2 Weeks
Mg per cycle	8	24	80	240	240
Cost per cycle (USD)	205	615	2,051	6,153	6,153
Cost per year (USD)	4,922	14,766	49,221	147,663	147,663
Relative cost versus std (%)	3	10	33	100	100
Patients treated versus std (No.)	30	10	3	1	1

NOTE. Dose estimated for an 80-kg patient. Calculations consider a cost of US $25.63 per mg, per Centers for Medicare and Medicaid Services Medicaid information.[21] These calculations do not reflect total treatment cost because they only consider medication expenditures.
Abbreviations: std, standard dosage; USD, US dollars.

Renner, A., Burotto, M., Rojas, C. 2019. Immune Checkpoint Inhibitor Dosing: Can We Go Lower Without Compromising Clinical Efficacy? Journal of Global Oncology, 1.(ASCO)

Financial barrier should be reduced to benefit more patients

- ❑ Both pembrolizumab and nivolumab have significant efficacy at much lower doses than those approved
- ❑ This should be tested in RCT
- ❑ **It is unlikely the pharmaceutical industry will be interested in such a subject**
- ❑ Independent institutions, universities, or collaborative groups would have to take on this challenge

„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."


Cancer

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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

For more information please contact:

Paul STOLK, Chief Executive Officer stolk.p.a@gmail.com

Dr. Tibor BAKACS, Chief Scientific Officer tiborbakacs@gmail.com