Is there a role for radiation in the field of intratumoral immunotherapy?

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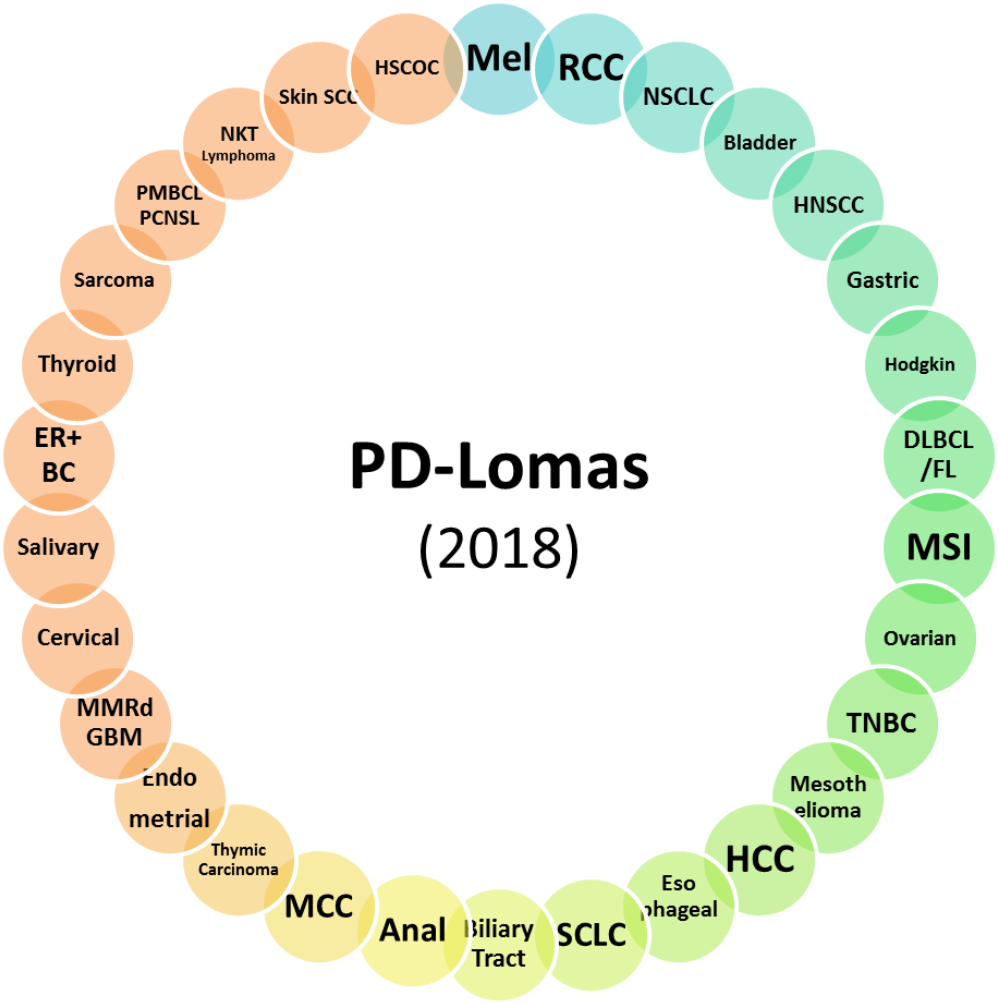
Drug Development Dpt (DITEP)
INSERM U1015

IMMUNORAD 18

Gustave Roussy Immunotherapy Program
Get a GRIP on Cancer

The IO Paradigm:
Cancer is an Auto-Dysimmune Disorder



Hirsch L et al, British Journal of Cancer (2018), in press

Current Challenges for I-O

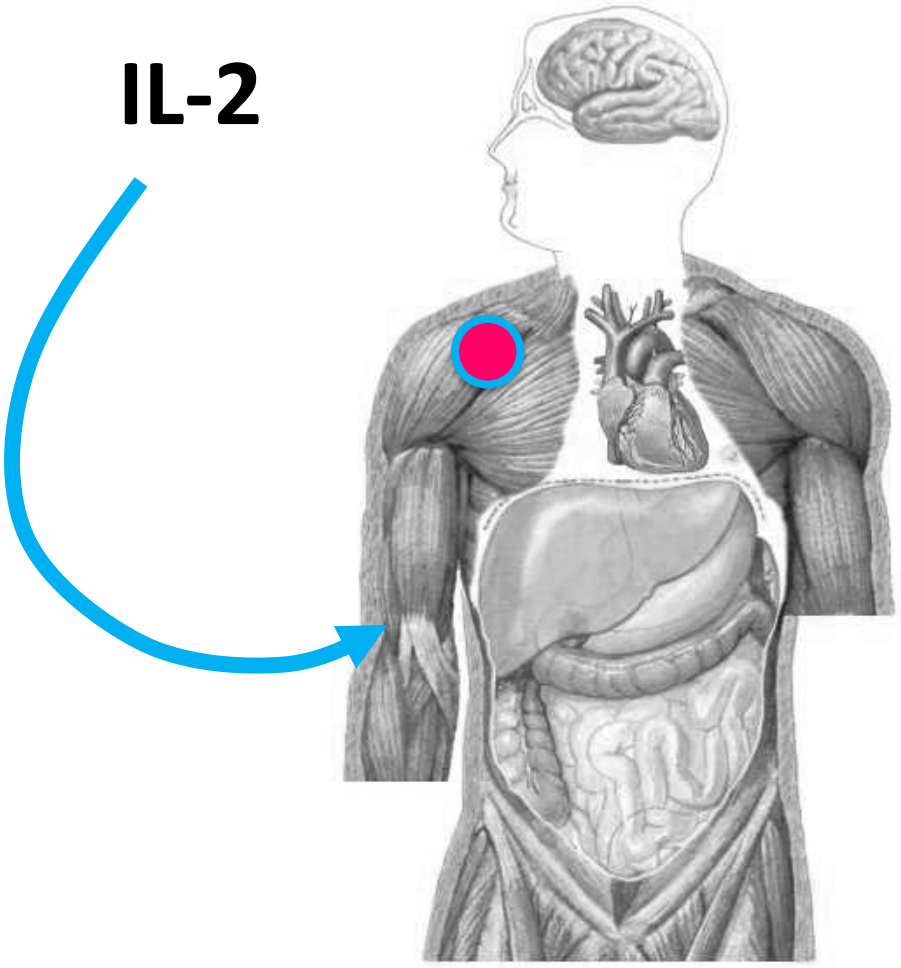
Better Identify Patients
who can benefit from
anti-PD(L)1 monotherapy

Overcome
the primary resistance
to anti-PD(L)1 monotherapy

Avoid Secondary Resistance
(Quality of the Anti-Tumor Immunity)

Address Incidence
& Severity of irAEs

IL-2

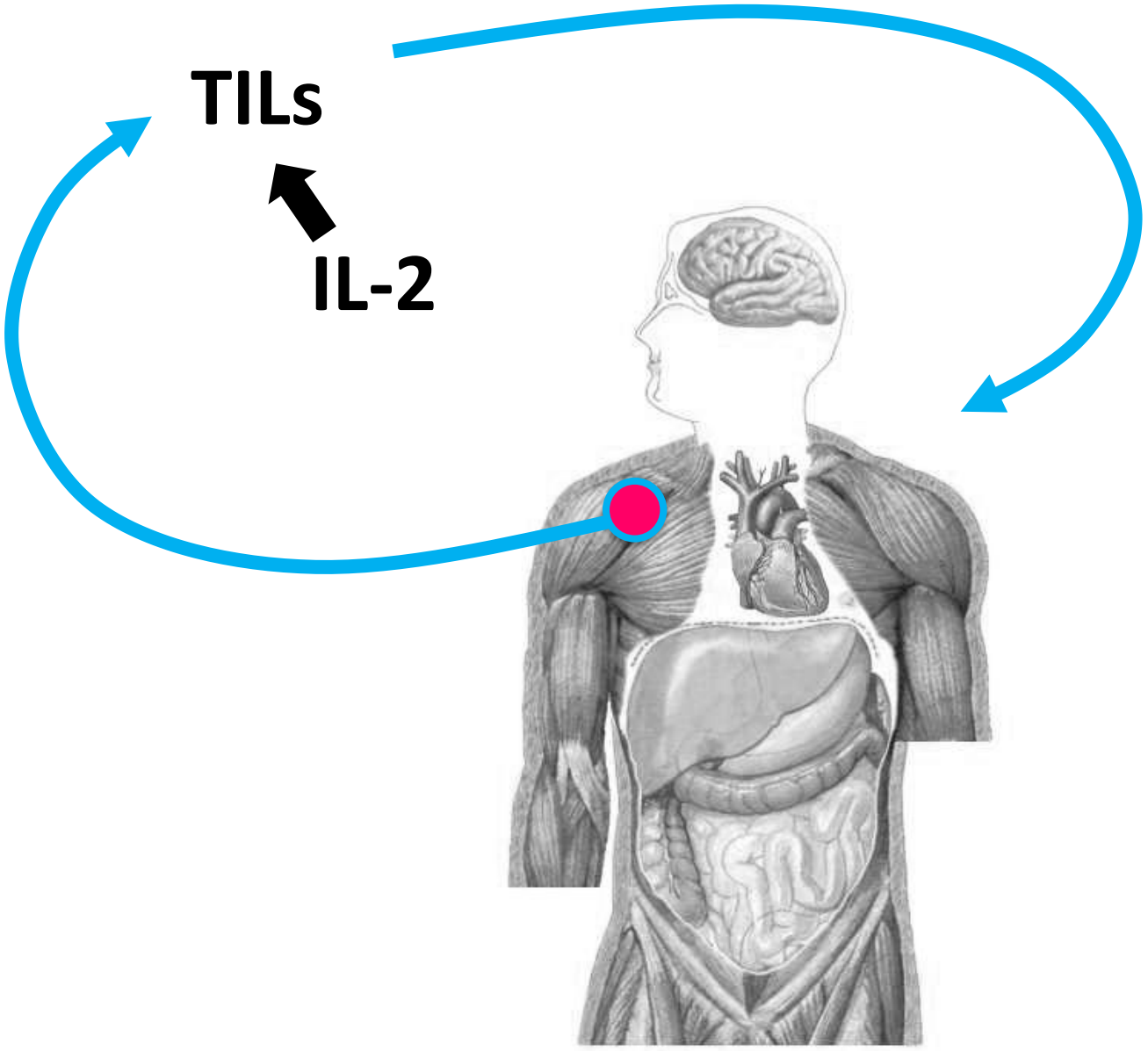


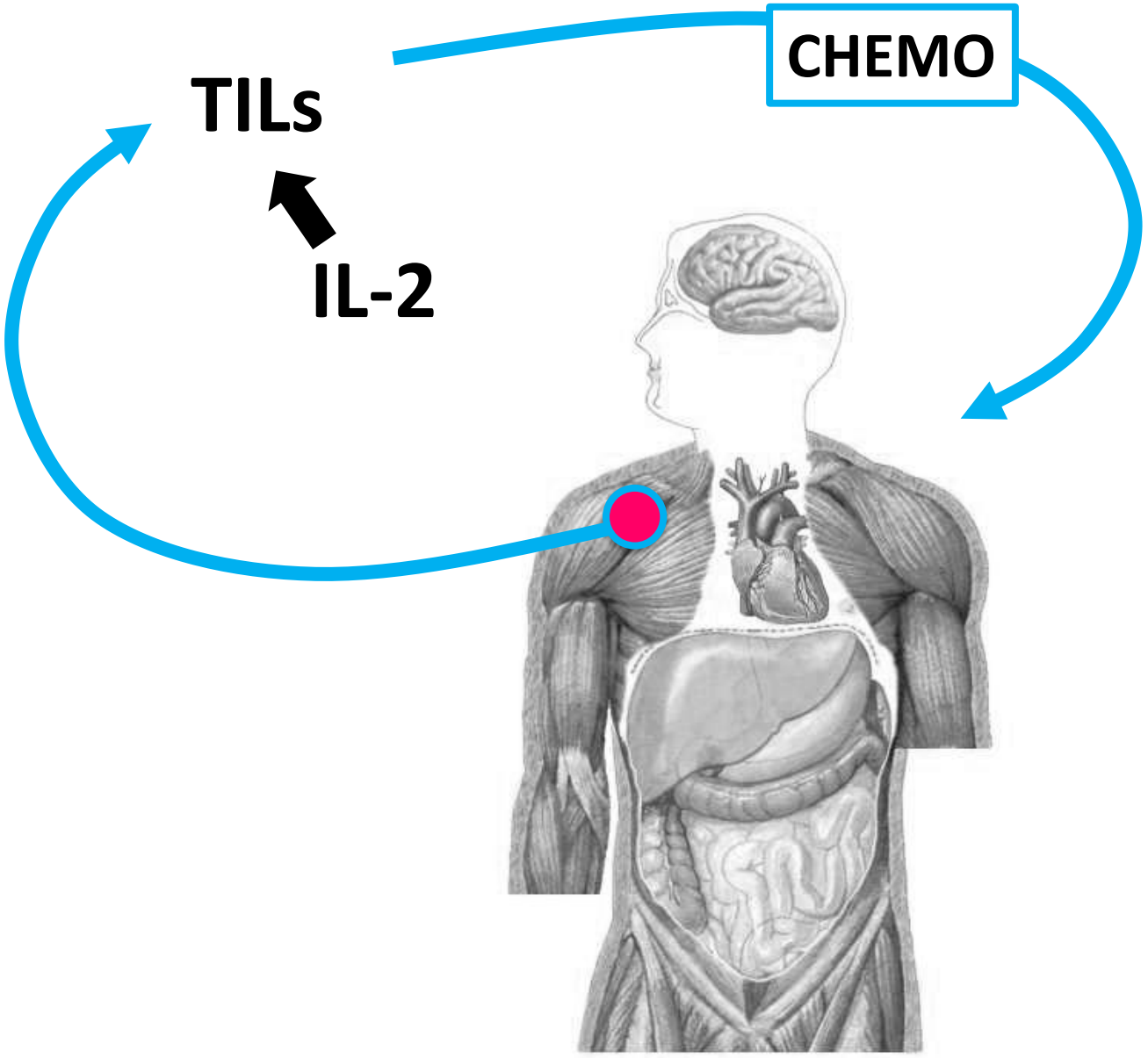
Low ORR
Toxicity
Tregs+++

BUT

Immune
Mediated
CANCER CURE

ORR=30%





ORR=30%

ORR=70%

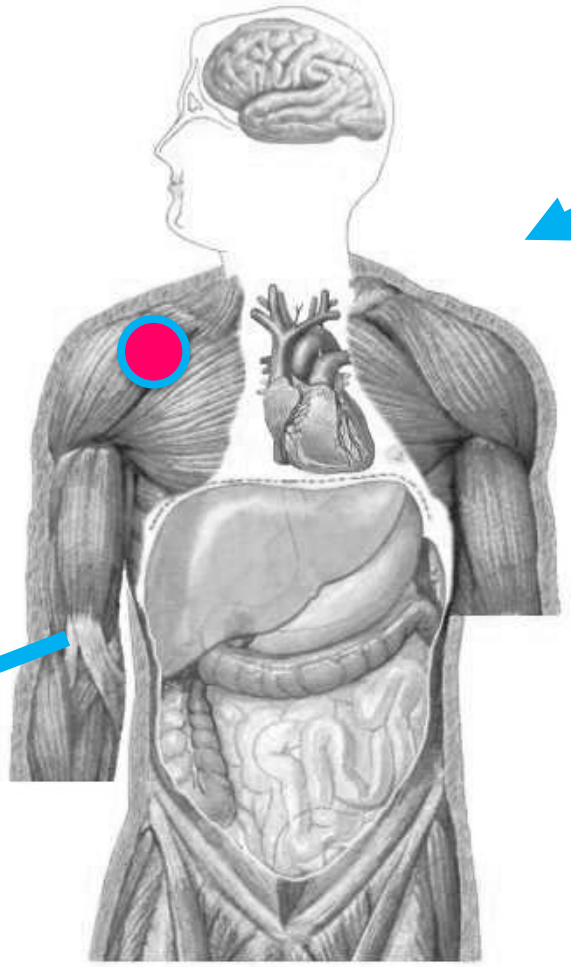
High Efficacy
Polyclonal

BUT

Very
Limited
Feasability

CAR-T

CHEMO

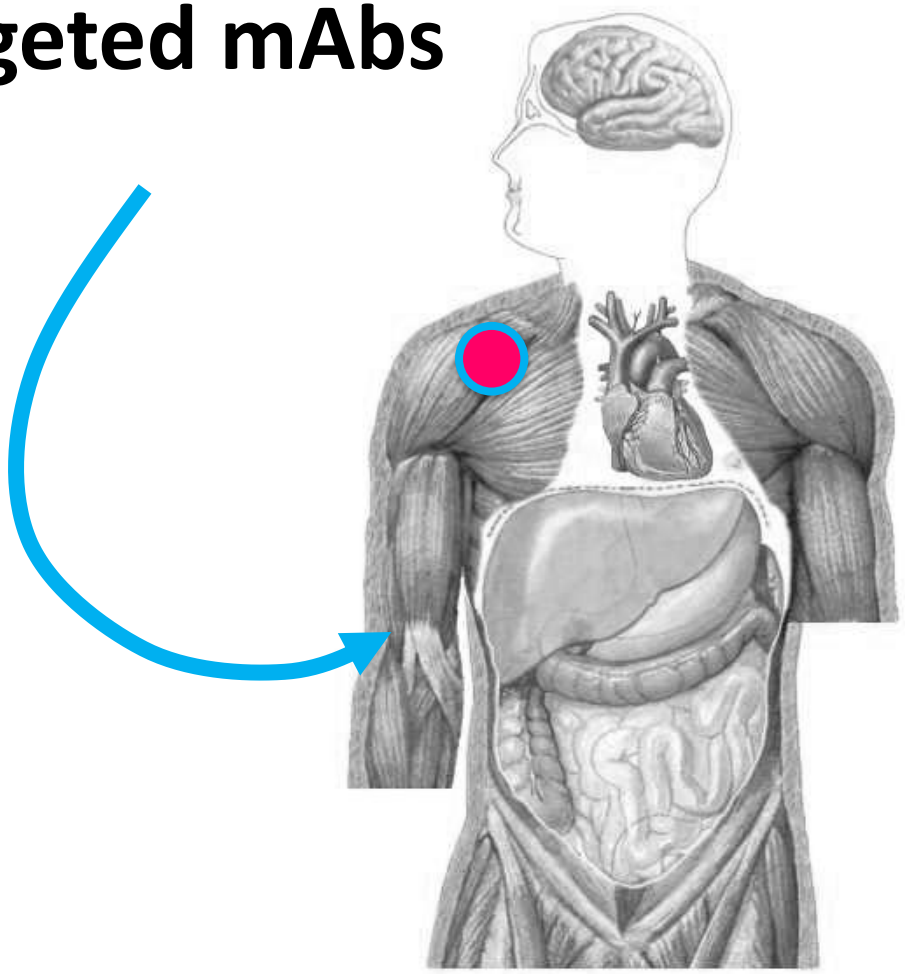


High Efficacy

BUT

Limited Targets
Tumor Escape
Feasability
Cost

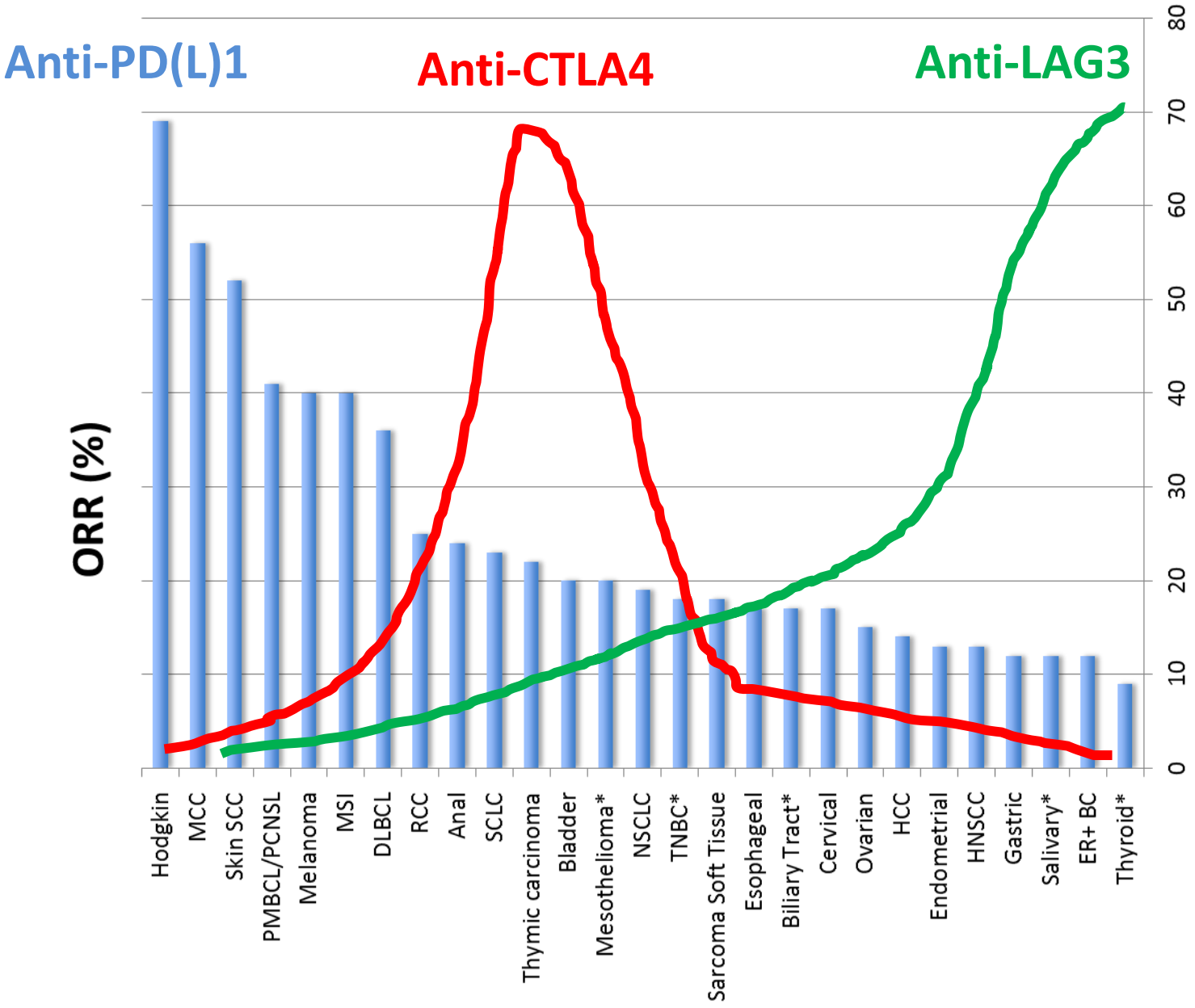
Immune Checkpoint Targeted mAbs



Significant Efficacy
Drug in a bottle

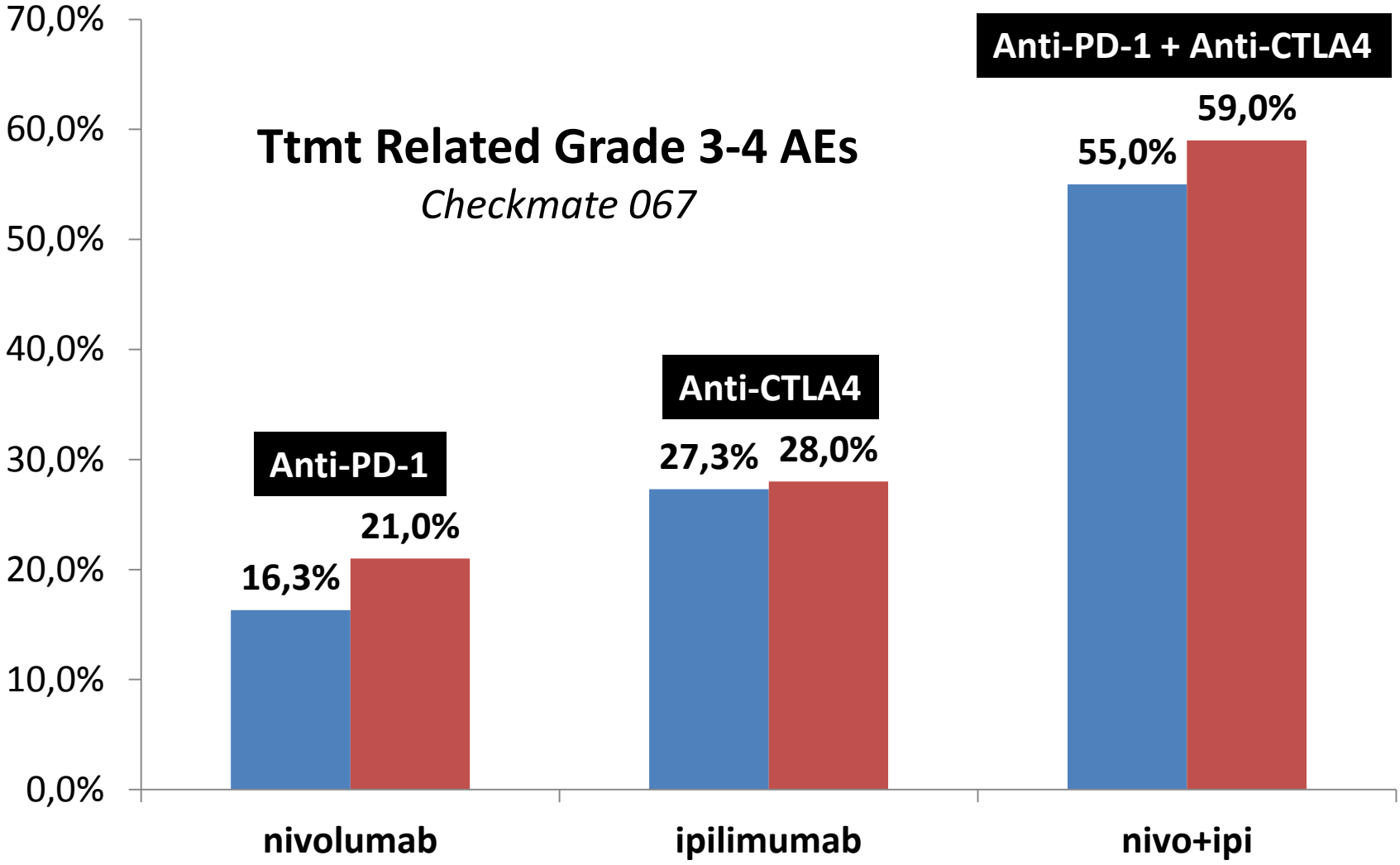
BUT

Primary R
Escape
Toxicities



Hirsch L et al, British Journal of Cancer (2018), in press

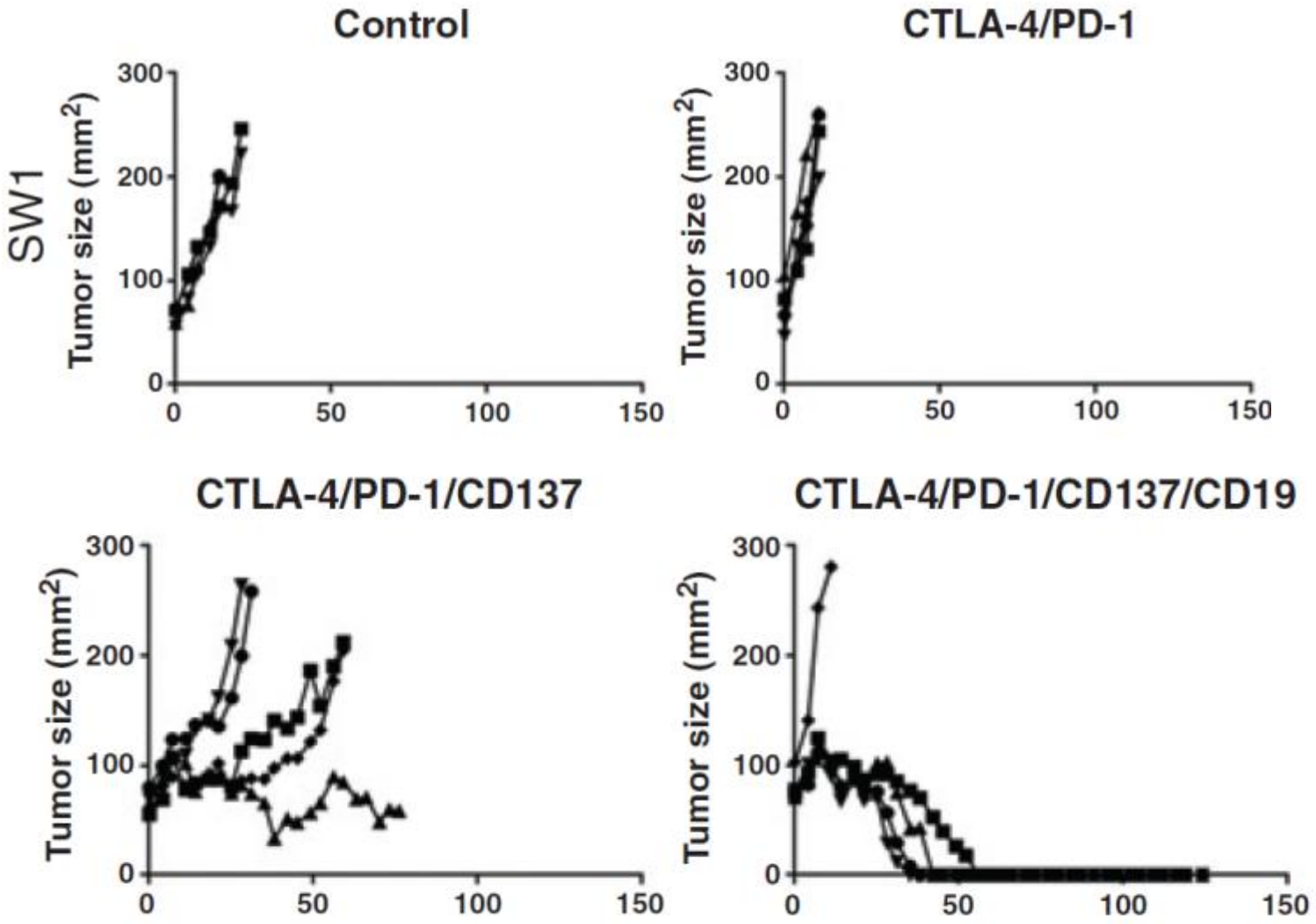
irAEs: on-target /*off-tumor*



Larkin, J., et al. (2015). NEJM. *373*, 23–34.

Wolchok, J. D. *et al.* NEJM. 377, 1345–1356 (2017).

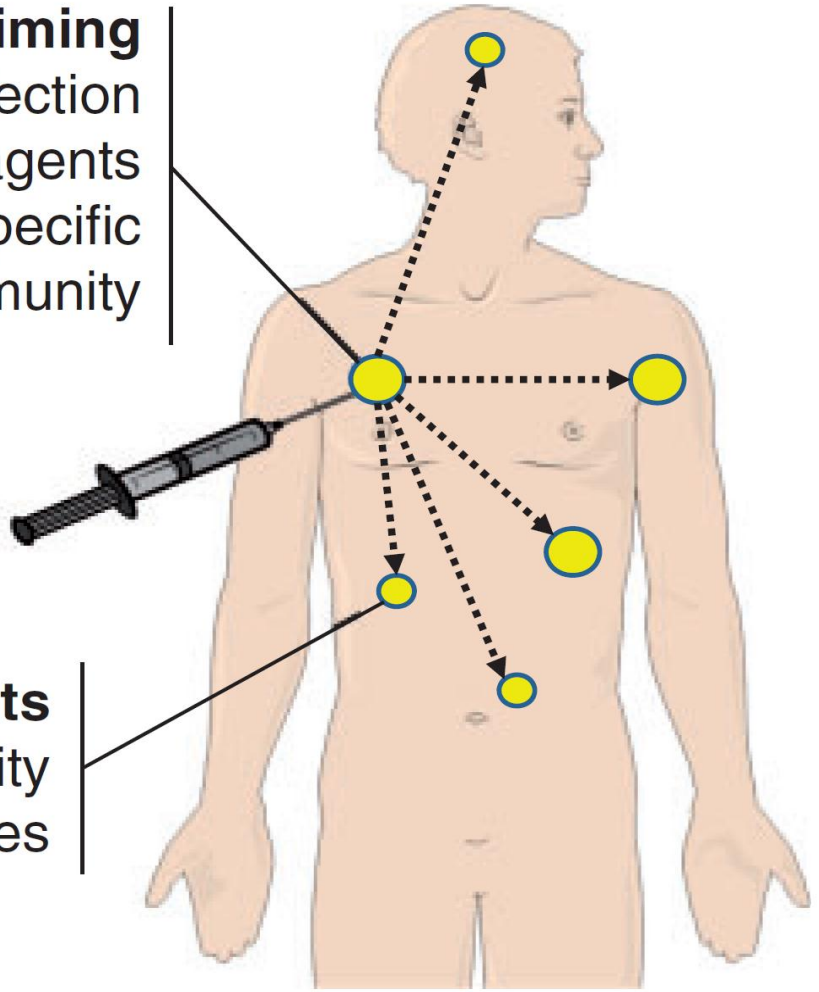
intratumoral combinations: on-target /*on-tumor*



Dai M *et al. Clin Cancer Res.* 2015 Mar 1;21(5):1127-38

Human Intra-Tumoral Immuno-Therapy (HIT-IT)

Local priming
Intra-tumoral Injection
of Immunostimulatory agents
to trigger tumor-specific
Immunity



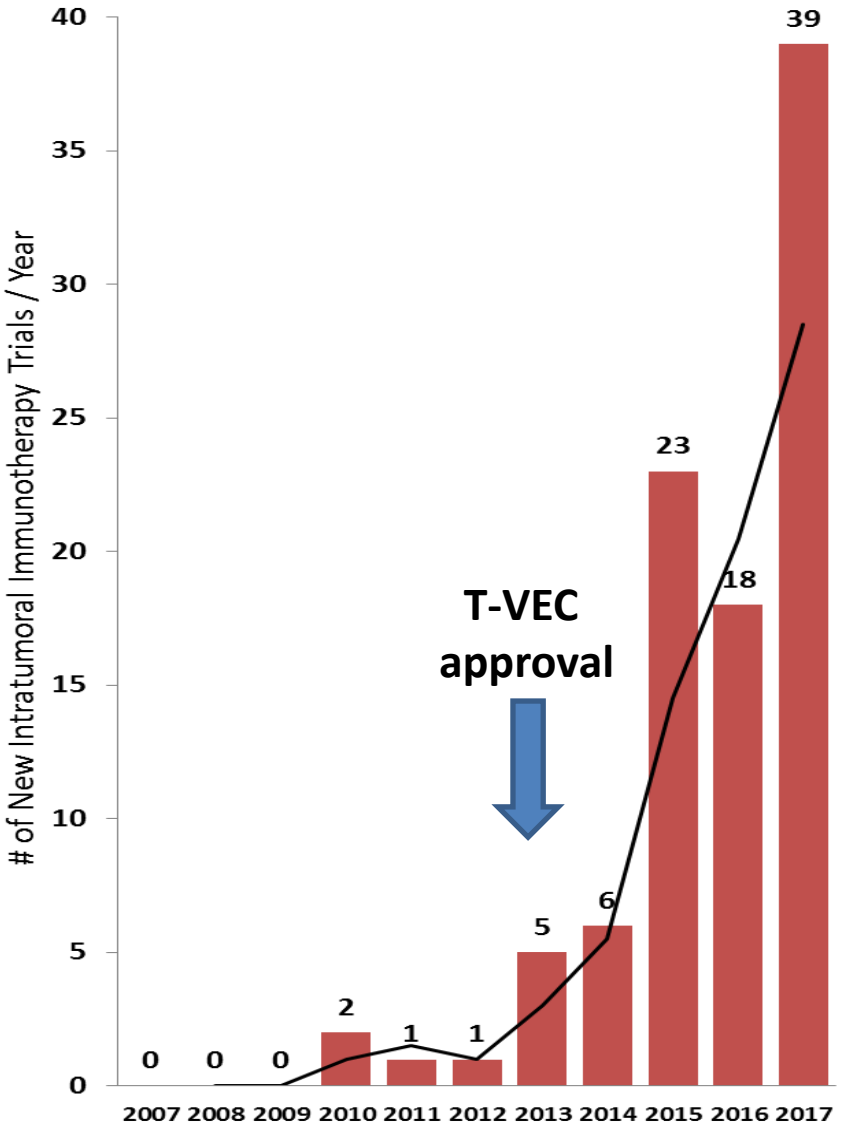
Distant effects
Systemic anti-tumor immunity
against non-injected tumor sites

Marabelle, A., Tselikas, L., de Baere, T., and Houot, R. (2017). Ann. Oncol. 28, xii33-xii43.

HIT-IT: Usual Skepticism

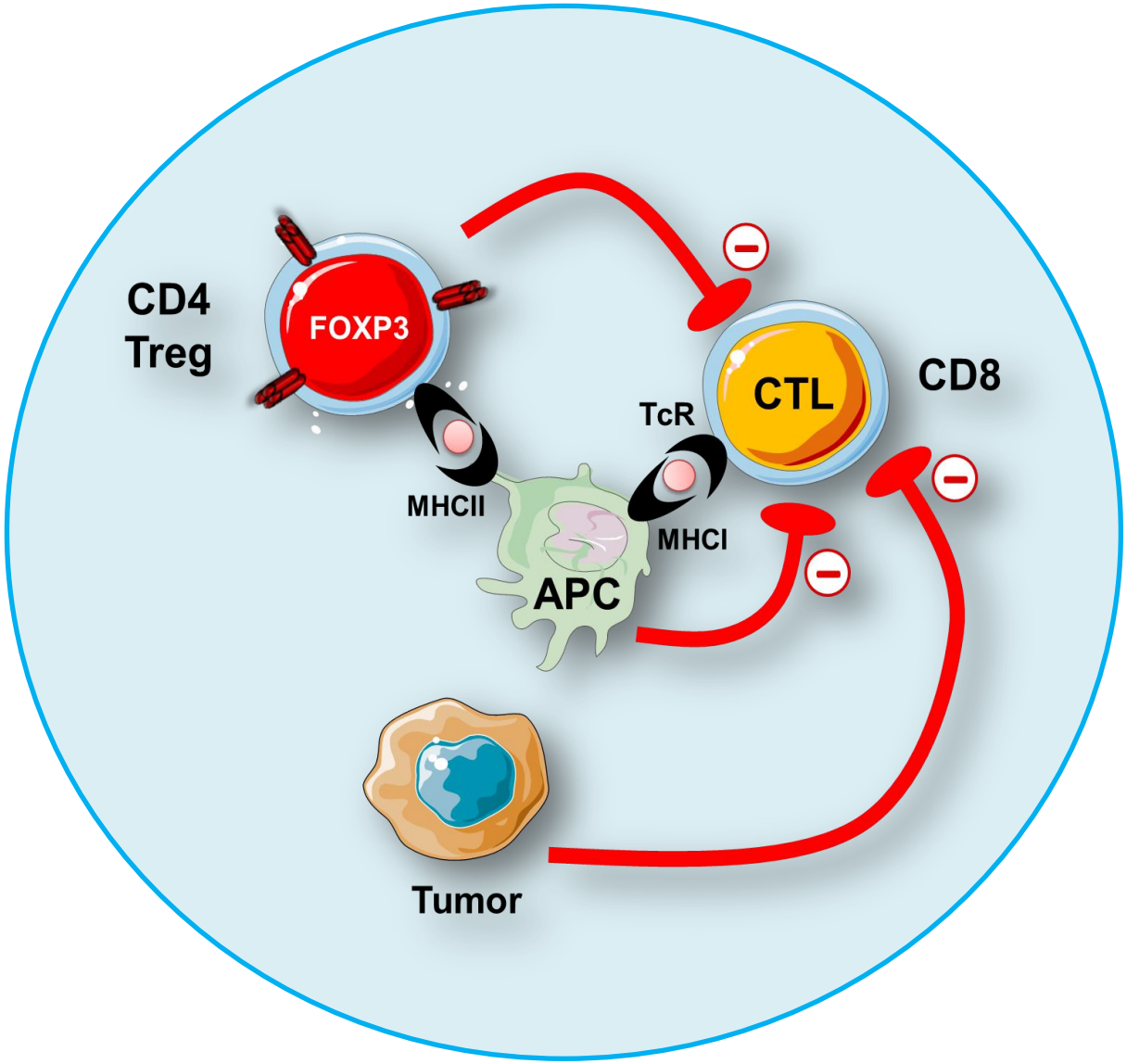
- **Feasibility**
- **Acceptability**
- **Implementation**
- **Ability to register an intratumoral drug**

Number of New Intratumoral Immunotherapy Trials / Year (clinicaltrials.gov)

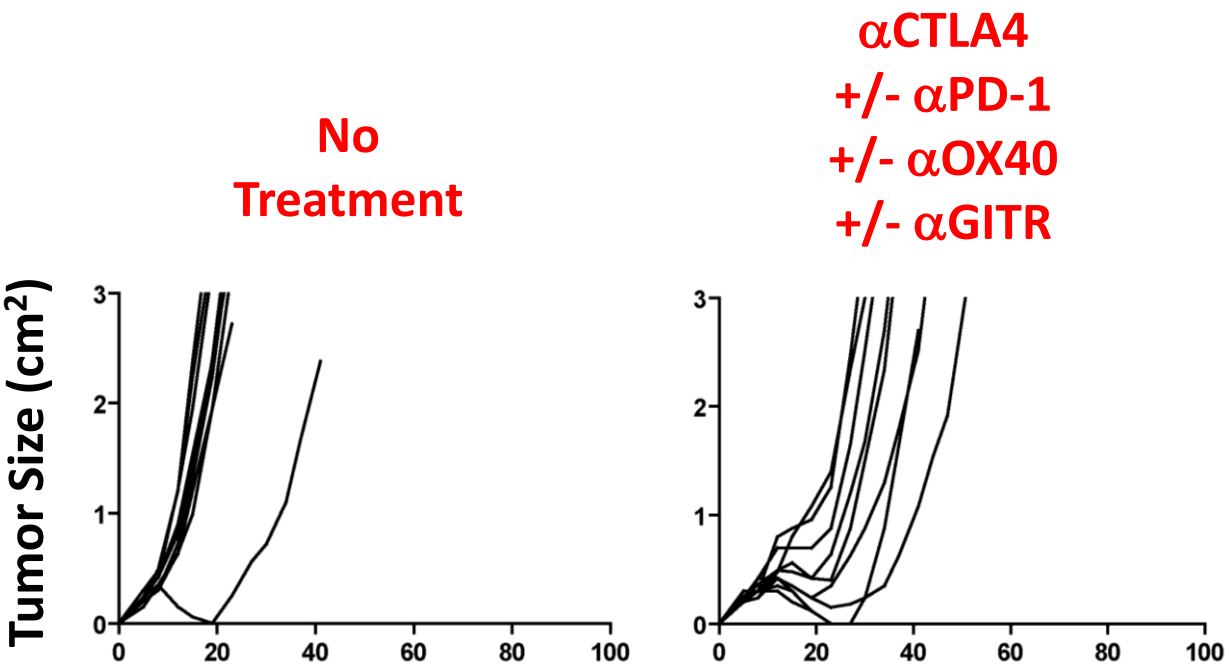


Intratumoral Immunotherapy 2018

The Equat*/On* to be solved

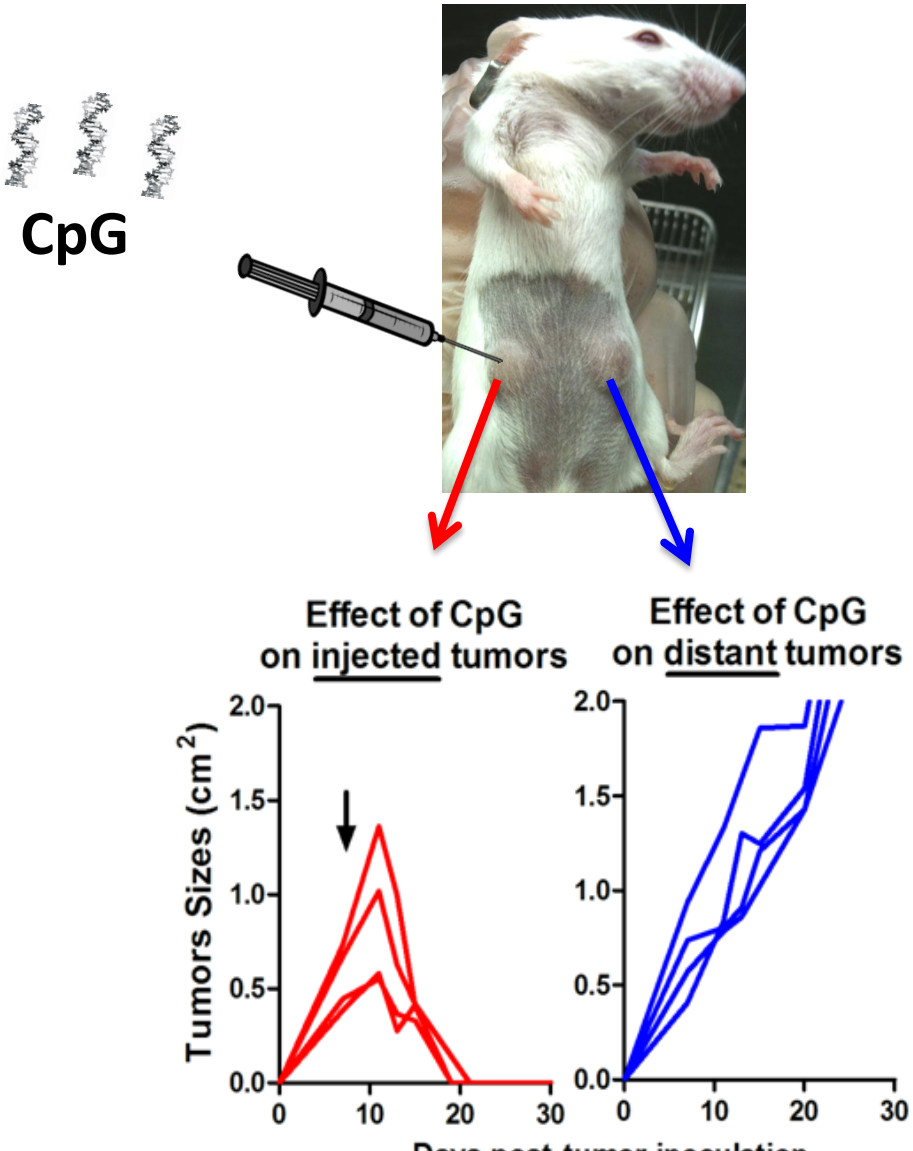


A20 B-cell Lymphoma: A Pre-clinical Model of Resistance to Immune Checkpoint Targeted Therapies

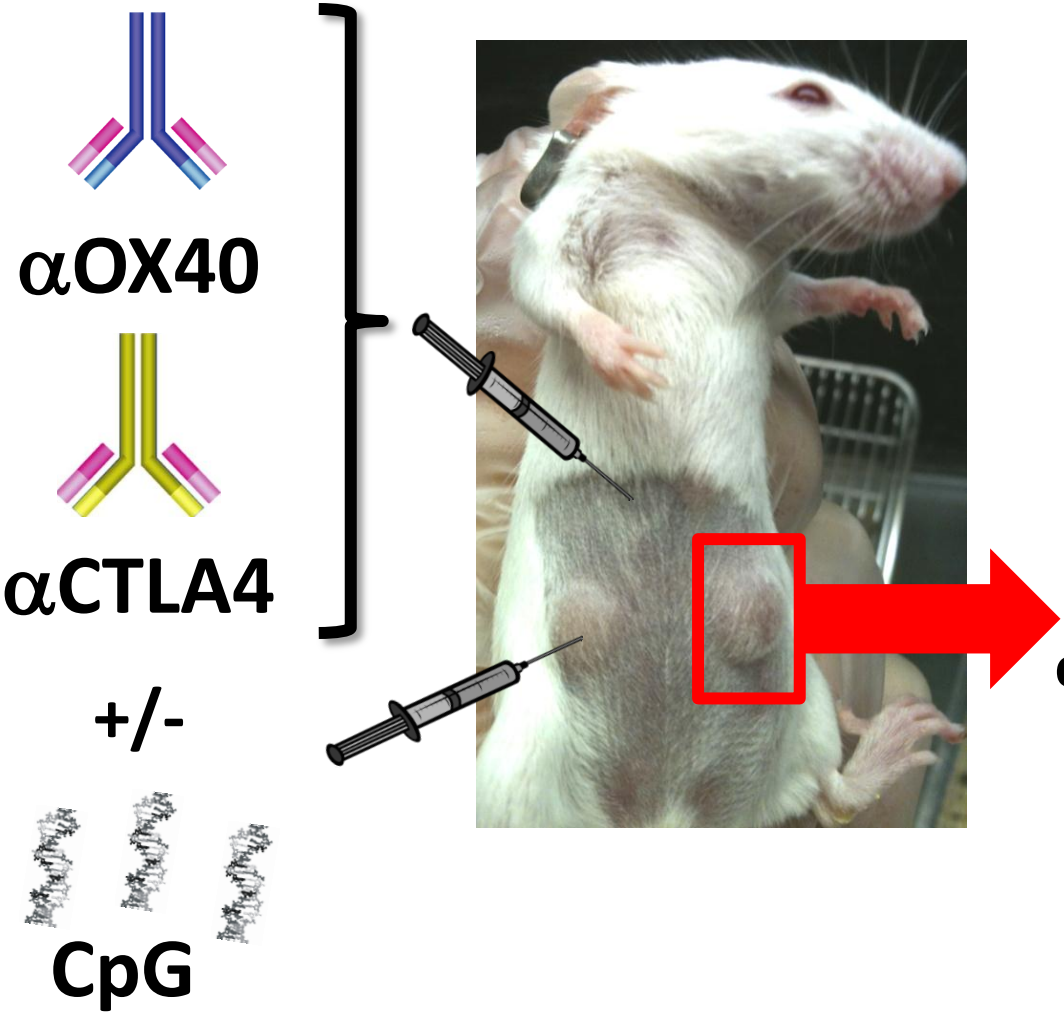


Houot R, Levy R. Blood 2009

Local Efficacy of Intratumoral TLR9 agonists

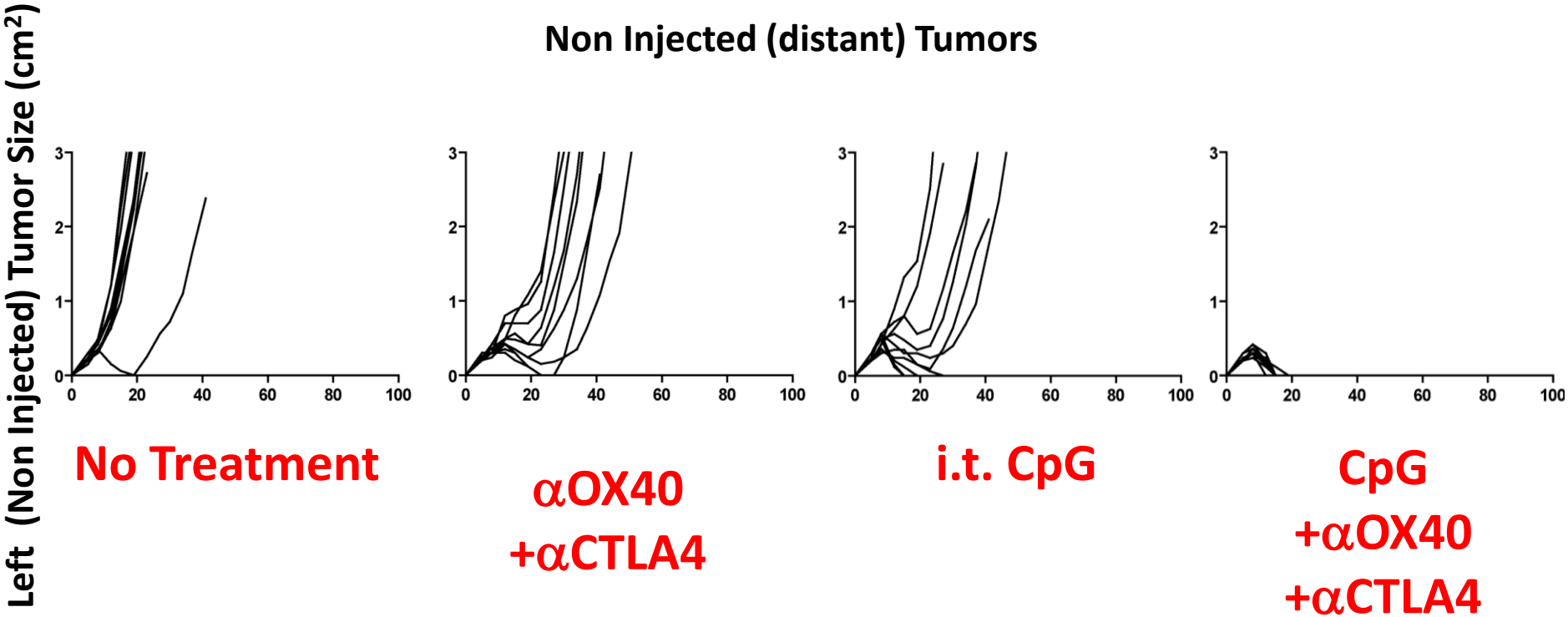


Abscopal Responses Upon Intratumoral Priming



Houot R, Levy R. Blood 2009

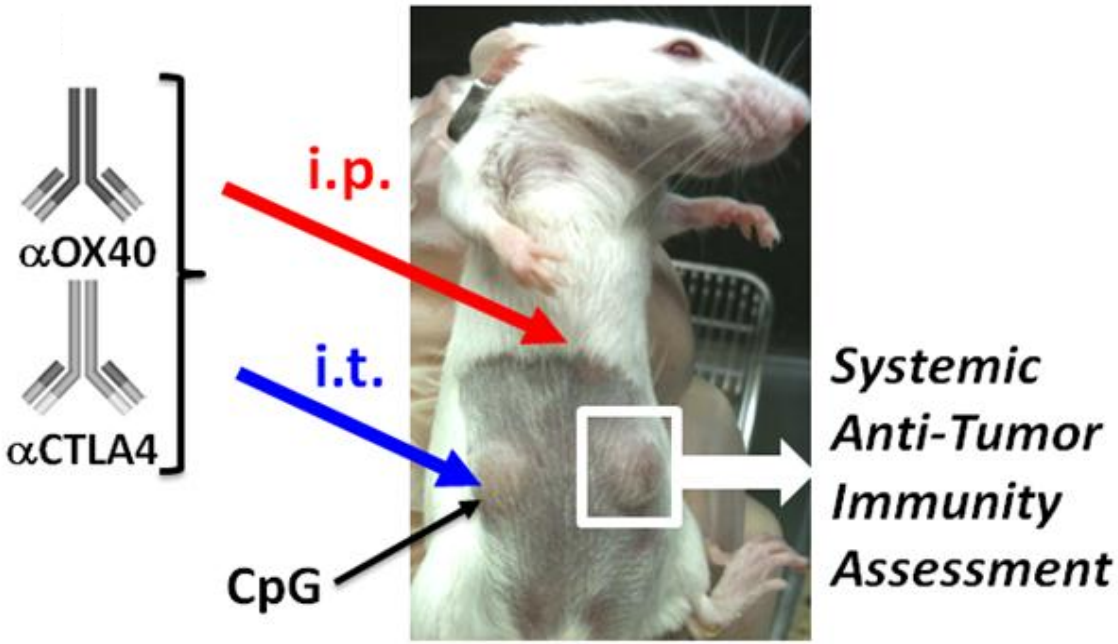
Overcome Immune Checkpoint Blockade Resistance with combinations of TLRago and imAbs



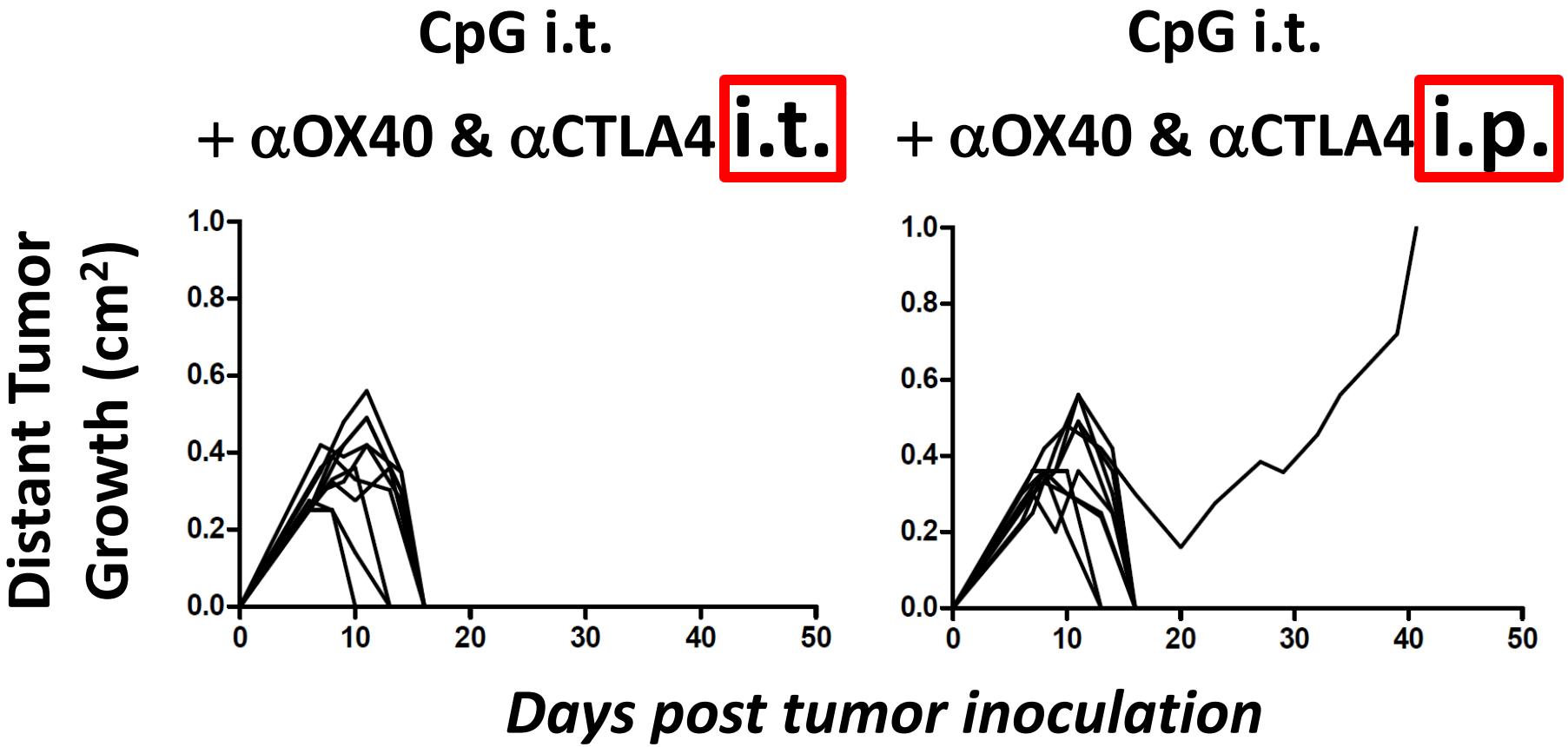
Houot et al. Blood, 2009 113: 3546–52.

Sagiv-Barfi I, et al. PNAS, 2015;112:E966–72.

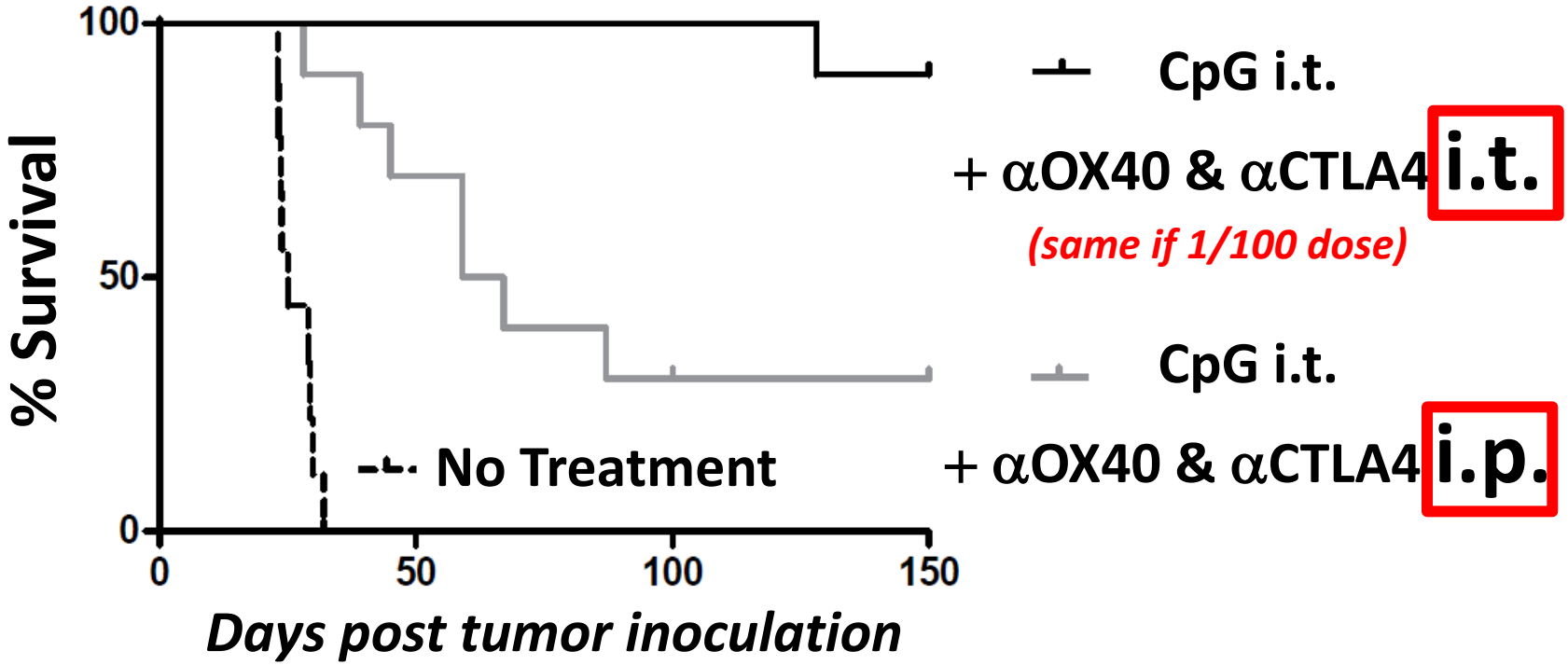
Systemic vs Local Immunomodulation: Effect on Contra-Lateral Tumor Growth



Systemic vs Local Immunomodulation: Effect on Contra-Lateral Tumor Growth



Intra-tumoral immunomodulation does better than Systemic immunomodulation



Marabelle A, et al. J Clin Invest 2013; Jun 3; 123:2447–63.

William Coley

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES.

MAY, 1893.

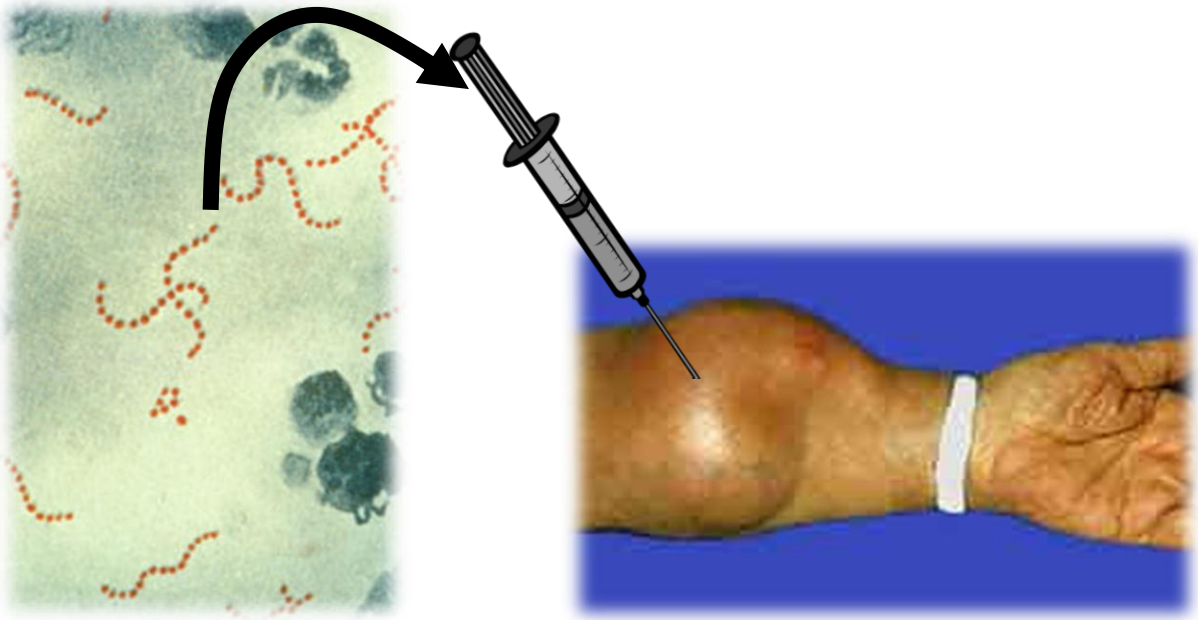
THE TREATMENT OF MALIGNANT TUMORS BY REPEATED INOCULATIONS OF ERYSIPELAS: WITH A REPORT OF TEN ORIGINAL CASES.[1]

By WILLIAM B. COLEY, M.D.,

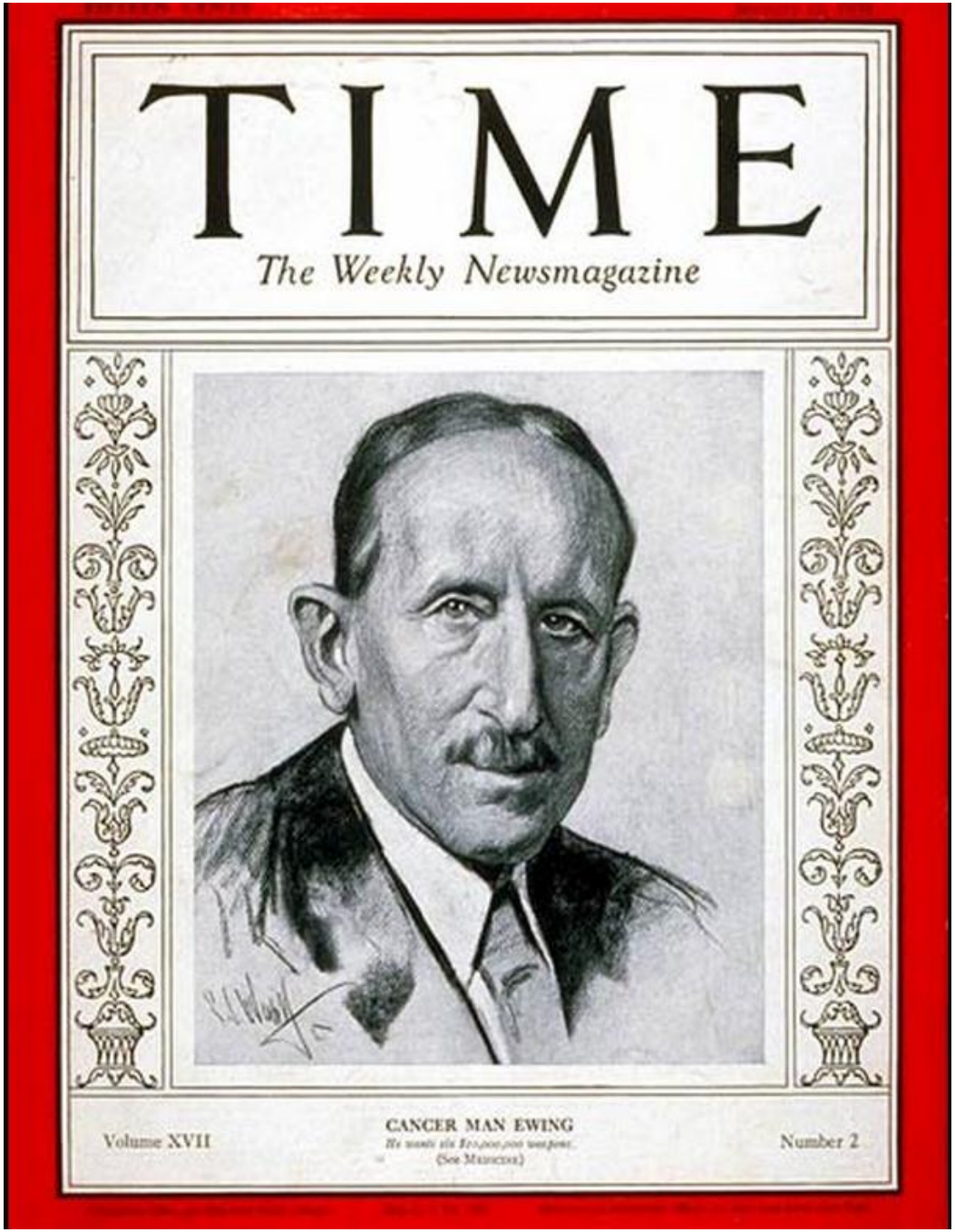
ASSISTANT SURGEON TO THE HOSPITAL FOR RUPTURED AND CRIPPLED; INSTRUCTOR IN SURGERY IN THE POST-GRADUATE MEDICAL SCHOOL, NEW YORK.

"…on May 2, 1891, I inoculated a case of sarcoma"

"At the end of two weeks, the tumor had disappeared"



Streptococcus pyogenes



James Ewing
1866-1943

BCG: off the shelf TLR4 agonist

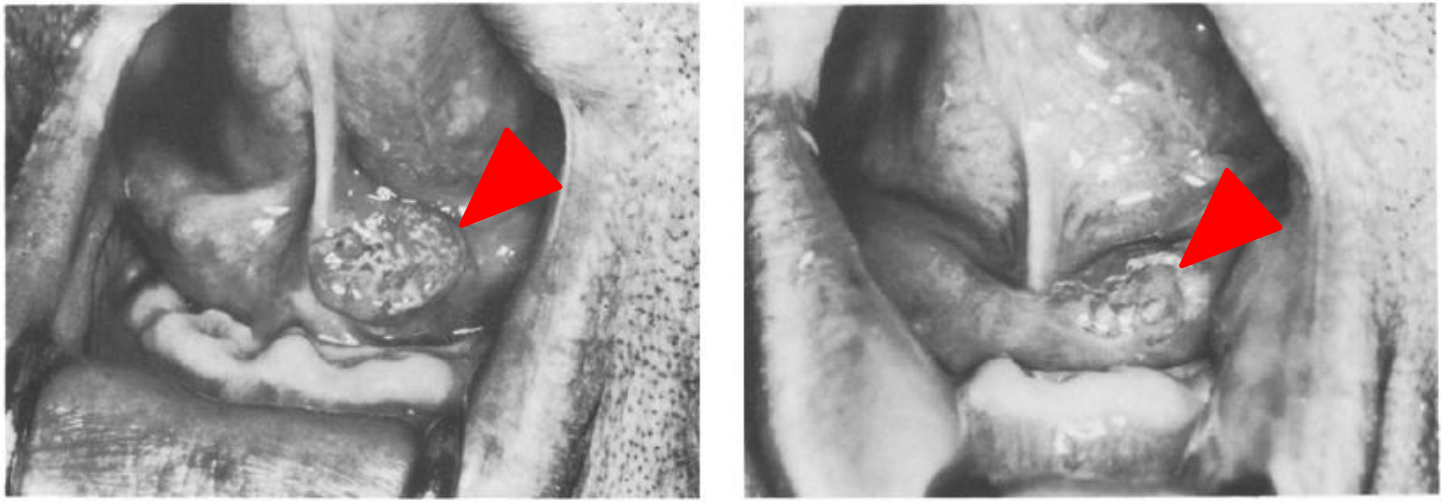


Fig. 4a and b. Squamous cell carcinoma of the oral cavity before (**a**) and 3 weeks after (**b**) a single injection of BCG-CWP

Randomized Clinical Study on Intratumoral BCG-cell Wall Preparation (CWP) Therapy in Patients with Squamous Cell Carcinoma in the Head and Neck Region

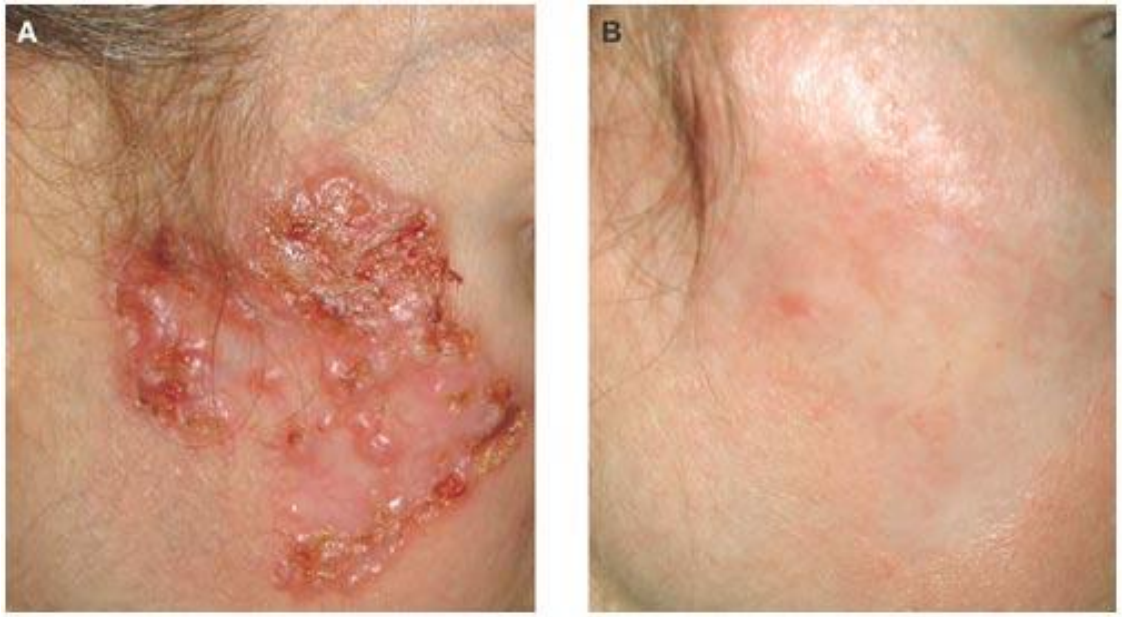
Cancer Immunol Immunother (1981) 12: 71–79

Intratumoral *Bacillus Calmette-Guérin* Immunotherapy prior to Surgery for Carcinoma of the Lung: Results of a Prospective Randomized Trial

Richard A. Matthay, Donald A. Mahler, Gerald J. Beck, et al.

Cancer Res 1986;46:5963-5968.

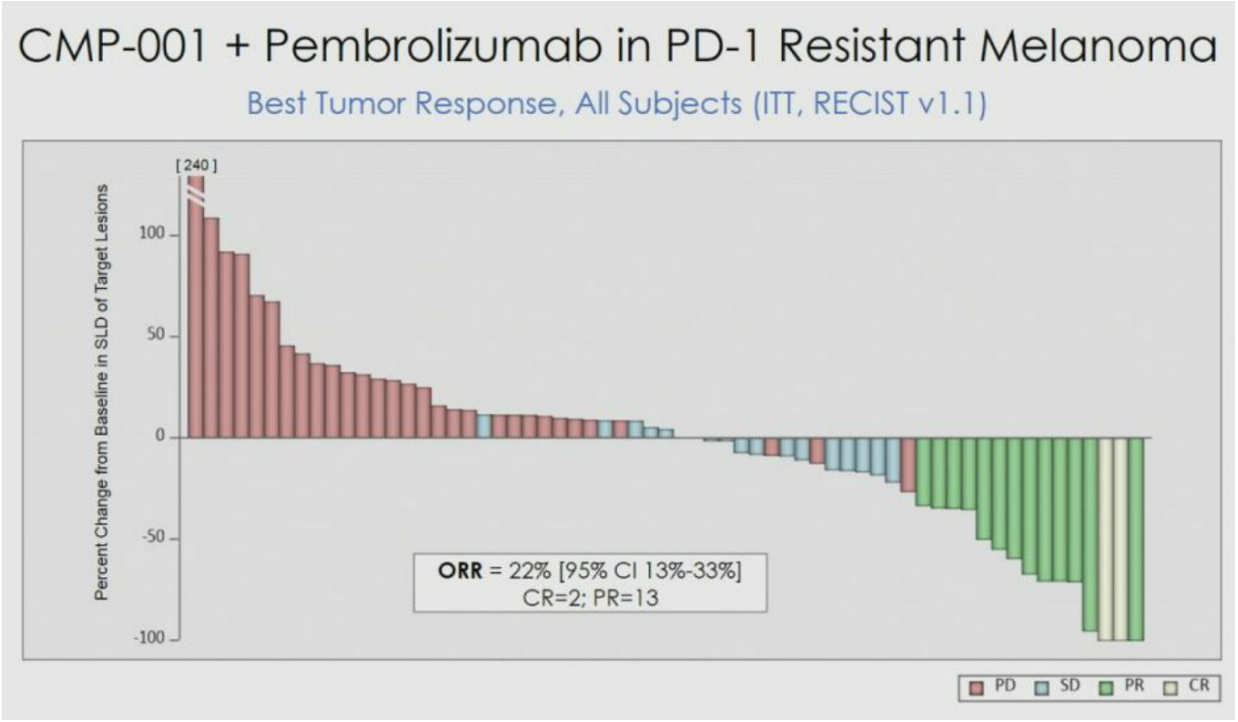
TLR7 ago (imiquimod) on Basal-cell Carcinoma

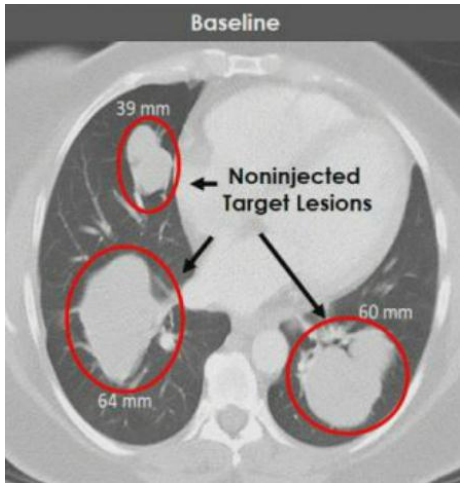


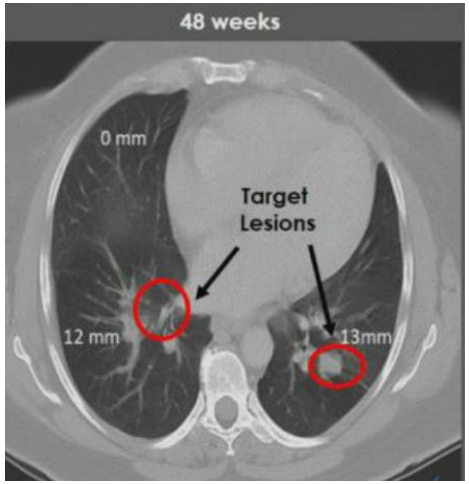
Neville JA *et al.* (2007) Management of nonmelanoma skin cancer in 2007 *Nat Clin Pract Oncol* **4**: 462–469

nature CLINICAL PRACTICE ONCOLOGY

IT CMP-001 (Checkmate Pharma) + pembrolizumab in αPD-1 refractory Melanoma



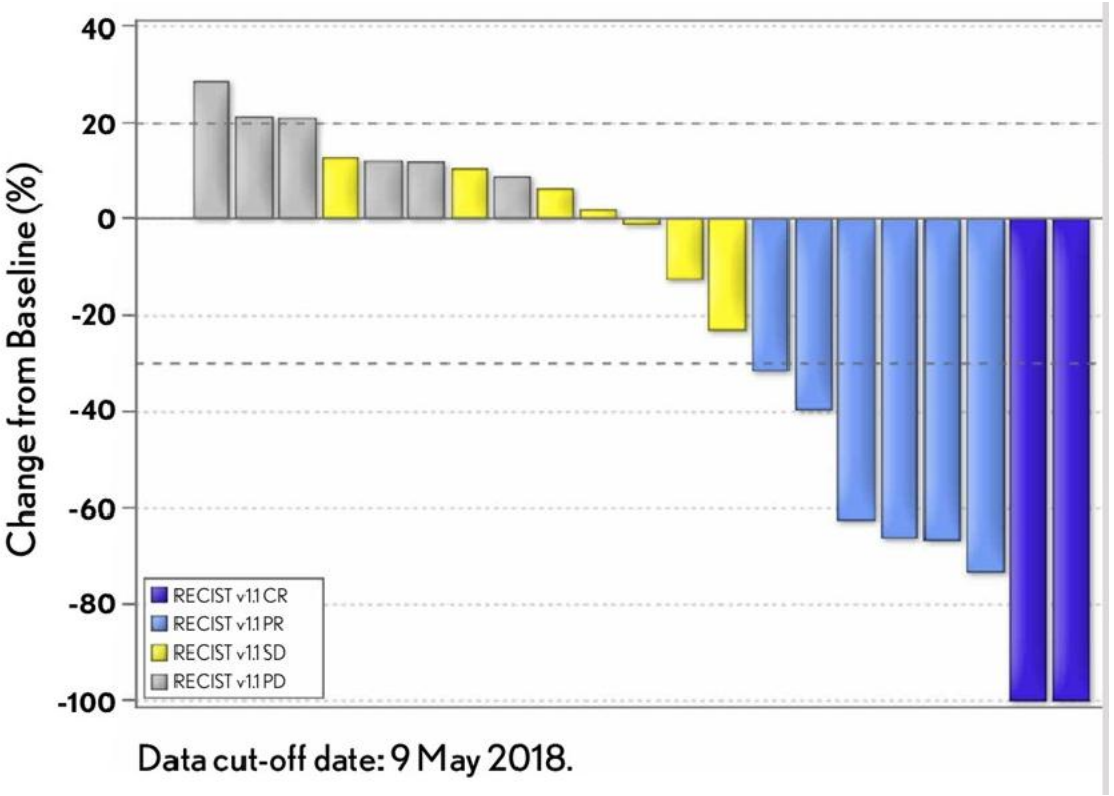




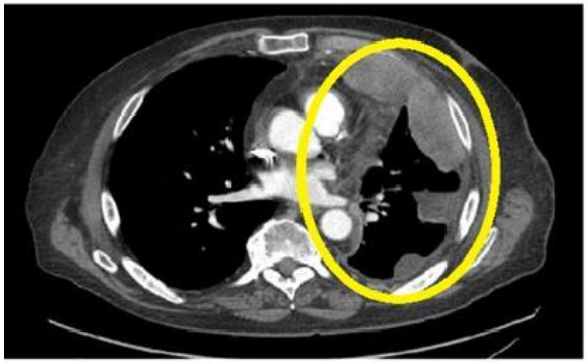
ORR = 22%

M.Milhem, Abstract #10610, AACR 2018

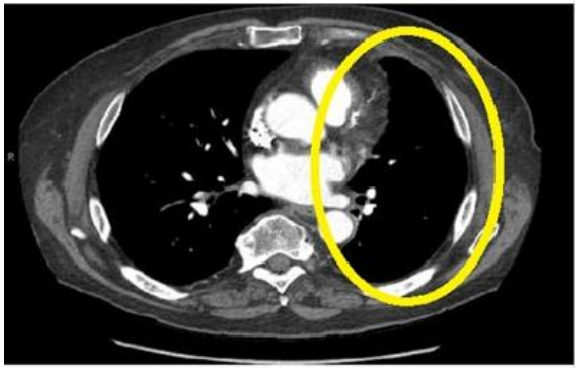
IT tilsotolimod (Idera Pharma) + ipilimumab in αPD-1 refractory Melanoma



ORR= 38,1%
(8/21 Pts)



Pretreatment
Uninjected tumor



Posttreatment 24 weeks
Uninjected tumor

A.Diab et al, ASCO 2018

HIT-IT: Actual Challenges

- **Dose (+/-)** → *dose vs drug escalation ?*
- **Regimen** → *rationale for Q3W cycles?*
- **PK/PD** → *what is relevant?*
- **Trial Design & DLTs** → *health agencies & EC?*
- **Imaging assessment criteria** → *itRECIST ?*
- **Definition of PD/PR** → *clinical benefit?*

EXPERT MEETING ON HUMAN INTRATUMORAL IMMUNOTHERAPY (HIT-IT)

Paris, March 8th 2018

Aim

To provide guidance and to help structure the development of HIT-IT

Scope

Intratumoral injection of immunostimulatory products (exclusion of cryotherapy, HIFU, irradiation,…)

Participants

PHARMA/BIOTECHS

Archie	Tse	Merck
Michael	Imperiale	Nektar
Shah	Rahimian	Idera
Dominique	Tersago	Bioncotech
Edwin	Klumper	Lytix
Maaike	Hendriks	Aduro
Rakesh	Kumar	MedImmune
Martin	Stern	Roche
Katarina	Öhrling	Amgen
Cristian	Massacesi	Pfizer
Ilian	Tchakov	EISAI pharma

ACADEMIA

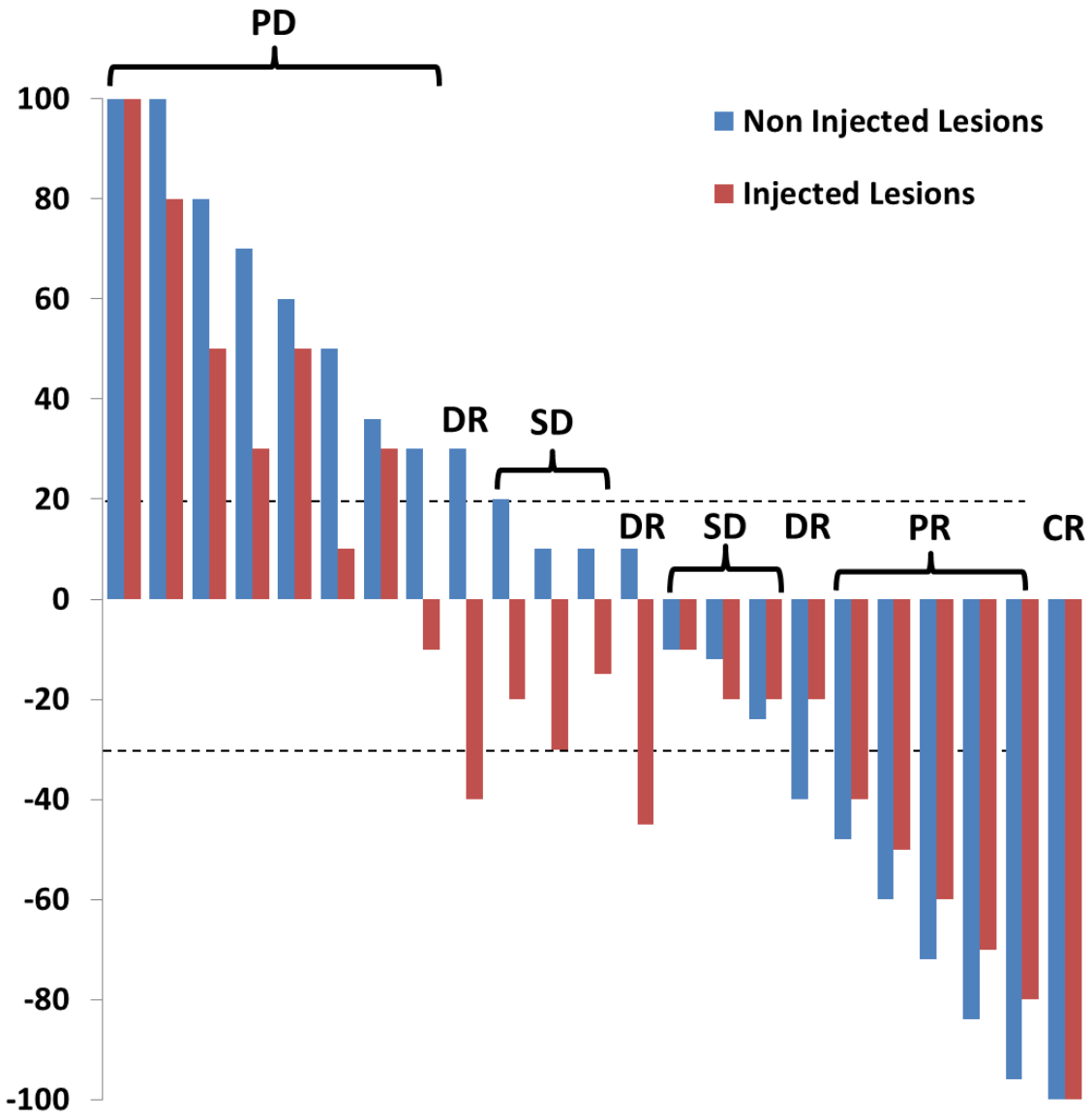
Josep	Tabernero	Val d'Hebron
John	Haanen	Netherlands Cancer Institute
Joshua	Brody	Mount Sinai Hospital
Robert	Andtbacka	Huntsman Cancer Institute
Kevin	Harrington	Institute of Cancer Research ICR
Ignacio	Melero	Universidad de Navarra
Rom	Leidener	Providence Portland Medical Center
Thierry	de Baere	Gustave Roussy
Caroline	Robert	Gustave Roussy
Paolo	Acierto	Istituto Nazionale Tumori
Jean-Francois	Baurain	Université catholique de Louvain
Aurelien	Marabelle	Gustave Roussy

Advantages of Intratumoral Immunotherapy

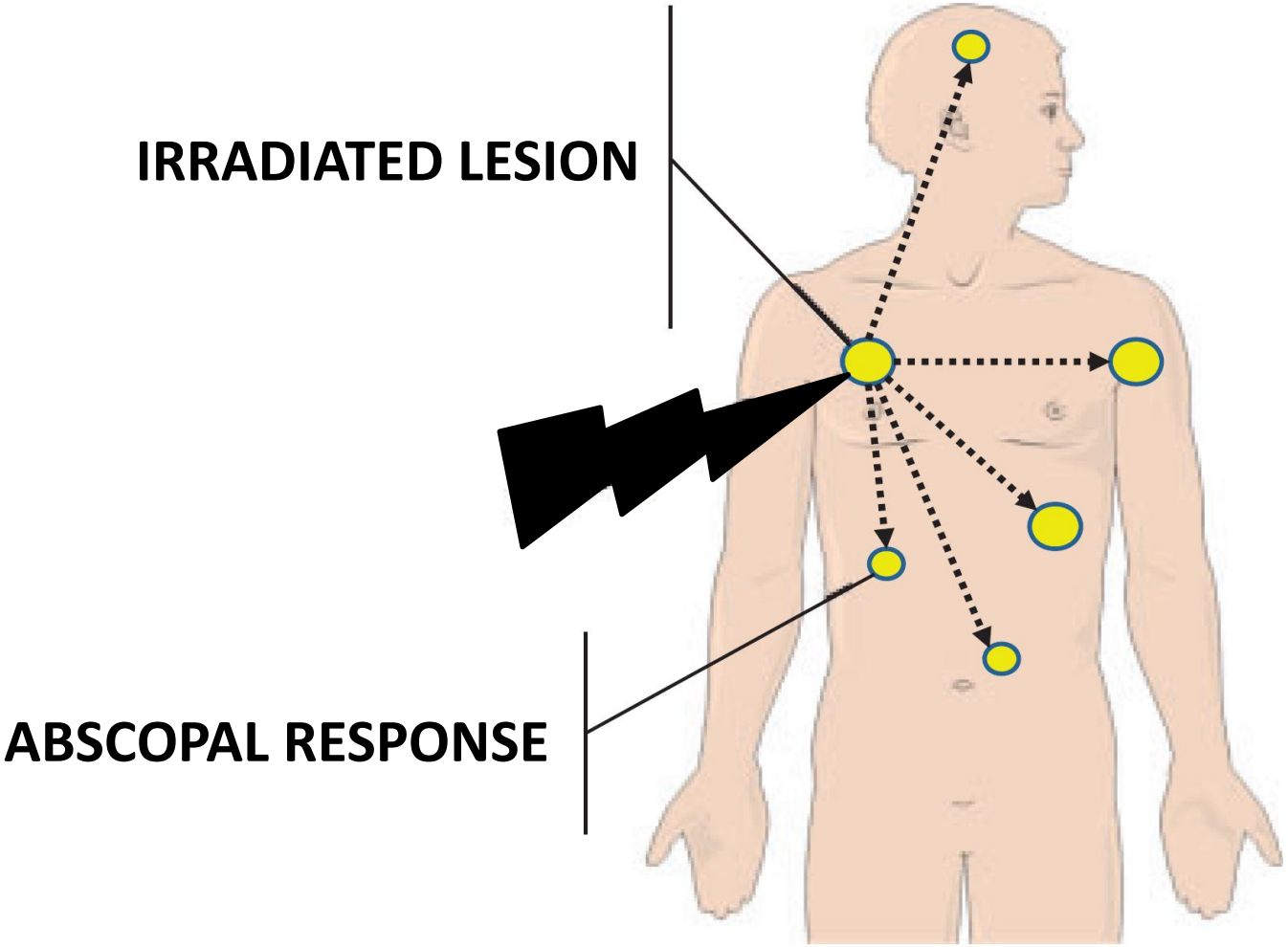
THERAPEUTIC PRINCIPLE	• No antigen (Ag) identification nor isolation required; stimulation against most antigenic tumor epitopes • Direct/better bioavailability of immunostimulatory drugs • On-target (intra-lesional) immune stimulation • Product draining into tumor draining lymph node • Ag diversity : response against the entire antigenic repertoire of a tumor (not limited to few tumor associated antigens); Polyclonal T and B-cell stimulation
PATIENT ELIGIBILITY	• No pre-treatment tumor material required • No HLA nor Ag restriction / Applicable to all patients • Injectable Tumor Lesion Available (Definition which depends on the expertise of the Interventional Radiologist)
DRUG PRODUCTION	• Off-the shelf (no ex vivo manipulation) • Cheaper
PATIENT SELECTION	• None (besides injectability)

Personalized Immunization / Universal strategy

Waterfall Plots for HIT-IT

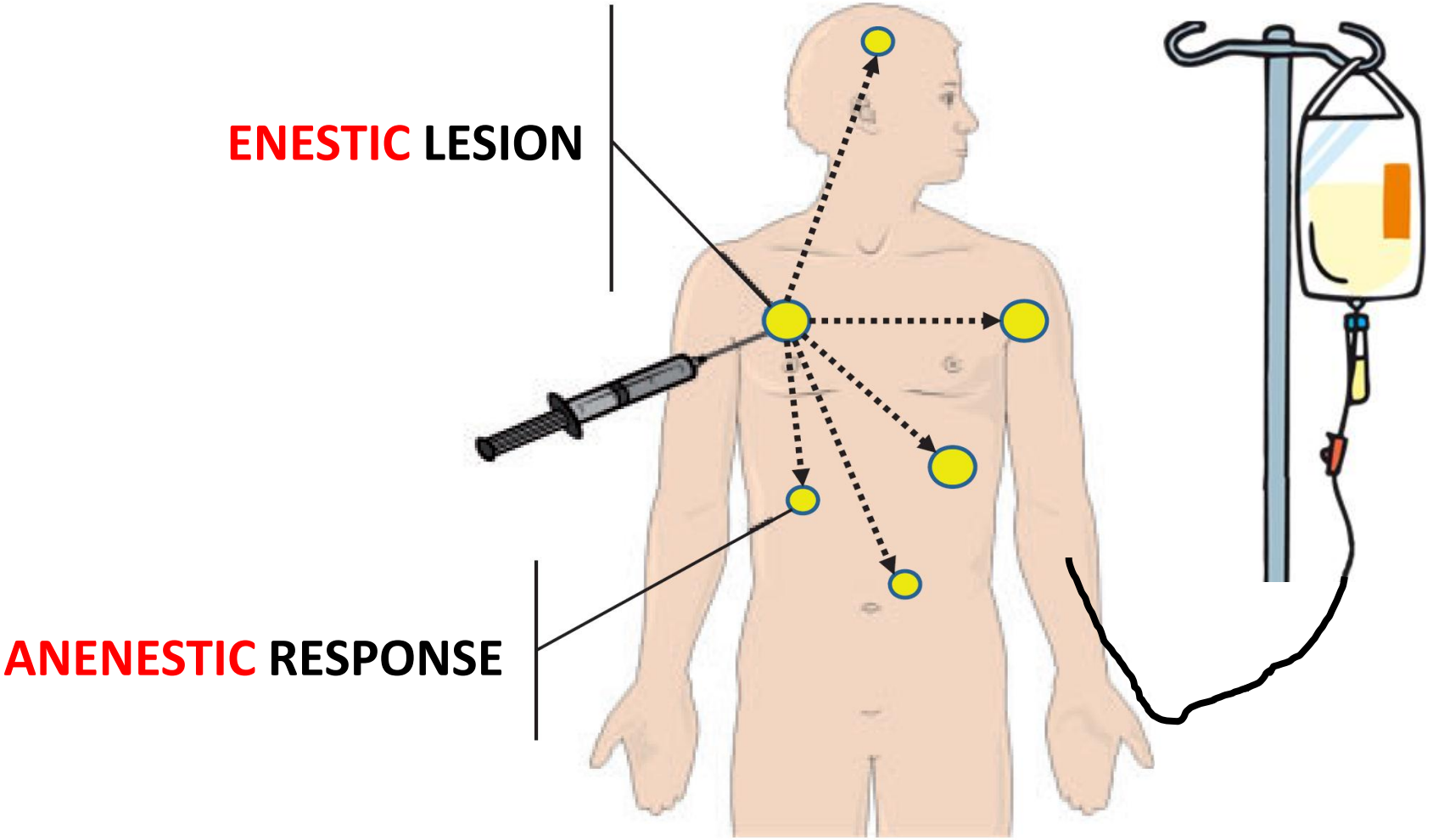


ABSCOPAL = IRRADIATION



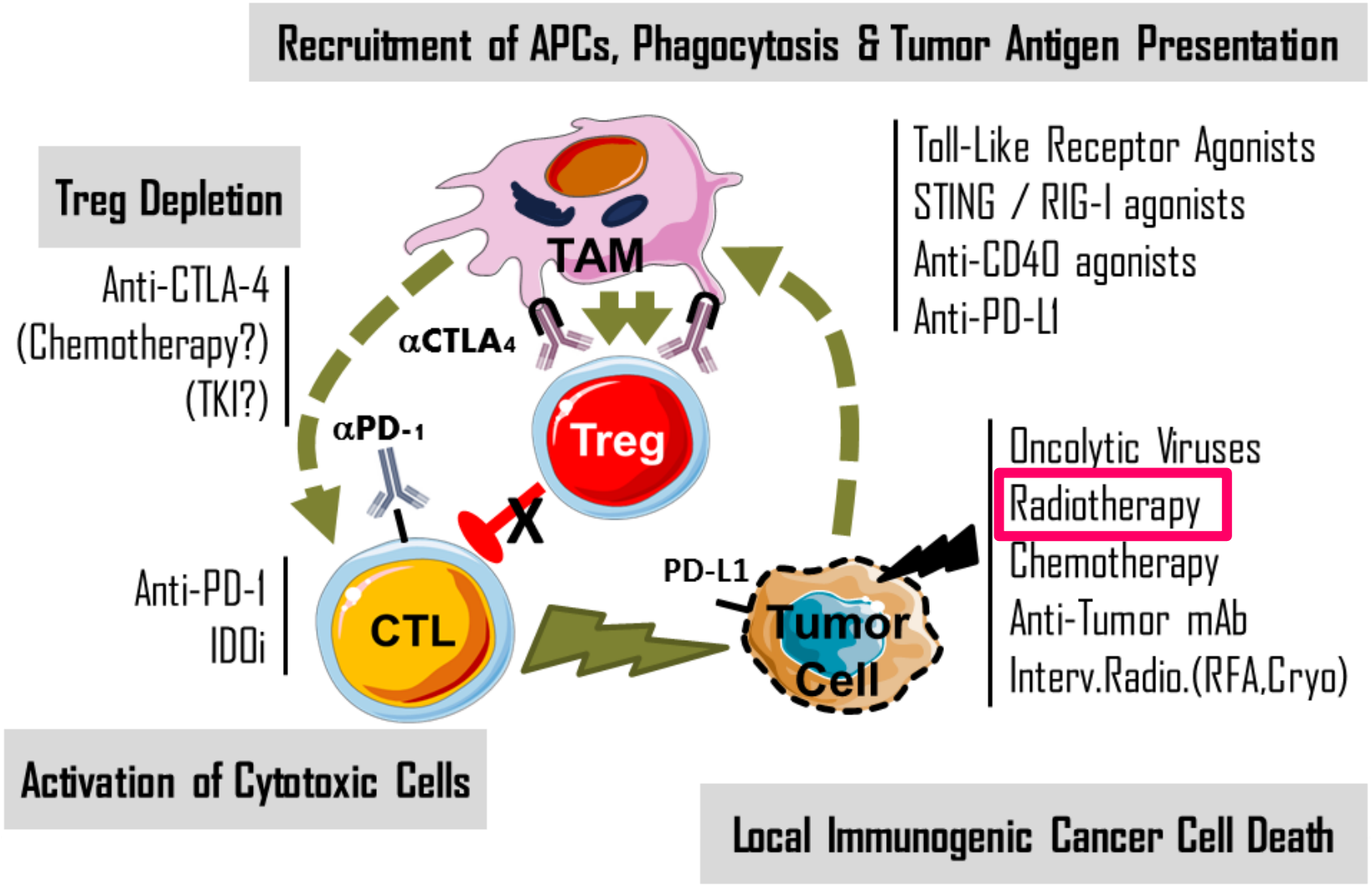
Marabelle, A., Tselikas, L., de Baere, T., and Houot, R. (2017). Ann. Oncol. *28*, xii33-xii43.

ENESTIC (*injected*) vs ANENESTIC (*non-injected*)



Marabelle, A., Tselikas, L., de Baere, T., and Houot, R. (2017). Ann. Oncol. *28*, xii33-xii43.

RATIONALE INTRATUMORAL COMBINATION THERAPIES



Marabelle, A., Tselikas, L., de Baere, T., and Houot, R. (2017). Ann. Oncol. *28*, xii33-xii43.

RT + HIT-IT

Nivolumab
Pembrolizumab
Durvalumab

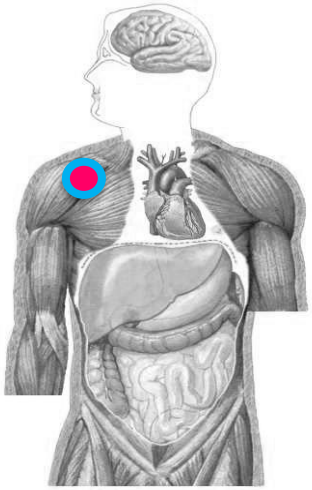
Nivolumab
Pembrolizumab
Atezolizumab
Durvalumab
Avelumab

DRUG DEVELOPMENT

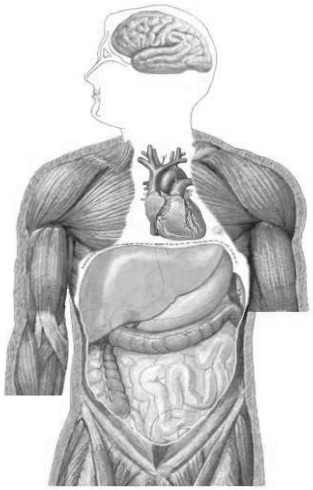
NEO-ADJUVANT

ADJUVANT

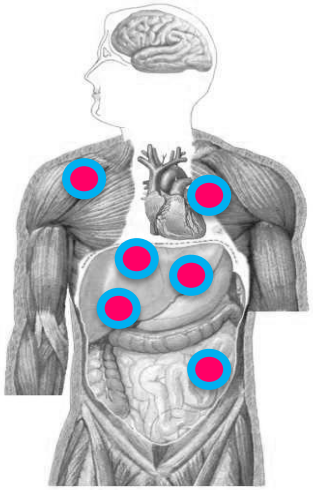
METASTATIC



SURGERY or CHEMO-RT



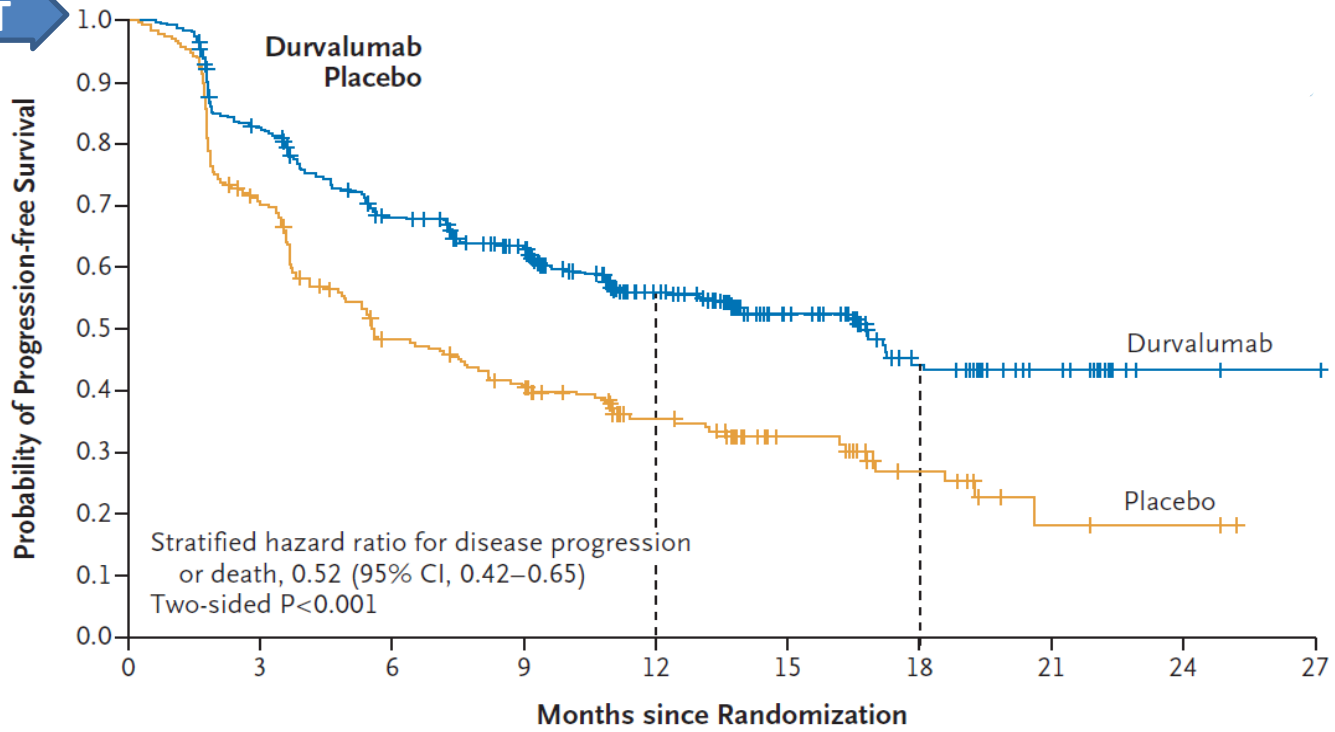
RELAPSE



DISEASE HISTORY

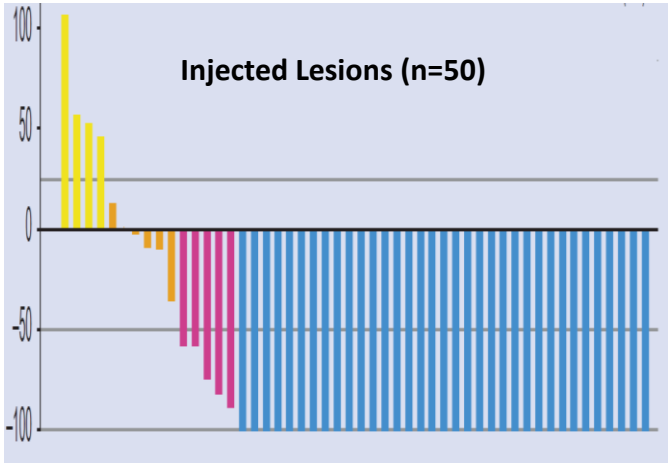
Neo-Adjuvant IT vs Adjuvant IV

NEO-ADJUVANT



Antonia, S.J., et al. (2017). Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer. N. Engl. J. Med. *377*, 1919–1929.

IT T-VEC + IV pembrolizumab in Melanoma



ORR = 57% (irRC)

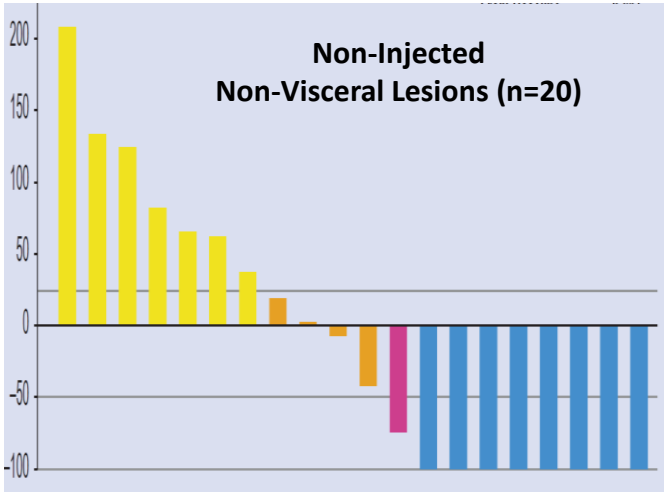
ORR pembro alone ~ 33%

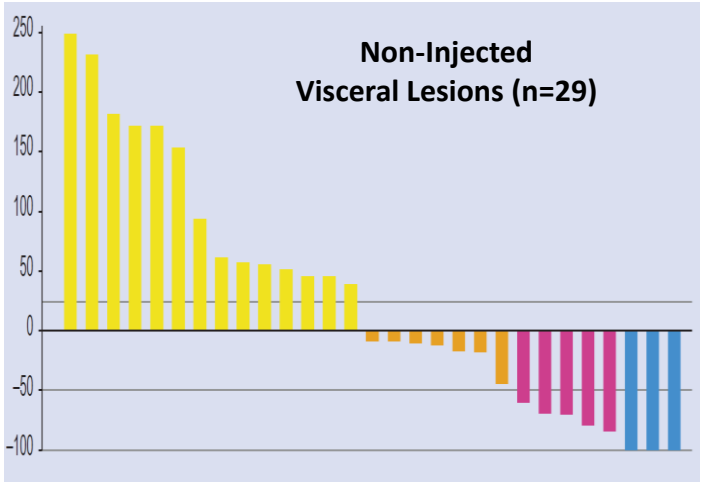
CR rate = 24% (irRC)

CR rate pembro alone ~ 6% (RECIST)

PFS at 9 month = 71%

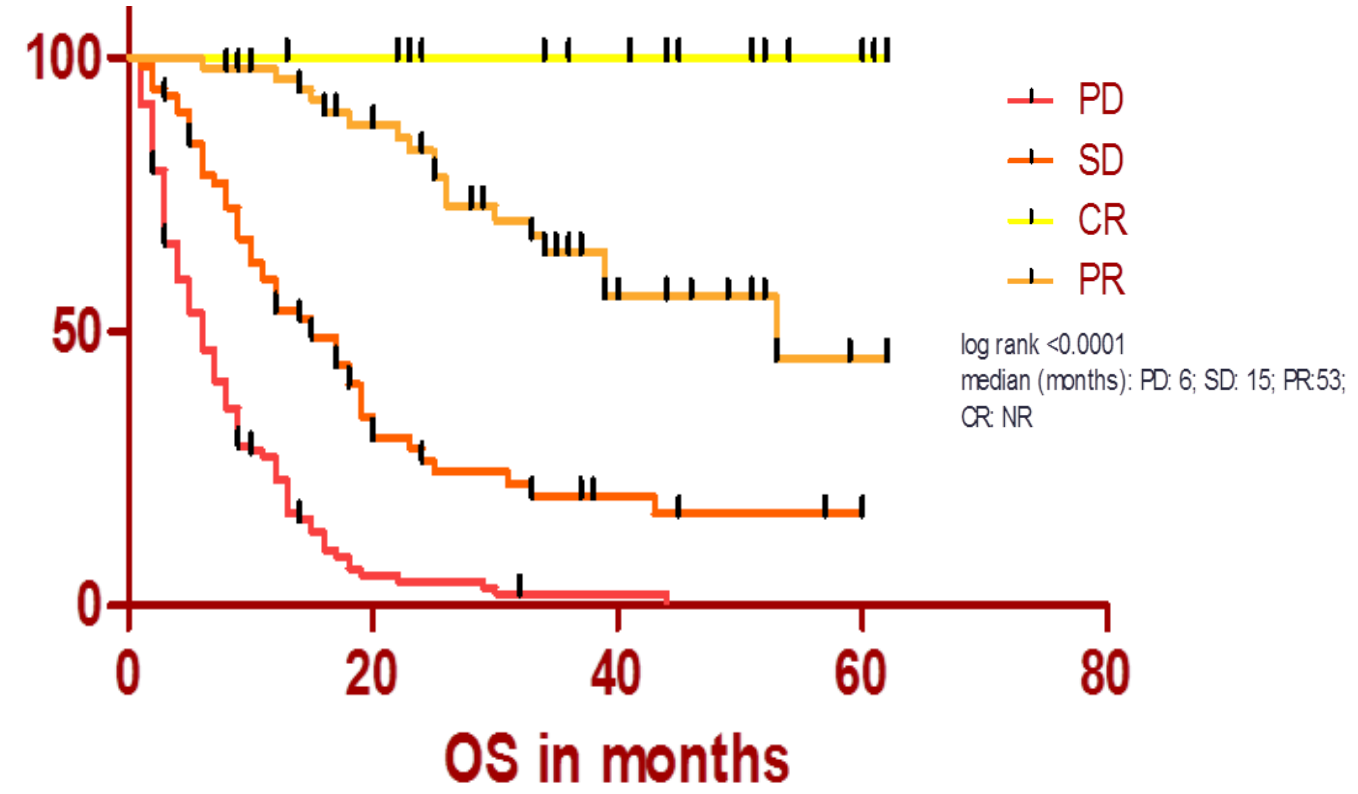
PFS at 9 months pembro alone ~40%





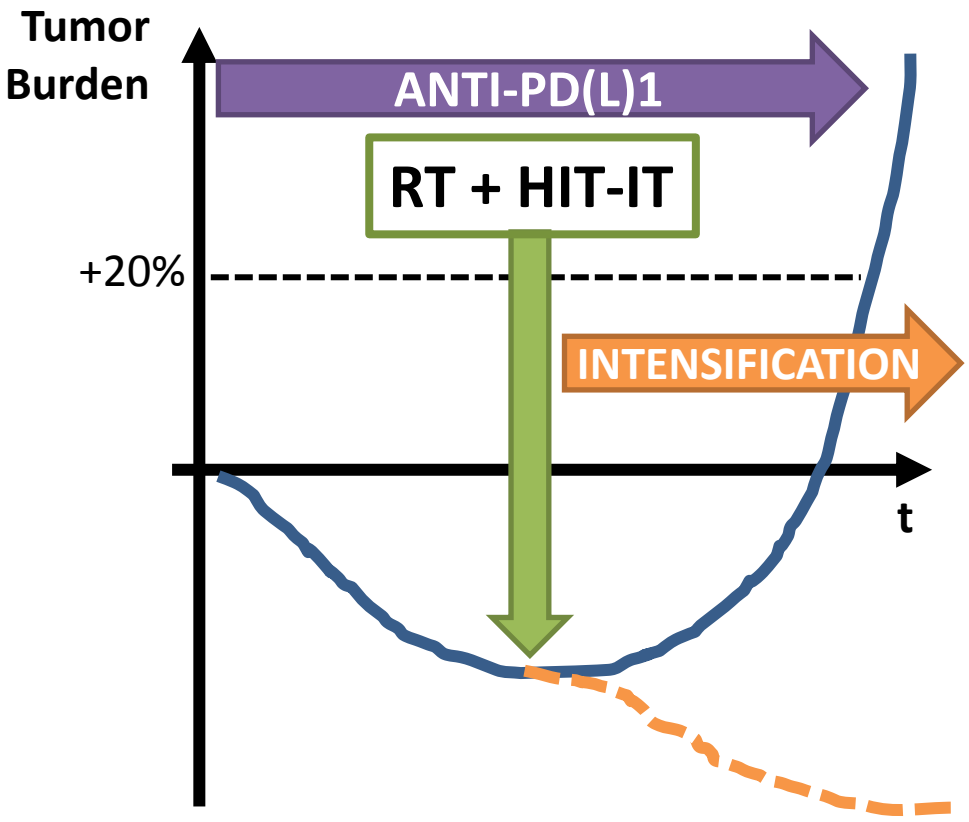
G.Long, ASCO 2016

Improving anti-PD(L)1 efficacy



ML Gauci et al. Clin Cancer Res (2018), *in press*

Stratification for Intensification



Current Questions for RT+HIT-IT

- Are some tumor sites better than others to generate a anti-tumor response in non injected sites ? (*prioritization*)

- Are the pre-existing immune infiltrates predictive of the efficacy or are their universal combination able to prime/enhance the anti-tumor immunity?

- Is concomitant treatment of several lesions better than sequential ? Is sequential injection of multiple lesions generating a prime/boosting effect?

- Is RT+HIT-IT generating a better memory anti-tumor immune response than RT alone or HIT-IT alone or systemic therapy ?

- Does RT+HIT-IT require combination with systemic treatment?

- Does neo-adjuvant RT+HIT-IT protect from post surgical relapses? Is lymphadenectomy harmful for the long term effect ?

Is there a role for radiation in the field of intratumoral immunotherapy?

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