A Marabelle, L Tselikas,, S Amary
S Dominiquin, S Farhane,

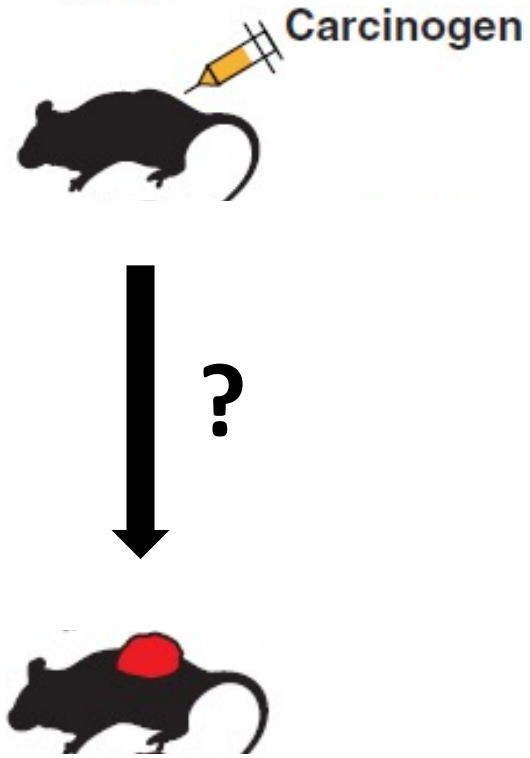
Intratumoral immunotherapy: Rationale and technique

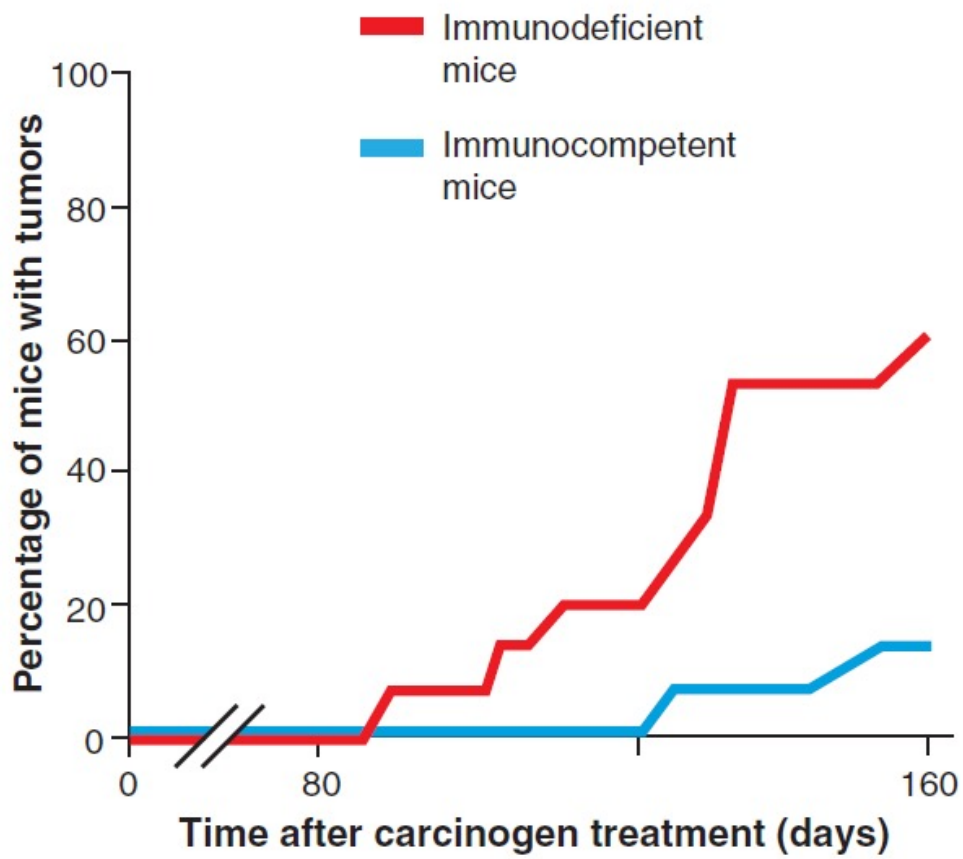
GUSTAVE ROUSSY
CANCER CAMPUS GRAND PARIS

Biotheris
CIC1428 Inserm

université PARIS-SACLAY

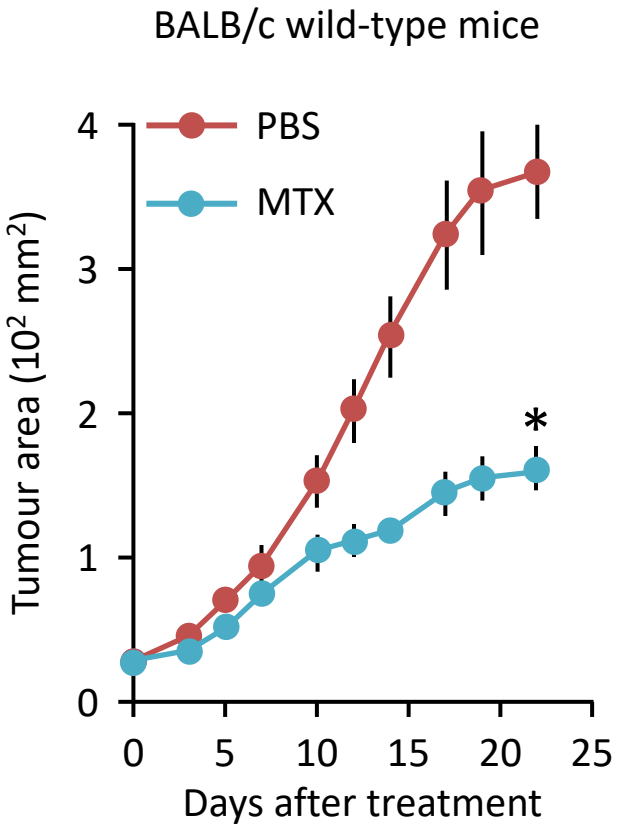
Immune Surveillance of Cancers





Schreiber RD, et al. Science 2011;331:1565–70.

Chemotherapy Efficacy & the Immune System

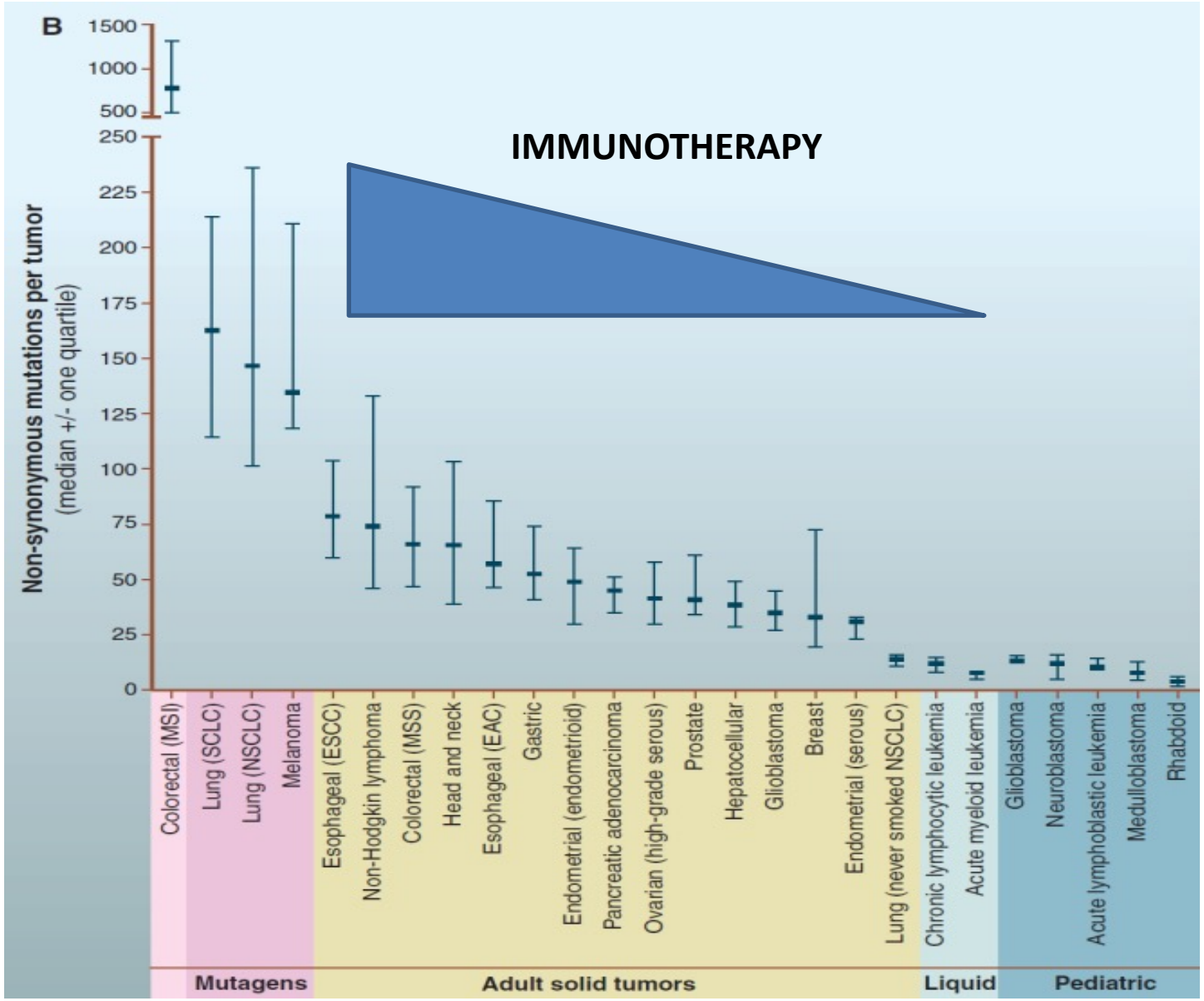


*P < 0.05; n = 10 mice per group; means ± SEM are shown.
MTX, mitoxantrone; PBS, phosphate-buffered saline (control).

Michaud M, et al. Science 2011;334:1573–7.

cell

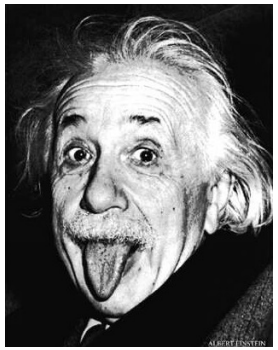
Immunogenicity of Cancers

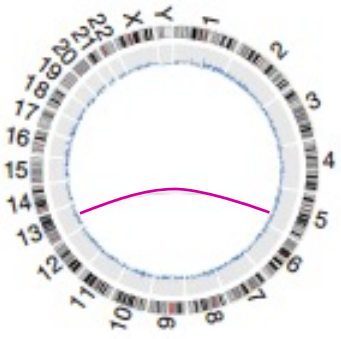


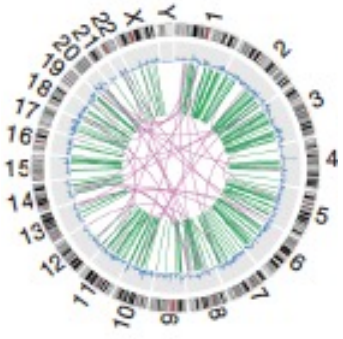
SCIENCE VOL 339 29 MARCH 2013

cell

Cancers in the Immune Targeted Era ?







Smart Cancers

- Small mutational load
- Immunotherapy is ineffective

Stupid Cancers

- Large mutational load
- Immunotherapy is effective

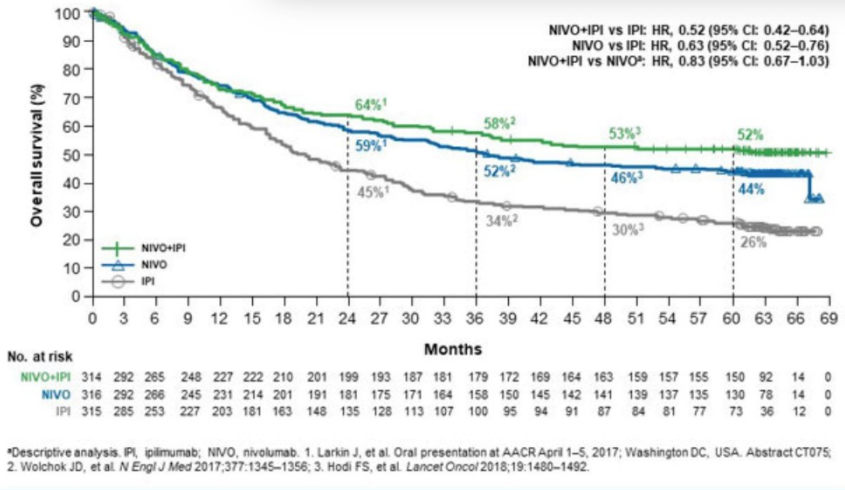
Adapted from G.Sledge & Stephens, PJ et al. Nature 462:1005-12, 2009.

Immune Related Adverse Events
On-target / *Off-tumor* Effects

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

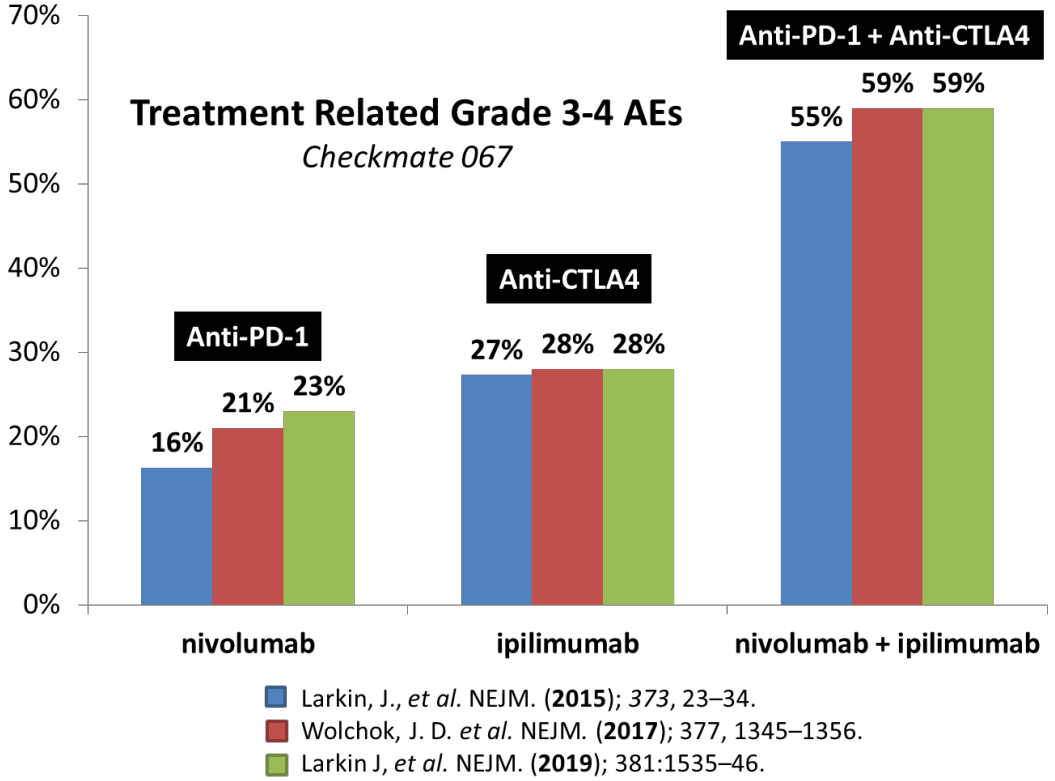
Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma



(Larkin J. N Engl J Med 2019;381:1535-46)

Imfinzi plus tremelimumab significantly improved overall survival in HIMALAYA Phase III trial in 1st-line unresectable liver cancer

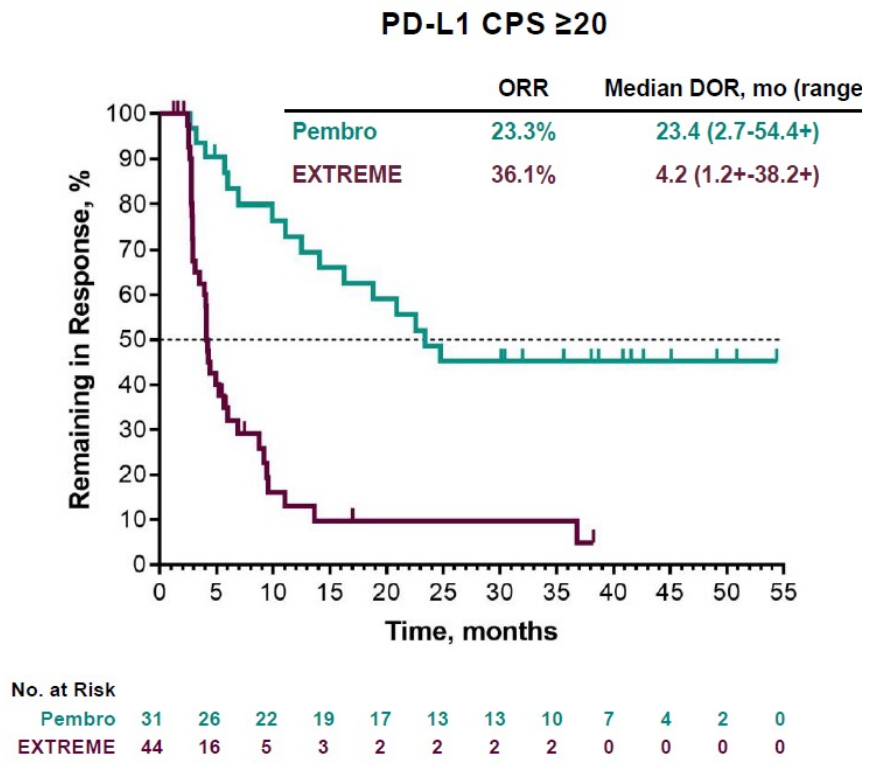
PUBLISHED
15 October 2021



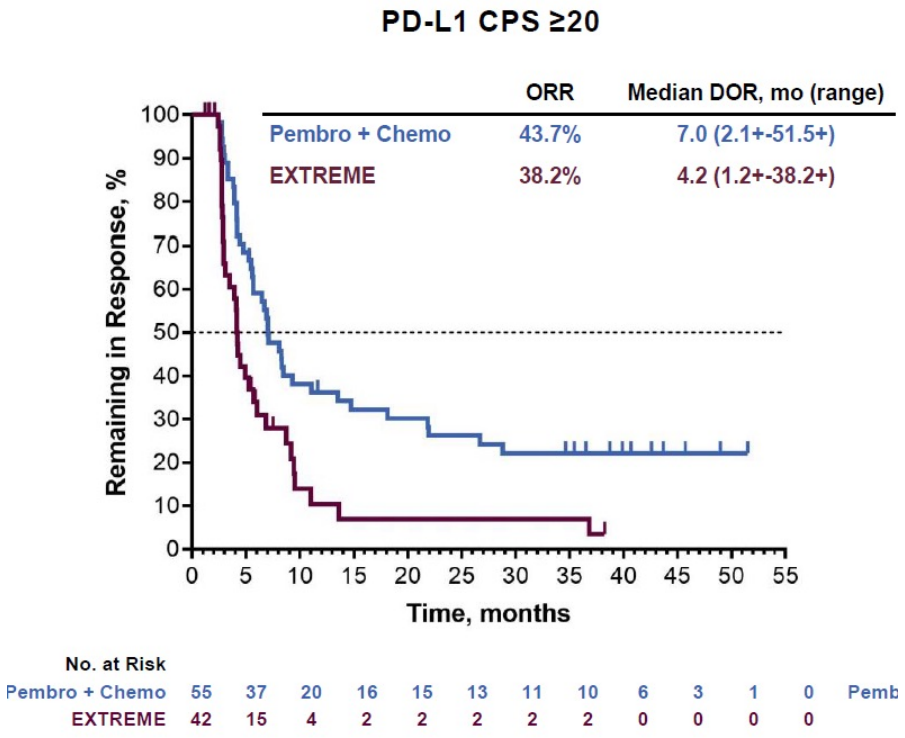
La cellule

1st line PEMBROLIZUMAB for HNSCC
KEYNOTE-048
Long-Term outcomes Greil et al. ESMO 2020

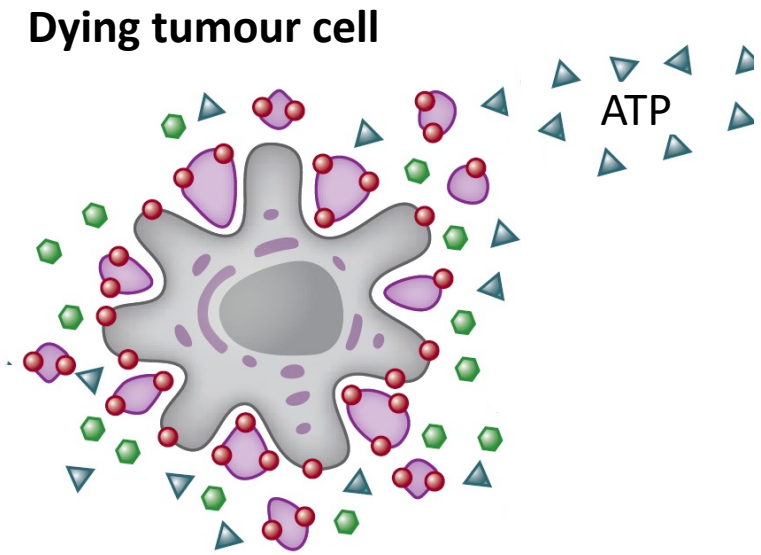
Pembro vs Chemo



Pembro+Chemo vs Chemo



Immunogenic cell death



Adapted from Kroemer G, et al. Annu Rev Immunol 2013;31:51–72.

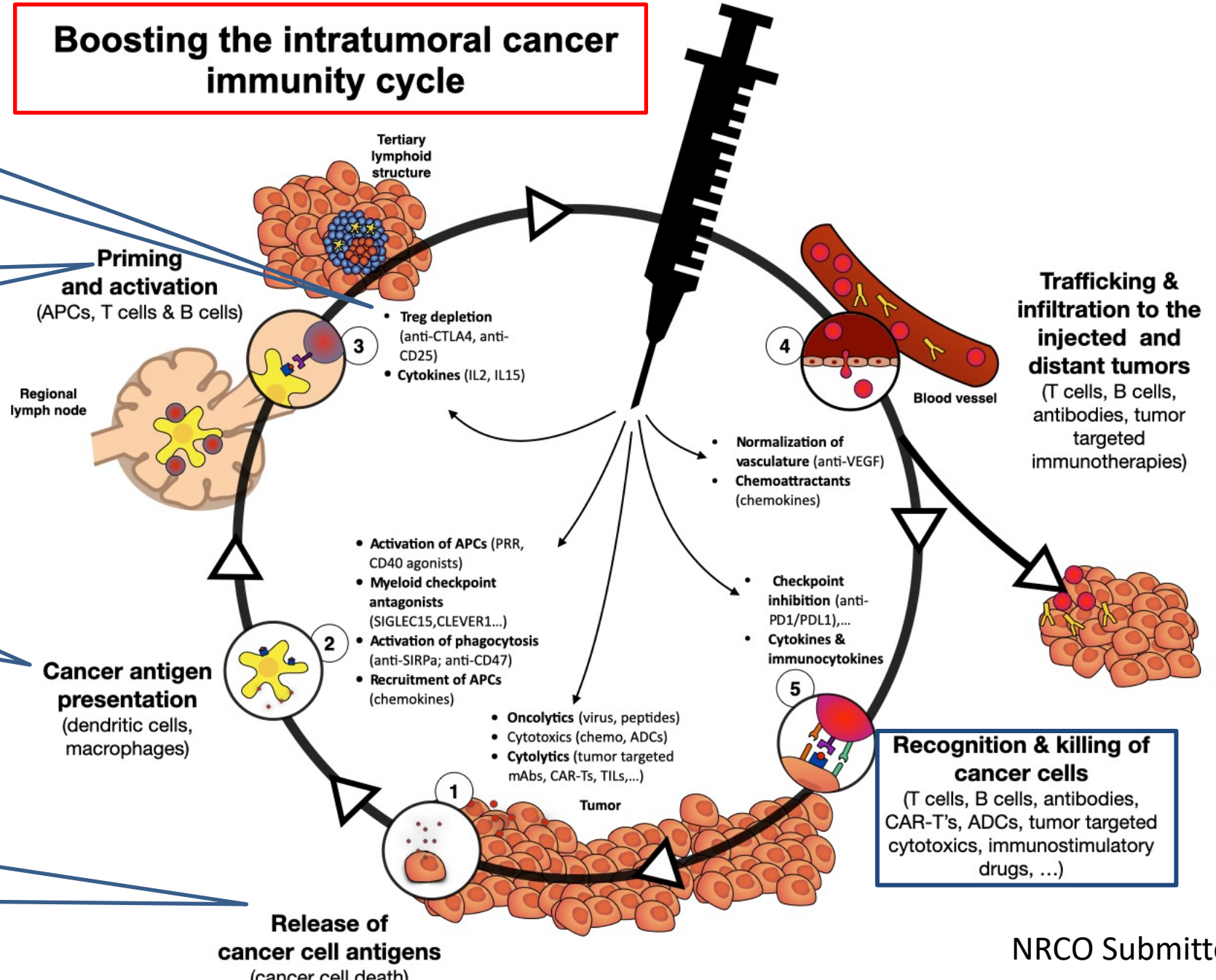
Boosting the intratumoral cancer immunity cycle

Block/ deplete immuno-suppressive cells
- **Tregs** (anti-CTLA4, etc.)
- **Macrophages** (anti-CSF1R, antiCCR5, etc.)

Activate immune effector cells
- **Coinhibitory mAbs** (anti-PD(L)1,-LAG3,-KIR, …)
- **Costimulatory mAbs** (anti-OX40,-CD137, …)
- **Cytokines** (PEG-IL-2, IL-12 Mrna, PEG-IL-10)
- **immunocytokines** (CEA-IL2, etc.)

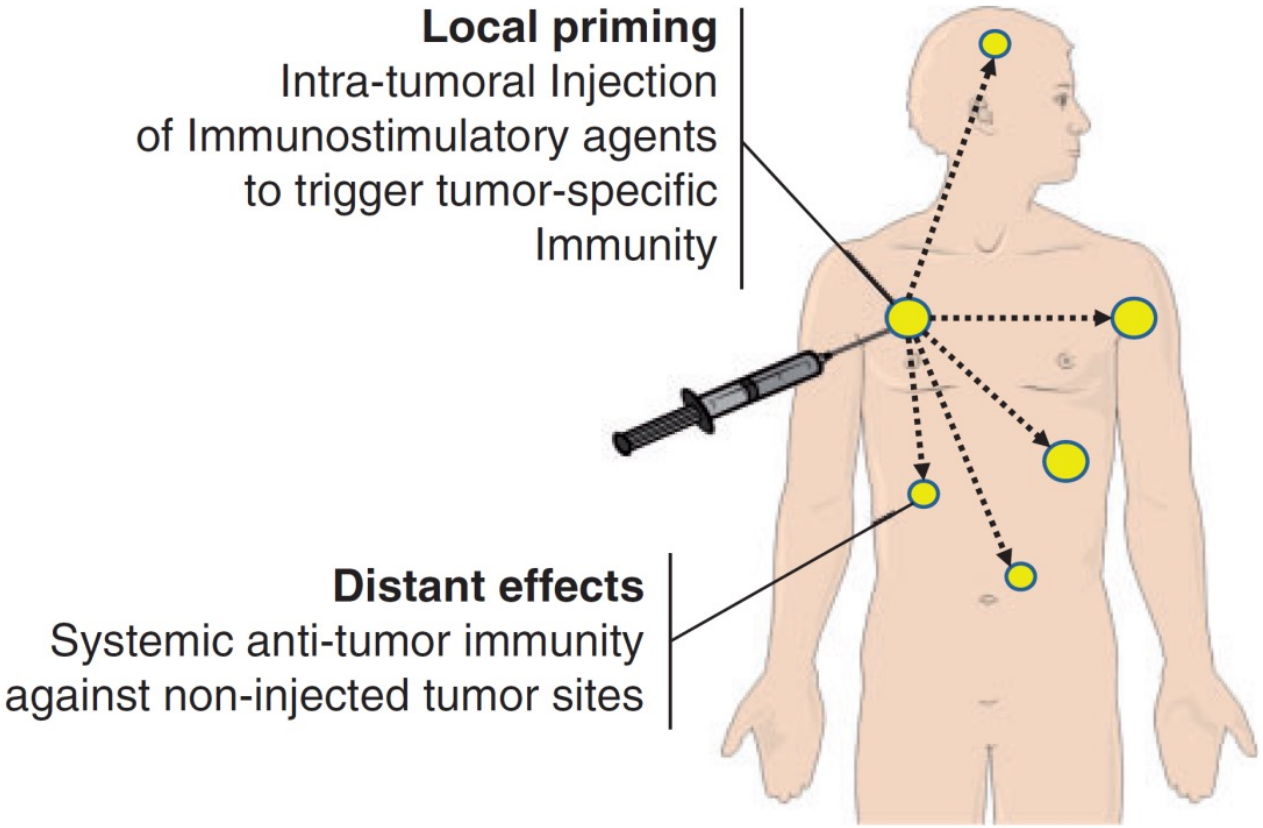
Enhance TA presentation
- **PRR agonists and analogs**
  - ✓ TLR agonists (TLR-3, 4, 7/8, 9)
  - ✓ STING agonists
  - ✓ Oncolytic Virus
  - ✓ Bacteria
- **Anti-CD40 agonistic mAb**
- **FLT3-ligand**
- **Gene therapy** (GM-CSF, FLT3, HSP, CD40L)
- **Dendritic cells**

Tumor antigen release
- **Oncolytic virus**
- **Tumor targeting mAbs**
- **Chemotherapy**
- **Radiation therapy**
- **Thermal ablation** (RFA, MWA, CRA)
- **TACE**
- **SIRT**



NRCO Submitted

Human Intra-Tumoral Immuno-Therapy (HIT-IT)
On-target / *On-tumor* Effects



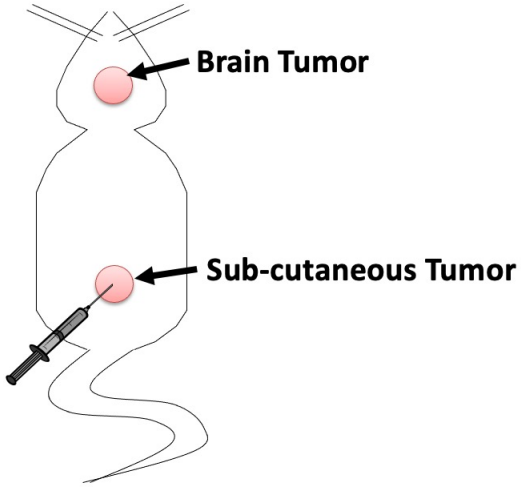
Usually 10% of systemic dose is injected

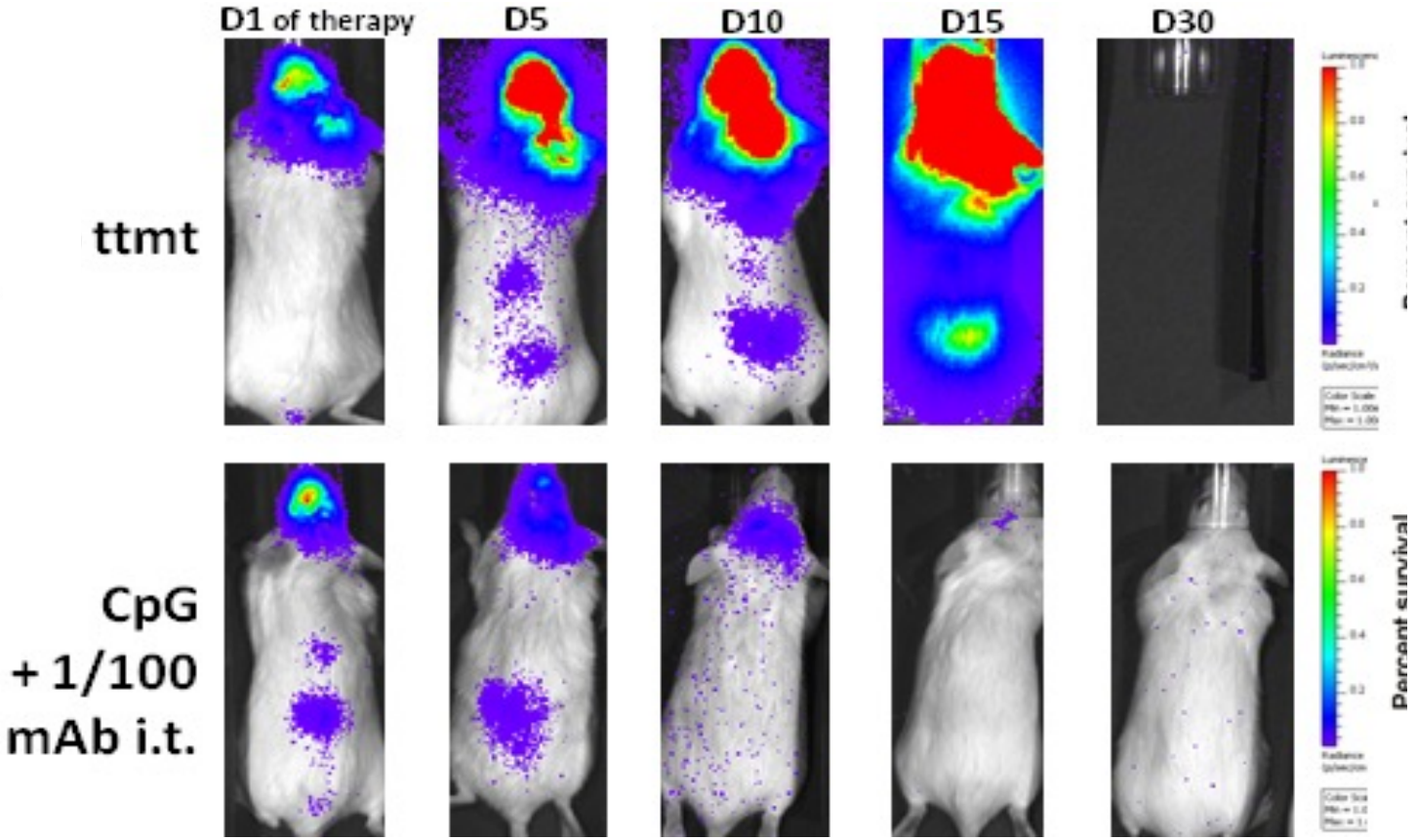
- High local concentration : efficacy / *On Target*
- Low systemic concentration : toxicity / *Off Target*

Yearly cost of Immunotherapy 40 / 100 k€

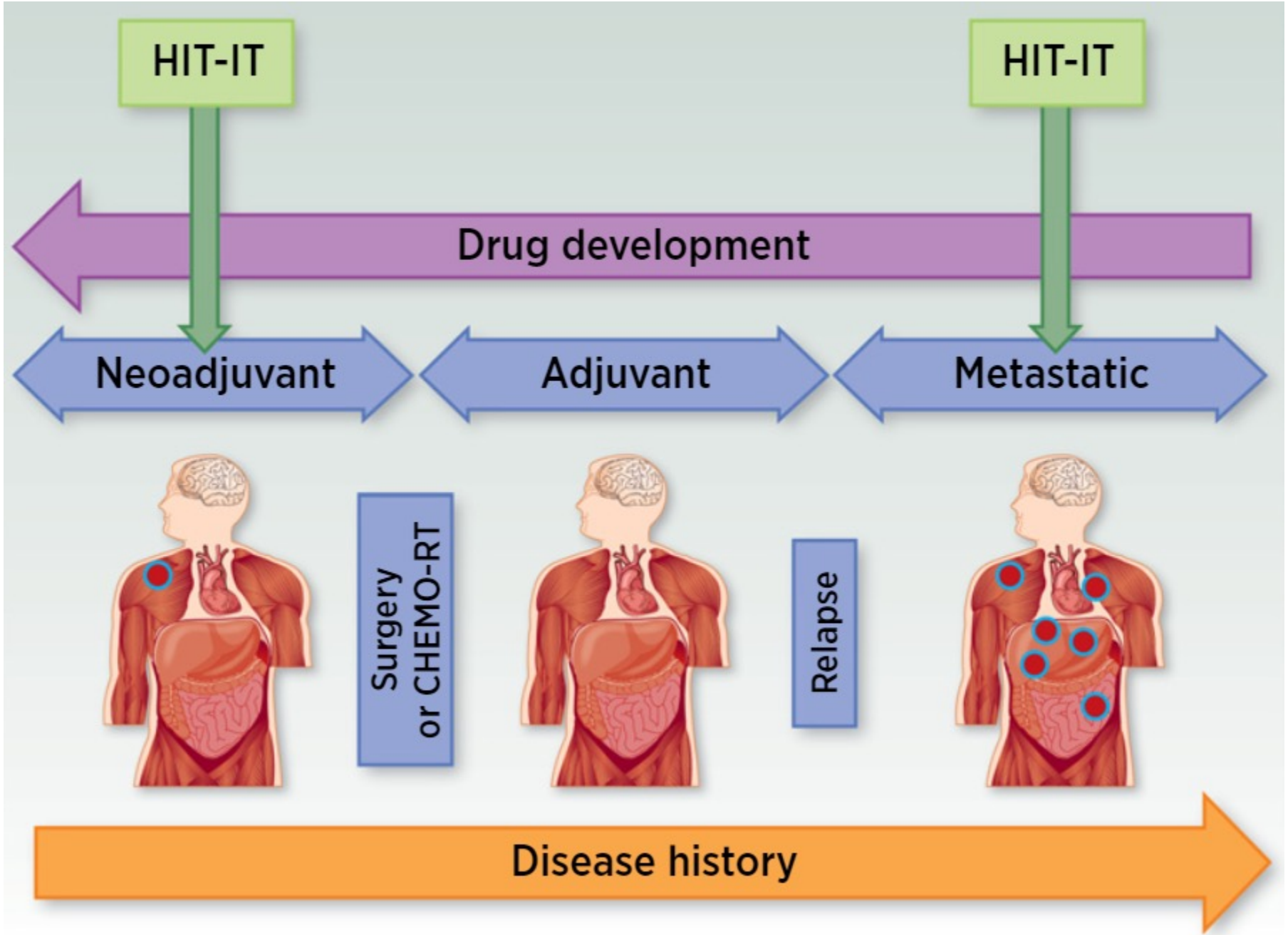
Marabelle, A. et al. (2017). Ann. Oncol. 28, xii33-xii43.

Intra-tumoral low dose immune checkpoint blockade can eradicate disseminated disease (including in the CNS)



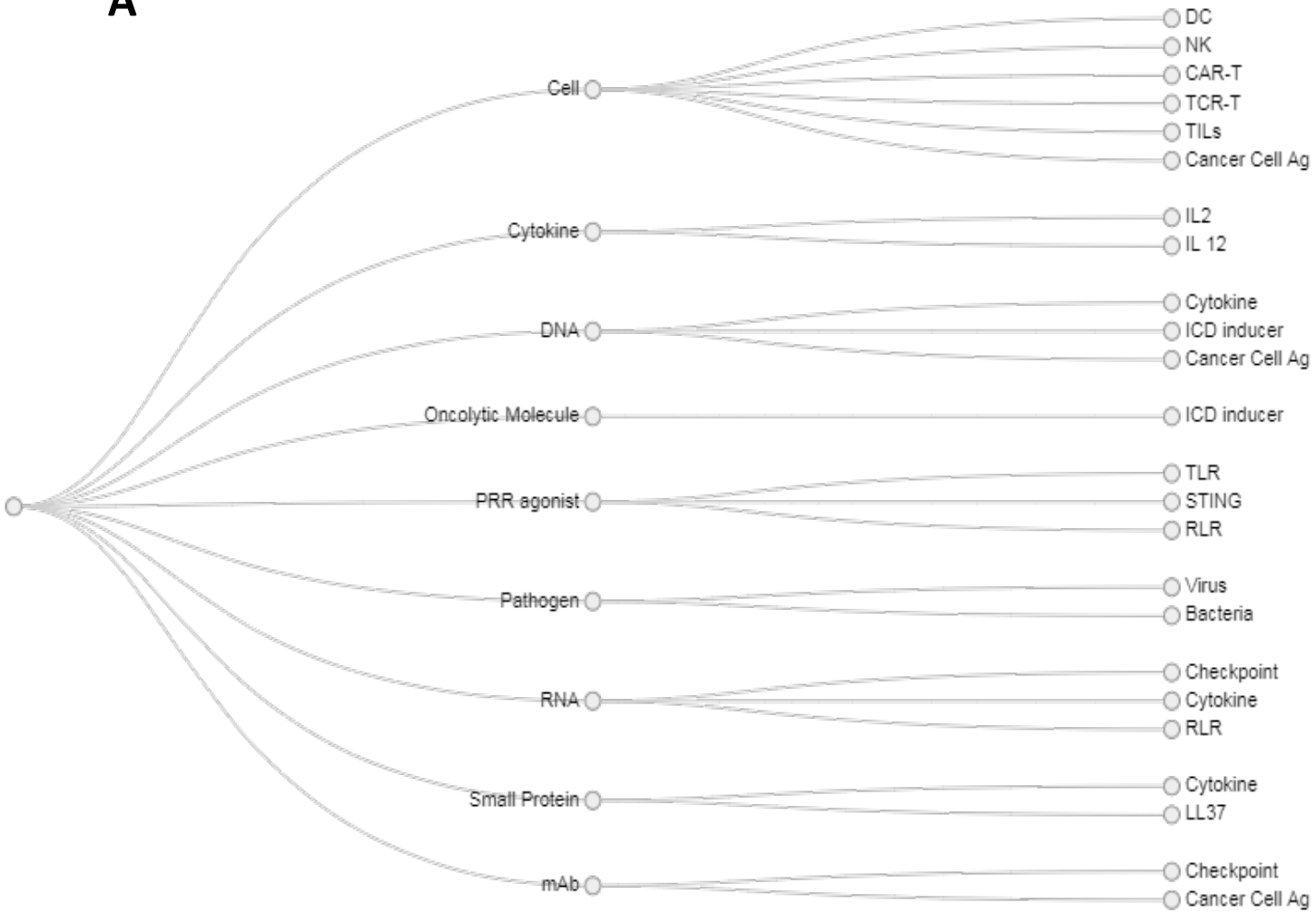


Marabelle A, et al. J Clin Invest 2013.

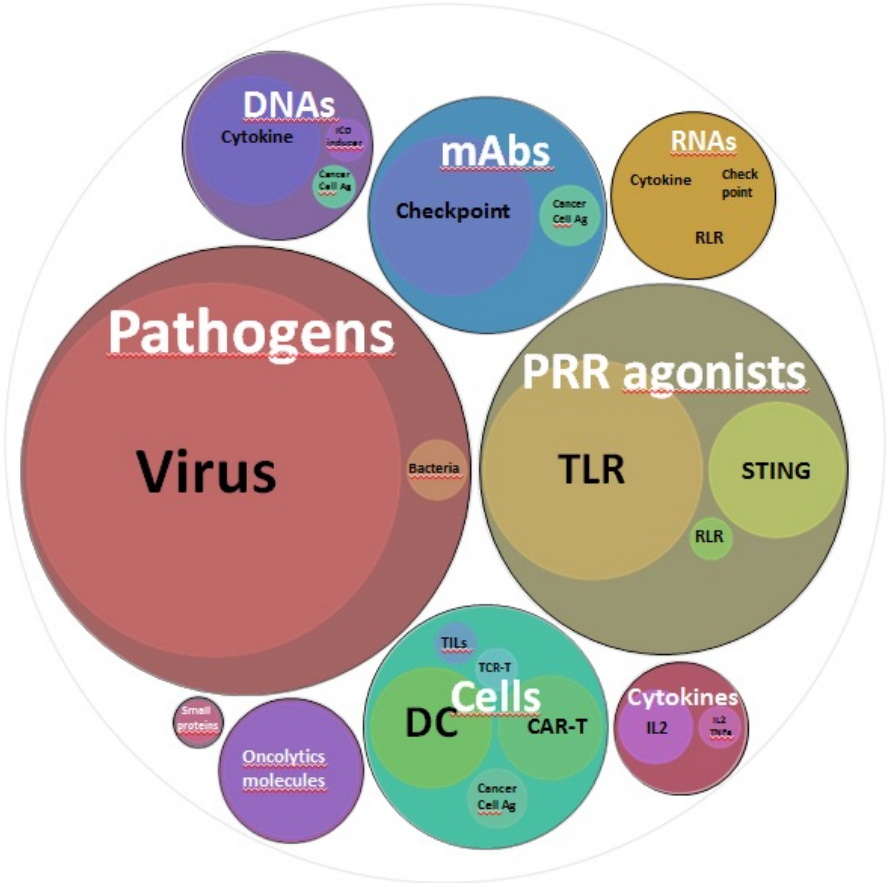


Champiat CCR 2020

A

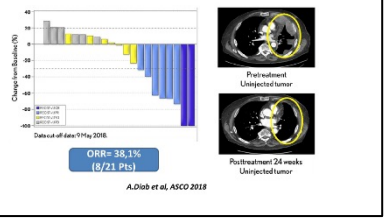


B



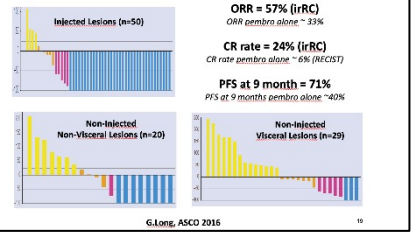
Champiat S, Nature Reviews Clinical Oncology Submitted

IT tilsotolimod (TLR9 agonist) + ipilimumab in αPD-1 refractory Melanoma



A.Diab et al, ASCO 2018

IT T-VEC + pembrolizumab in Melanoma



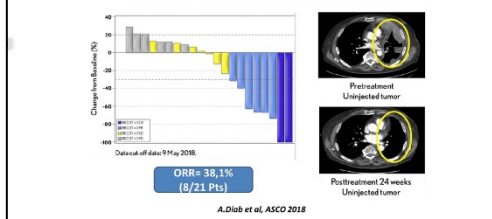
ORR = 57% (irRC)
ORR pembro alone ~ 33%

CR rate = 24% (irRC)
CR rate pembro alone ~ 6% (RECIST)

PFS at 9 month = 71%
PFS at 9 months pembro alone ~40%

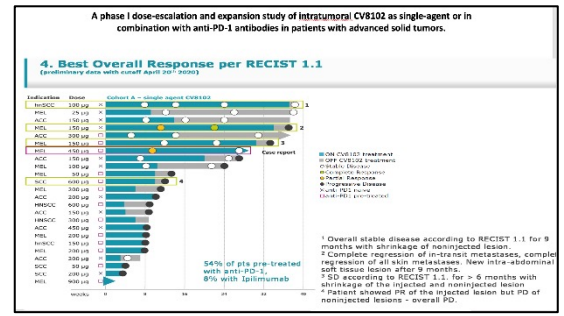
G.Long, ASCO 2016

IT tilsotolimod (TLR9 agonist) + ipilimumab in αPD-1 refractory Melanoma



A.Diab et al, ASCO 2018

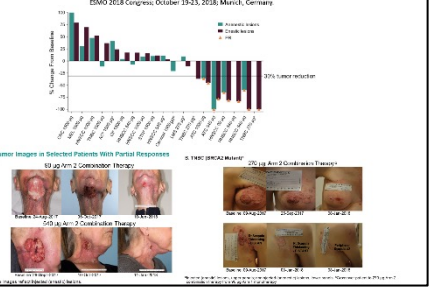
A phase I dose-escalation and expansion study of intratumoral CV8102 as single-agent or in combination with anti-PD-1 antibodies in patients with advanced solid tumors.



[1] Overall stable disease according to RECIST 1.1 for 9 months with shrinkage of noninjected lesion.
[2] Complete regression of in-transit metastases, complete regression of all skin melastases. New intra-abdominal soft tissue lesion after 9 months.
[3] SD according to RECIST 1.1. for > 6 months with shrinkage of the injected and noninjected lesion
[4] Patient showed PR of the injected lesion but PD of noninjected lesions - overall PD.

Preliminary Results of the First-in-Human Study of MK-1454, an Agonist of Stimulator of Interferon Genes (STING), as Monotherapy and in Combination With Pembrolizumab in Patients With Advanced Solid Tumors or Lymphomas

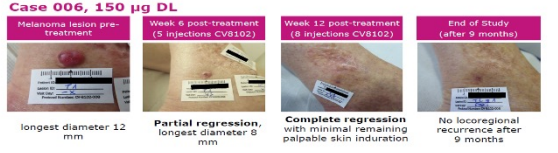
ESMO 2018 Congress; October 19-23, 2018; Munich, Germany



A phase I dose-escalation and expansion study of intratumoral CV8102 as single-agent or in combination with anti-PD-1 antibodies in patients with advanced solid tumors.

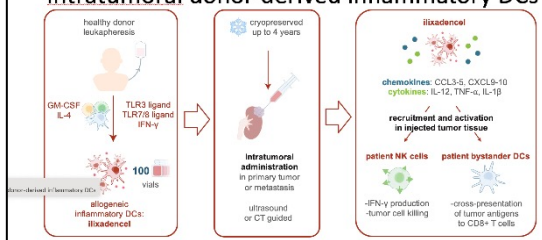
74-year-old female patient with stage IIIC melanoma with multifocal in-transit metastases

Case 006, 150 µg DL

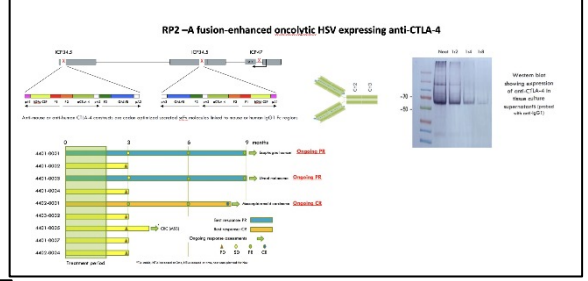


- Partial regression of the injected tumor lesion after 5 injections of CV8102
- Complete regression of in-transit metastases on MRI, complete regression of all skin metastases with minimal residual palpable induration of the injected lesion at week 12
- Patient continued to receive injections at monthly intervals for 9 months without locoregional recurrence
- New intraabdominal soft tissue lesion after 9 months

Ilixadencel: intratumoral donor-derived inflammatory DCs

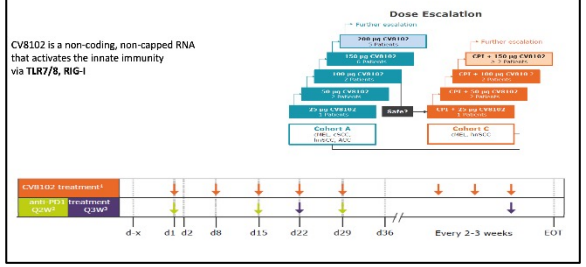


Initial results of a phase 1 trial of RP2, a first in class, enhanced potency, anti-CTLA-4 antibody expressing, oncolytic HSV as single agent and combined with nivolumab in patients with solid tumors

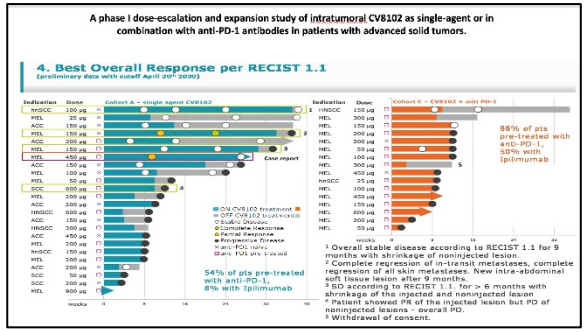


A phase I dose-escalation and expansion study of intratumoral CV8102 as single-agent or in combination with anti-PD-1 antibodies in patients with advanced solid tumors.

CV8102 is a non-coding, non-capped RNA that activates the innate immunity via **TLR7/8, RIG-I**



A phase I dose-escalation and expansion study of intratumoral CV8102 as single-agent or in combination with anti-PD-1 antibodies in patients with advanced solid tumors.



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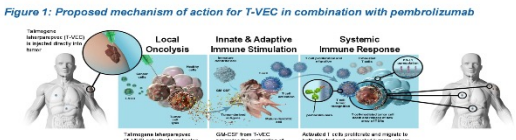
[2] Complete regression of in-transit melastases, complete regression of all skin melastases. New intra-abdominal soft tissue lesion after 9 months.
[3] SD according to RECIST 1.1. for > 6 months with shrinkage of the injected and noninjected lesion
[4] Patient showed PR of the injected lesion but PD of noninjected lesions - overall PD.
[5] Withdrawal of consent.

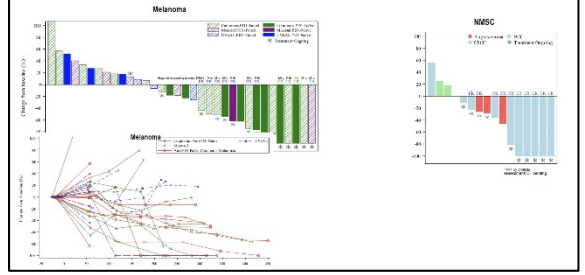
Talimogene laherparepvec (T-VEC) injected into liver tumors in combination with pembrolizumab

Early Safety From a Phase 1, Multicenter, Open-label Clinical Trial of Talimogene Laherparepvec (T-VEC) Injected Into Liver Tumors in Combination With Pembrolizumab

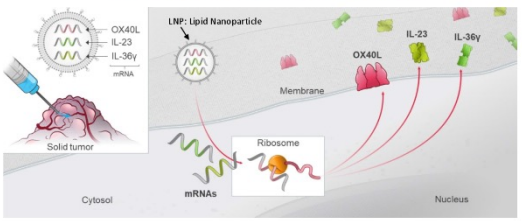
Figure 1: Proposed mechanism of action for T-VEC in combination with pembrolizumab



A multicenter, Phase 1/2 clinical trial of RP1, an enhanced potency oncolytic HSV, combined with nivolumab: Updated results from the skin cancer cohorts

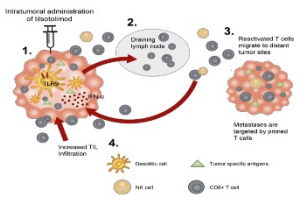


Intratumoral mRNA encoding for cytokines & soluble factors



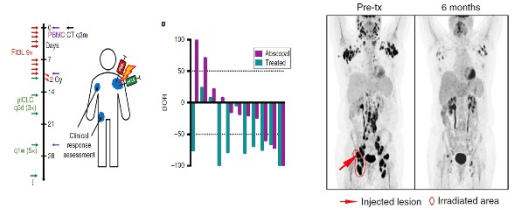
Patel, M. R., et al. (2020). A phase I study of mRNA-2752, a lipid nanoparticle encapsulating mRNAs encoding human OX40L, IL-23, and IL-36γ, for intratumoral (iTu) injection alone and in combination with durvalumab. Journal of Clinical

Intratumoral TLR9 agonist



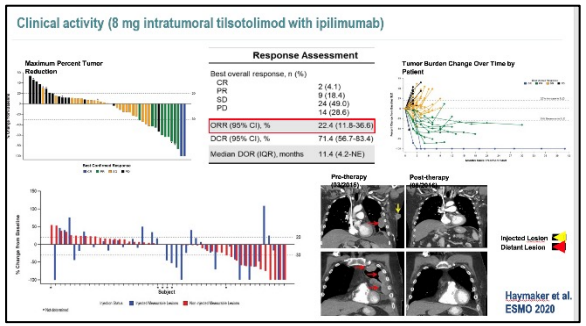
Haymaker et al. ESMO 2020

IT FLT3L & TLR3 agonist + 2x2Gy RT in Follicular Lymphoma



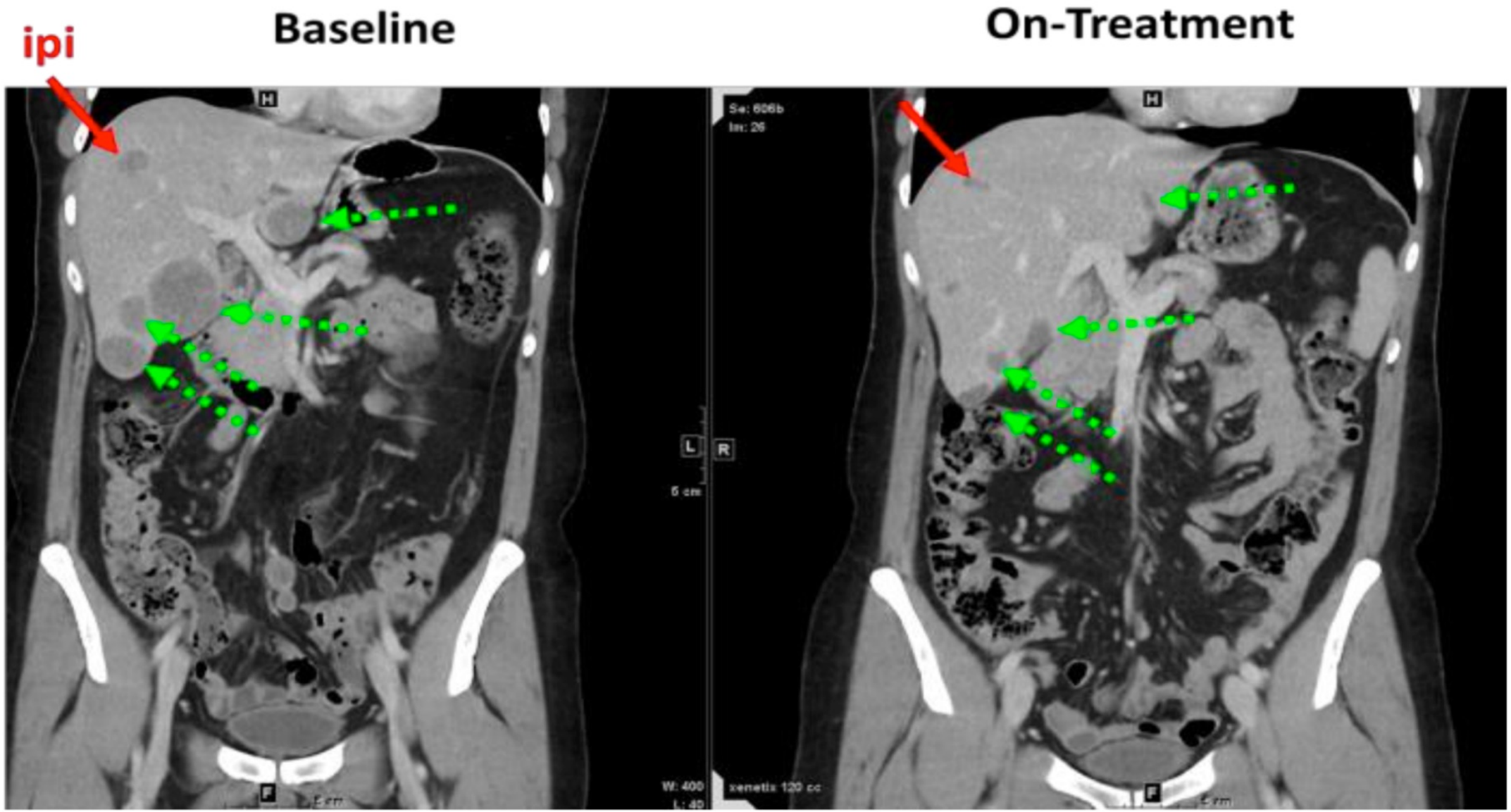
Hammerich L, et al. Systemic clinical tumor regressions and potentiation of PD1 blockade with in situ vaccination. Nat Med 2019.

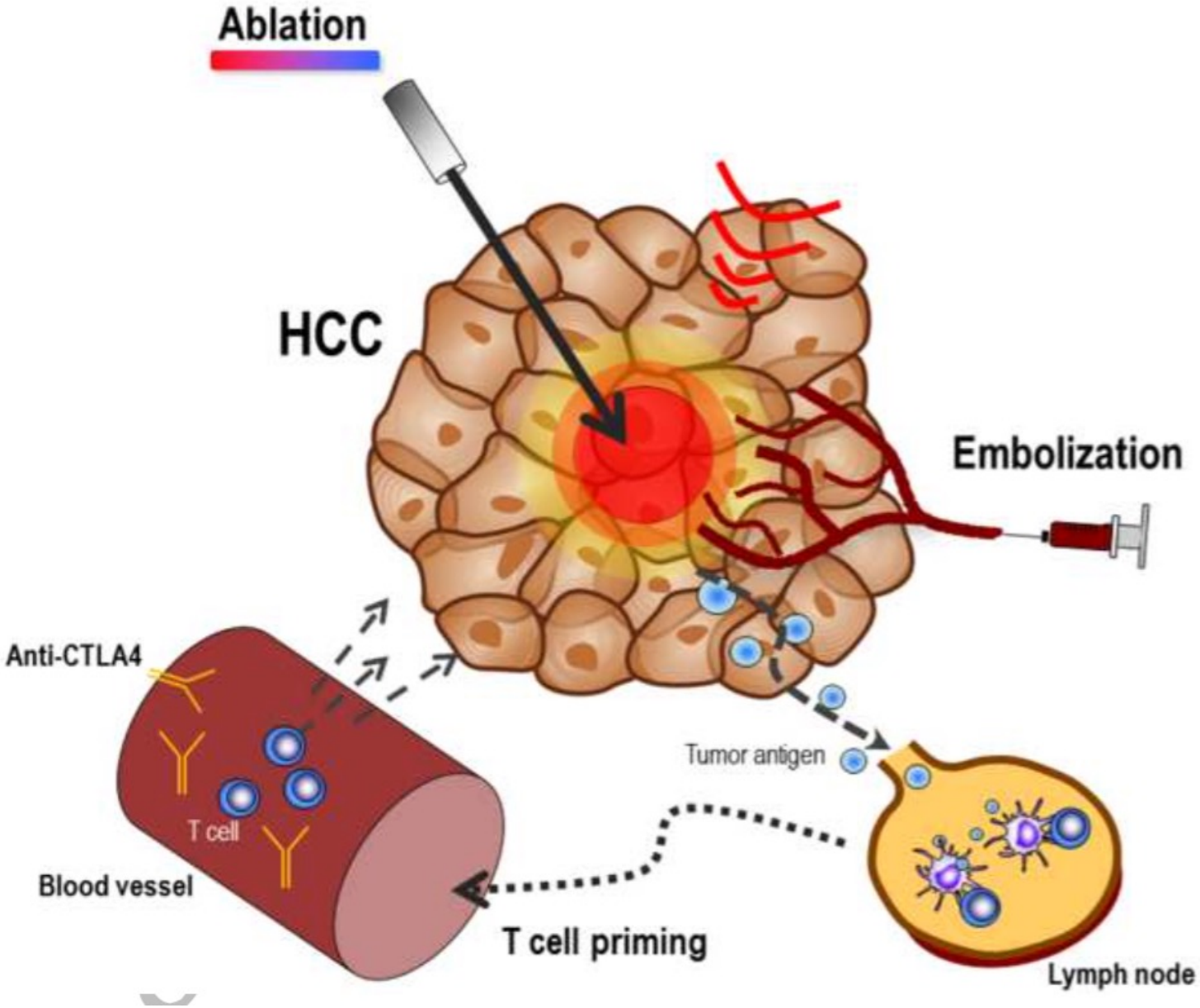
Clinical activity (8 mg intratumoral tilsotolimod with ipilimumab)



Haymaker et al. ESMO 2020

Distant Intra-Liver Response



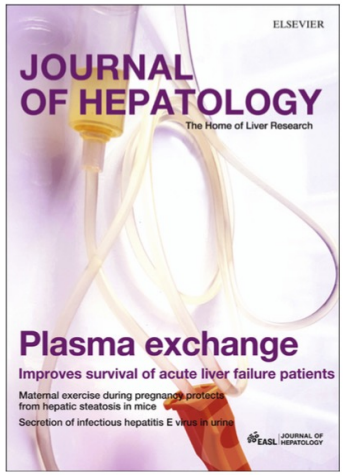


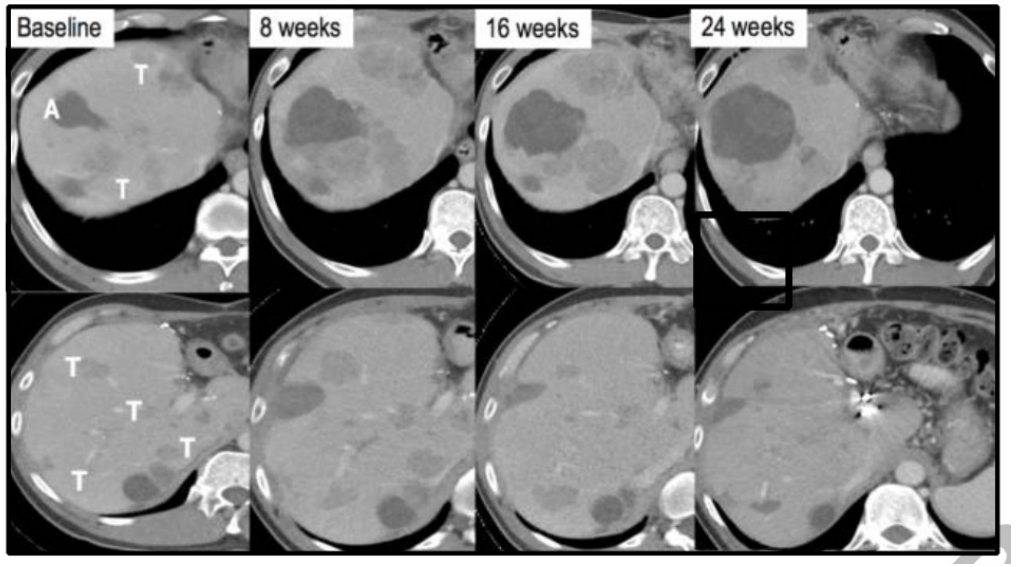
(J Hepatol. 2017 March ; 66(3): 545–551)

Accepted Manuscript

Tremelimumab in Combination with Ablation in Patients with Advanced Hepatocellular Carcinoma

Austin G. Duffy, Susanna V. Ulahannan, Oxana Makorova-Rusher, Osama Rahma, Heiner Wedemeyer, Drew Pratt, Jeremy L. Davis, Marybeth S. Hughes, Theo Heller, Mei ElGindi, Ashish Uppala, Firouzeh Korangy, David E. Kleiner, William D. Figg, David Venzon, Seth M. Steinberg, Aradhana M. Venkatesan, Venkatesh Krishnasamy, Nadine Abi-Jaoudeh, Elliot Levy, Brad J. Wood, Tim F. Greten





- 28 HCC patients (RFA, CRA or TACE) 6 weeks after tremelimumab

- accumulation of intratumoral $CD8^+$ T-cells
- PR (26.3%) outside of the areas which received local treatment

- increase in the ablated area (A)
- Tumor (T) worsening appearances at 8 weeks with subsequent improvement and in some cases resolution at 24 weeks.

(J Hepatol. 2017 March ; 66(3): 545–551)

EMERALD-1 (locoregional HCC)

Phase 3, randomised, double-blind, placebo-controlled study (recruiting)

Study population

- Confirmed HCC
- Unsuitable for curative therapy, e.g. surgical resection, ablation, transplantation
- Disease amenable to TACE
- No extrahepatic disease
- Child-Pugh A to B7
- ECOG 0 or 1
- Exclude Vp3 and Vp4
- Exclude patients with clinically significant cardiovascular disease or history of arterioembolic event

R

Arm A
TACE + durvalumab

Arm B
TACE + durvalumab + bevacizumab

Arm C
TACE + placebo

Primary endpoint:

PFS for Arm A versus Arm C (BICR)

Secondary endpoints:

PFS for Arm B versus Arm C (BICR), OS, PROs

Other endpoints:

Safety, immunogenicity, PK

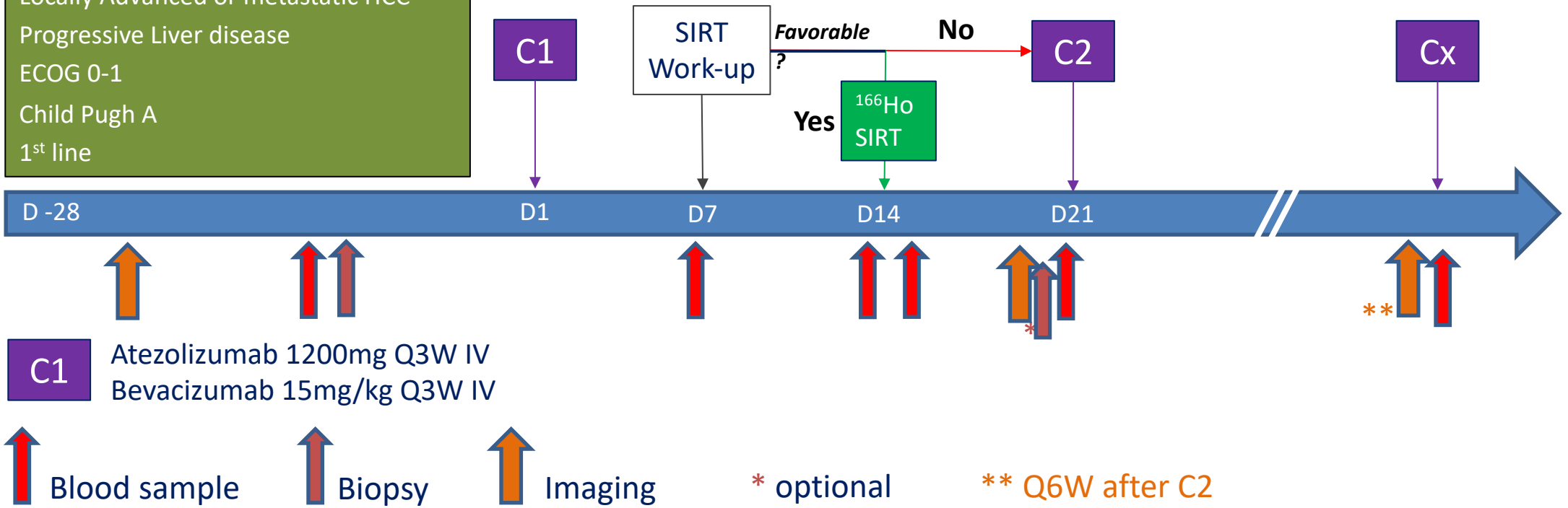
BICR, blinded independent central review; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PROs, patient-reported outcomes; TACE, transarterial chemoembolisation

http://clinicaltrials.gov/ct2/show/NCT03778957

HOLMBRAVE: Study evaluating safety and efficacy of selective intra-arterial ^{166}Holmium radiation therapy in combination with atezolizumab and bevacizumab for non resectable Hepatocellular carcinoma.

DRC : ok
€ : ok
CSET : ok
CPP/ANSM/ASN : en cours

SCREENING
Locally Advanced or metastatic HCC
Progressive Liver disease
ECOG 0-1
Child Pugh A
1st line



IGR
Beaujon
Cochin
Grenoble
Montpellier

C1 Atezolizumab 1200mg Q3W IV
Bevacizumab 15mg/kg Q3W IV

Blood sample Biopsy Imaging * optional ** Q6W after C2

Phase IIa, Simons 2 Stage : 17 + 16 patients évaluables => **Obj : ORR@6m: 50% mRECIST**

Advantages of In Situ Immunization over Cancer Vaccines

	CANCER VACCINES	INTRATUMORAL IMMUNOTHERAPY
THERAPEUTIC PRINCIPLE	• Tumor-specific targets identification • Off-target (off tumor) immune stimulation • Product draining into cutaneous lymph node • Mono- or pauci-clonal T-cell stimulation	• No antigen identification nor isolation required • On-target (intra-lesional) immune stimulation • Product draining into tumor draining lymph node • Polyclonal T and B-cell stimulation
PATIENT ELIGIBILITY	• Peptide Vaccines: ✓ Antigen Expression ✓ MHC-I restriction • Neo-Epitope Vaccine: ✓ Tumor material available ✓ Blood for germinal control	• No pre-treatment biopsy required • No MHC restriction • Injectable Lesion Available
DRUG PRODUCTION	• Out-licensed adjuvant • GMO facility if encoded into viral vector • Peptide Vaccines: GMP peptides • Neo-Epitope Vaccine: Identification of neo-antigen: *DNA/RNA sequencing, HLA-I binding prediction, HLA-I peptide elution,* GMP production for every patient	• Off-the shelf

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

ESMO
SPECIAL ARTICLE
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Starting the fight in the tumor: expert recommendations for the development of human intratumoral immunotherapy (HIT-IT)

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Annals of Oncology

Dose Determination: per patient vs per lesion, fixed dose/various volumes or fixed concentration.

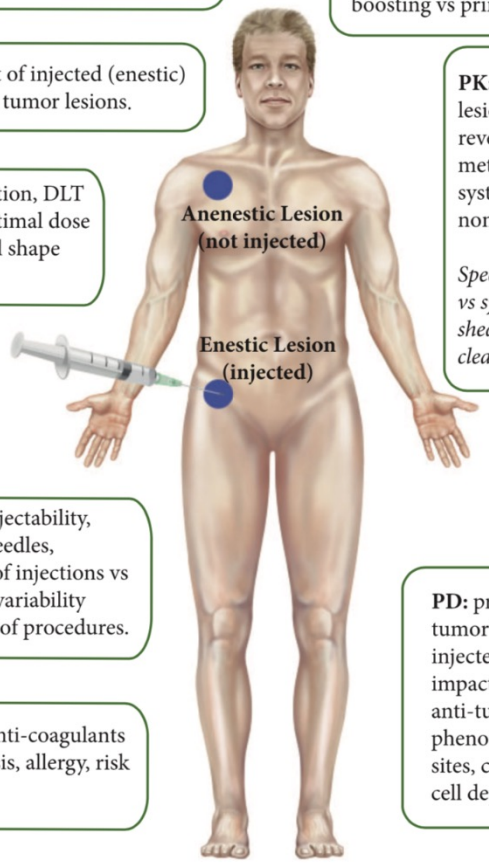
Trial Design: dose vs drug escalation, lesion, escalation, vs dose-intensity escalation, priming vs boosting vs prime-boosting.

Efficacy: separate assessment of injected (enestic) and non-injected (anenestic) tumor lesions.

PK: tumor vasculature, volume of lesion vs volume, target expression, reversibility of binding, local metabolism, ADAs, phagocytosis, systemic vs local PK in injected vs non-injected lesions.

Specific issues for oncolytic viruses: local vs systemic replication, distribution, shedding, metabolic vs immune clearance.

Dose escalation: DLT definition, DLT period duration, MTD vs optimal dose vs PD read-out for RP20, bell shape curve effects.



Intratumoral Injections: injectability, locations, sizes, guidance, needles, syringes, volumes, number of injections vs number of injected lesions, variability inter-operators, consistence of procedures.

PD: pre-treatment and on-treatment tumor biopsies of injected and non injected lesions, local and systemic impact of therapy, quality, of the anti-tumor immunity, immune phenotyping in injected and non injected sites, cell recruitment vs cell activation vs cell depletion, timing of events.

Patient Exclusion Criteria: anti-coagulants or significant bleeding diathesis, allergy, risk of vascular catastrophe.

Thank you

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