Human Intratumoral Injections: Rationale and Technique

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Gustave Roussy Immunotherapy Program
Get a GRIP on Cancer

UNIVERSITÉ PARIS SUD
FACULTÉ DE MÉDECINE

ÉCOLE DES SCIENCES DU CANCER

Disclosures

Consultant: Terumo, Boston Scientific, Guerbet, Eisai, AstraZeneca

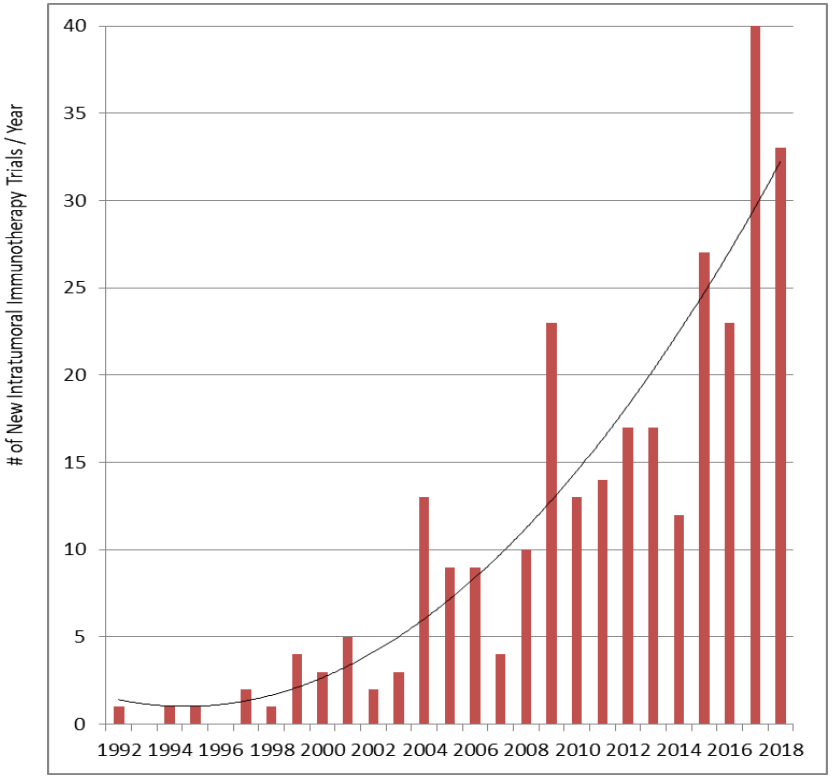
Grants/Research Support: Terumo

Speakers' Bureau: Terumo, Guerbet

Brand names are included in this presentation for participant clarification purposes only.
No product promotion should be inferred.

New Intratumoral Immunotherapy Trials/Year

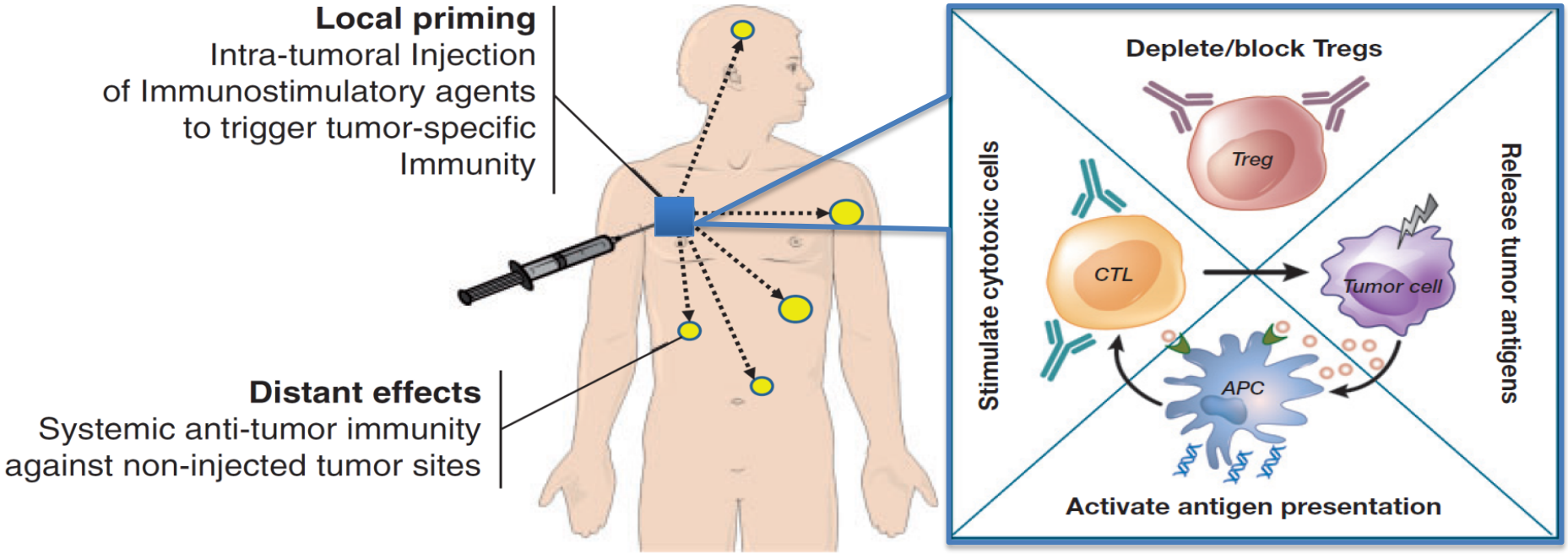
Clinicaltrials.gov



LYTIX (oncolytic pep.)
NIVIPIT (CTLA4)
MEDI9197 (TLR7/8)
MK1454 (sting)
ILLUMINATE (TLR9)
MK46-21 (RIG1)
M15-862 (antiCD40)
PRIMO (TLR9+Ipi)
ISILI (OX40, TLR9)
ISIC
HIPANIV (CTLA4)
…

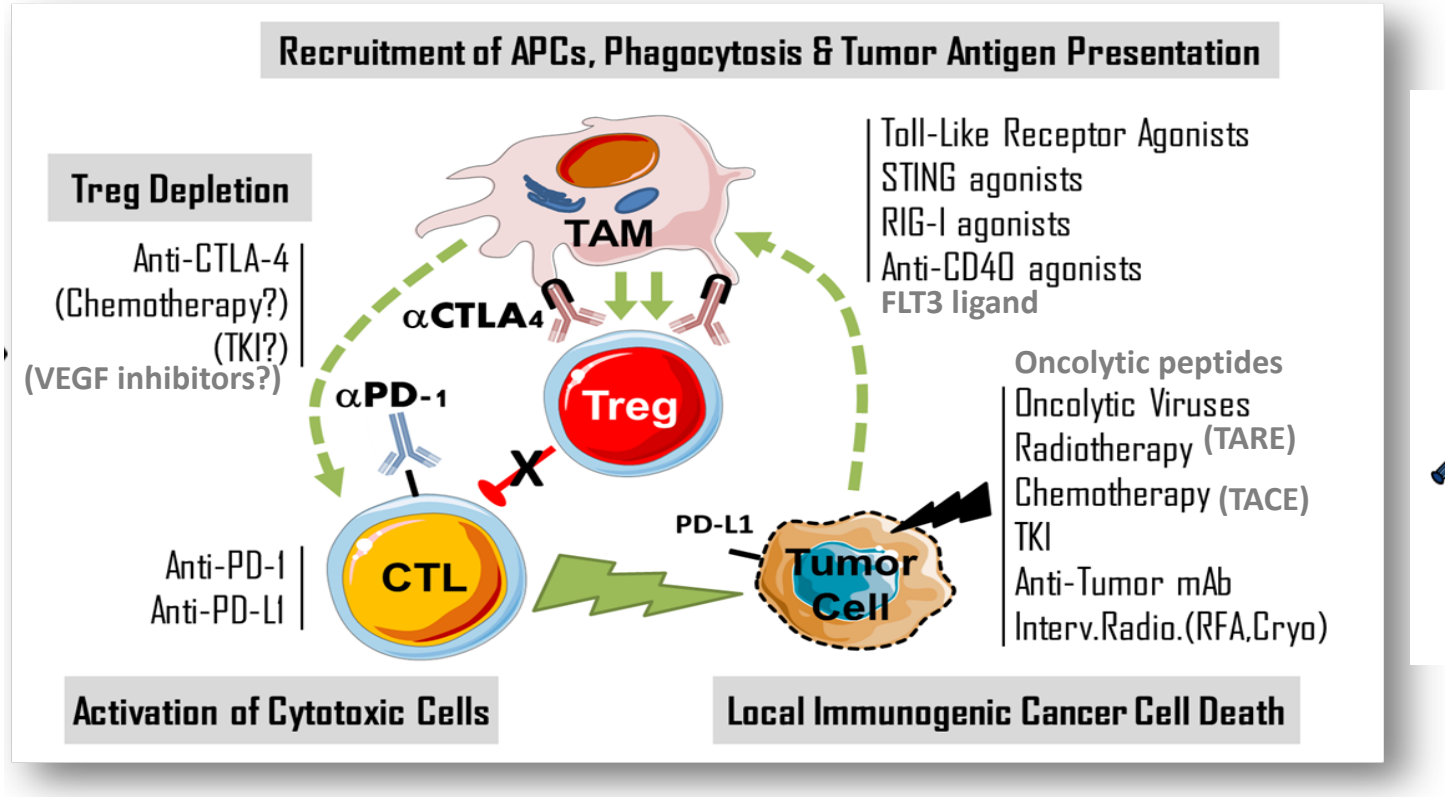
Human Intratumoral Immunotherapy (HIT-IT)

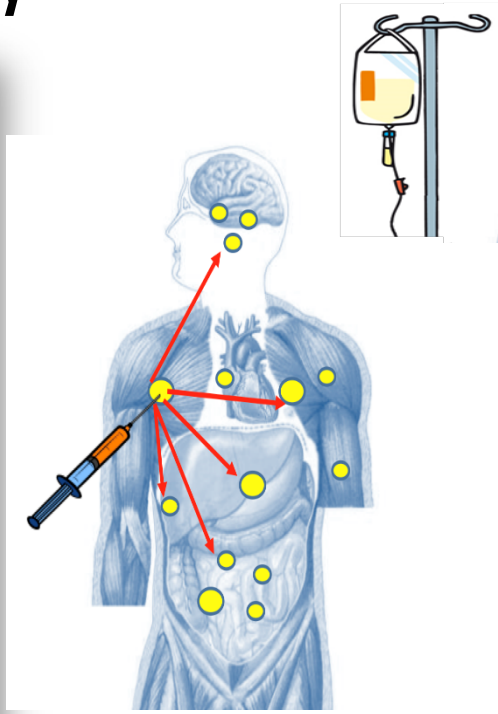
On-Target / On-Tumor Effects



Marabelle A, et al. *Ann Oncol*. 2017;28(suppl_12):xii33-xii43.

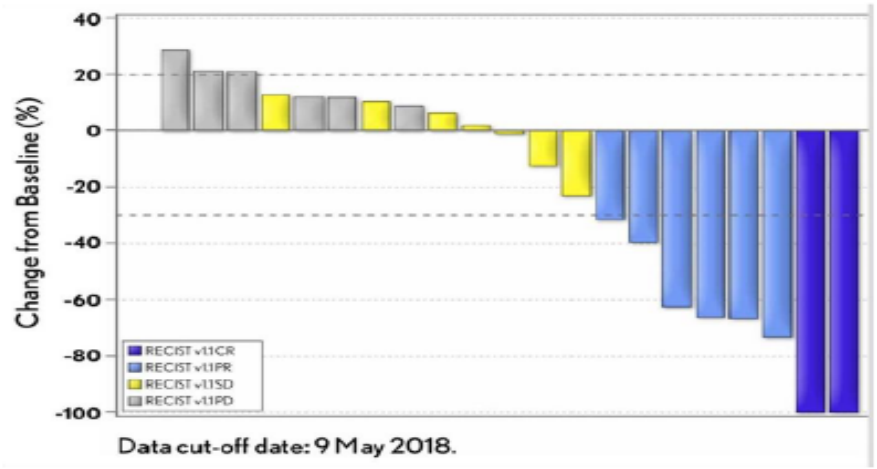
Potential Combinations for *In Situ Priming* of Anti-Tumor Immunity



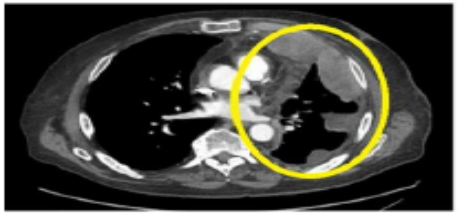


Adapted from Marabelle A, et al. *Ann Oncol*. 2017;28(suppl_12):xii33-xii43.

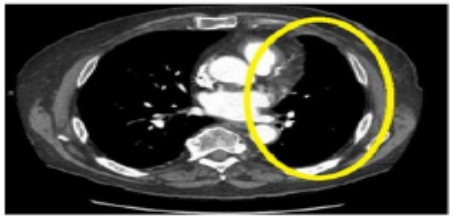
IT tilsotolimod (TLR9 agonist) + ipilimumab in αPD-1 refractory Melanoma



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



Pretreatment
Uninjected tumor



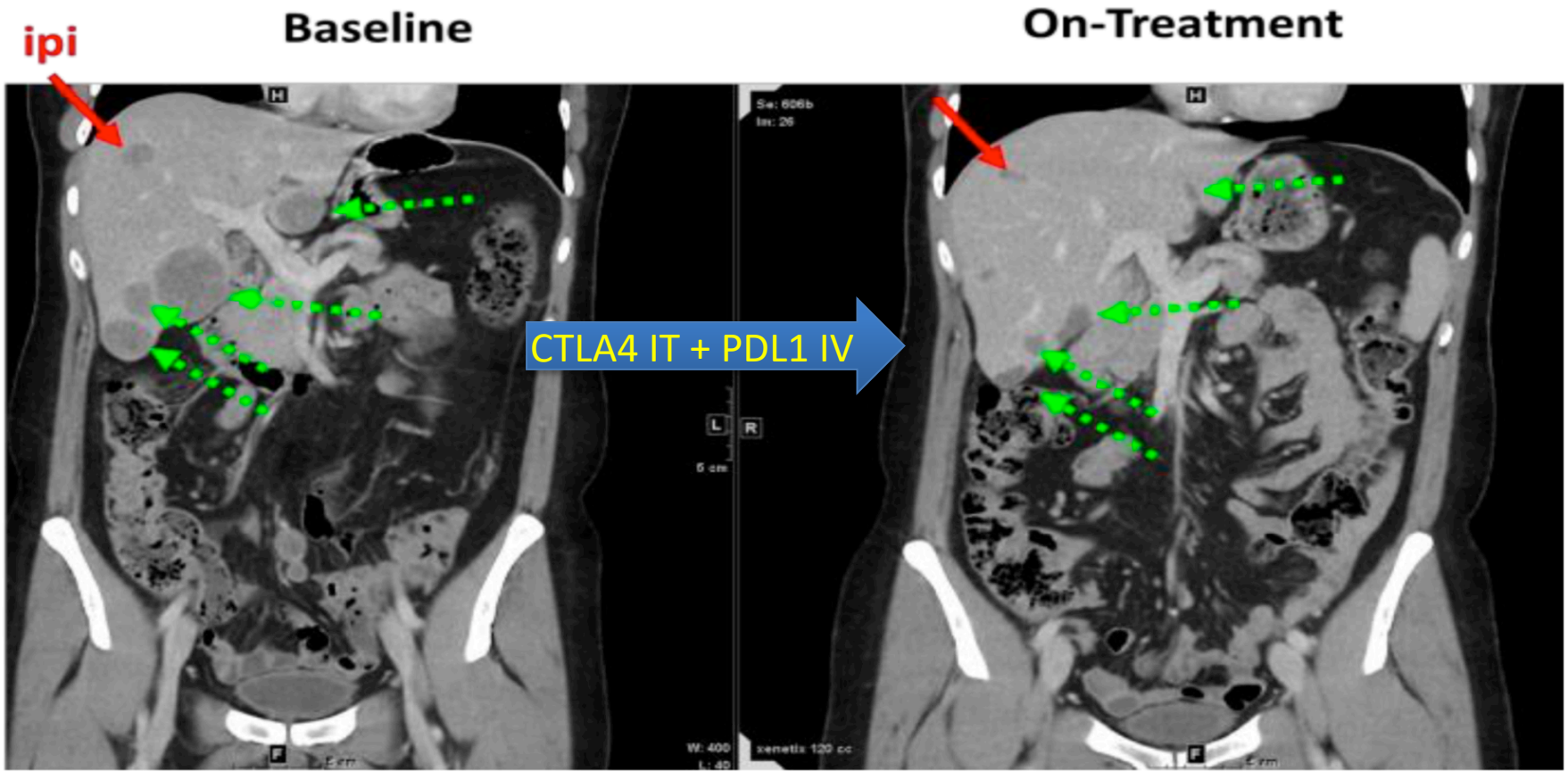
Posttreatment 24 weeks
Uninjected tumor

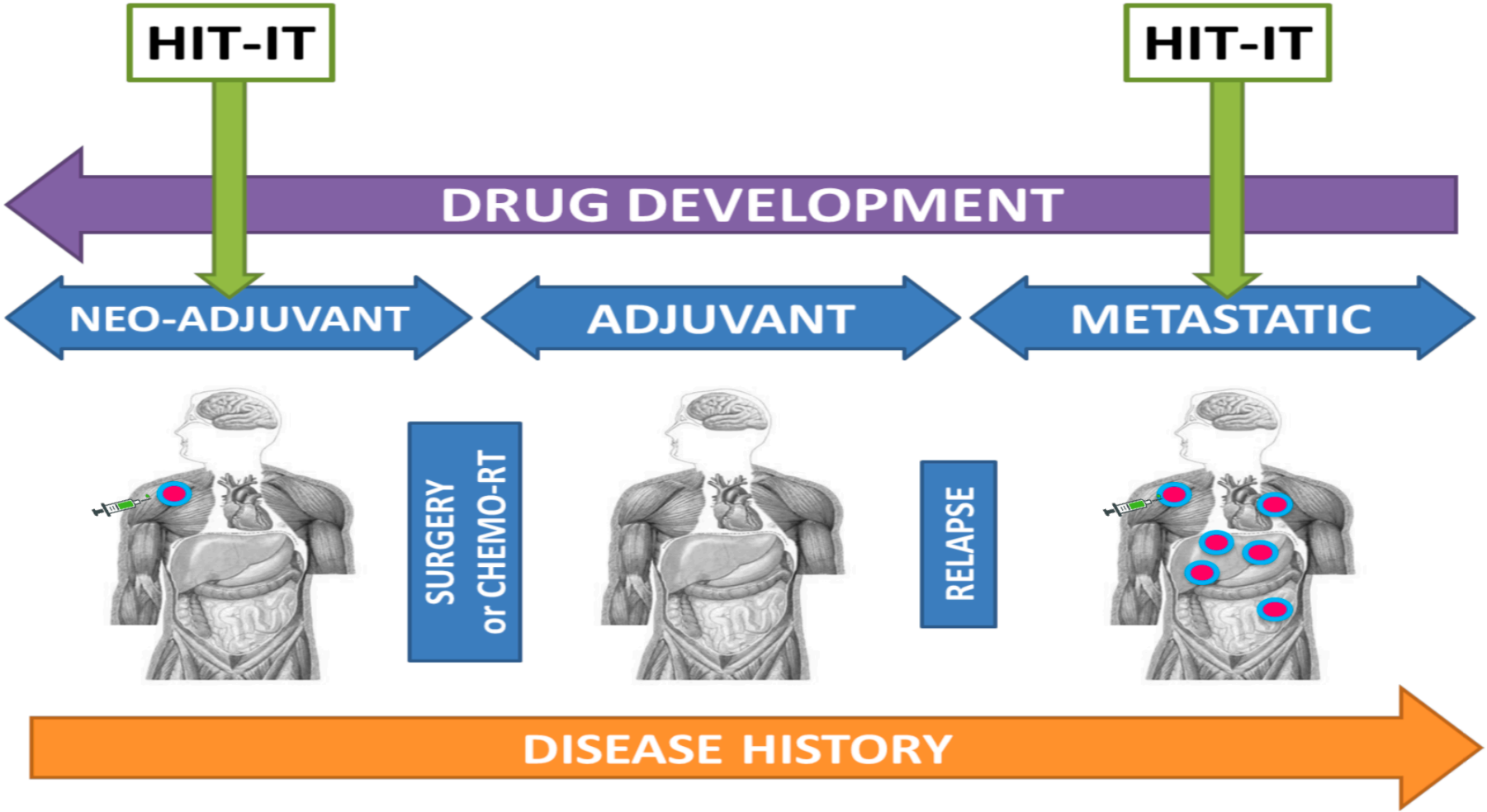
A.Diab et al, ASCO 2018

ILLUMINATE 301: A randomized phase III study of tilsotolimod in combination with ipilimumab compared with ipilimumab alone in patients with advanced melanoma following progression on or after anti-PD-1 therapy

ORR Data Anticipated Q1 2021

Distant Intra-Liver Response




HIT-IT
HIT-IT
DRUG DEVELOPMENT
NEO-ADJUVANT
ADJUVANT
METASTATIC
SURGERY
or CHEMO-RT
RELAPSE
DISEASE HISTORY

PRIMARY 2-YEAR RESULTS OF A PHASE 2, MULTICENTER, RANDOMIZED, OPEN-LABEL TRIAL OF EFFICACY AND SAFETY FOR TALIMOGENE LAHERPAREPVEC **(T-VEC) NEOADJUVANT (NEO) TREATMENT (TX) PLUS SURGERY (SURG) VS. SURG IN PATIENTS (PTS) WITH RESECTABLE STAGE IIIB-IVM1A MELANOMA (**NCT02211131)

Randomized 1:1 to 6 doses/12 wks of neo T-VEC then surg (Arm 1) vs. surg alone (Arm 2). Primary endpoint per protocol was recurrence-free survival (RFS) at 2-yrs.

neo T-VEC monotherapy improves

- increased rate of R0 surgical resections (ASCO 2019)
- **2-yr OS: 88.9% vs. 77.4% (HR 0.49, P = 0.050)**
- **2-yr RFS: 50.5% vs. 30.2% (HR 0.66, P = 0.038)**
- CD8+ density and PD-L1 H-score were higher in T-VEC arm ($P < 0.001$)
- Increased intratumoral CD8 + density post-tx correlated with longer RFS and OS

Presented at: ESMO Congress; September 27-October 1, 2019; Barcelona, Spain.

HIT – IT* Technical Challenges

* Human Intratumoral Immunotherapy

Marabelle A, et al. *Ann Oncol*. 2018;29(11):2163-2174.

HIT – IT* Technical Challenges

1. **Intratumoral**
   - Image guidance
   - Size of the target
   - Organ
   - Needle caliber

2. **Immunotherapy**
   - Target(s)
     - Prioritirization
     - Enestic* (injected) vs. anenestic° (non-injected) ~~Abscopal~~
   - Injection
     - Volume / Concentration
     - Monitoring / Visibility
     - Delivery platform

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* From “énesi,” which means “injection” in Greek

Marabelle A, et al. *Ann Oncol*. 2018;29(11):2163-2174.

HIT – IT* Technical Challenges

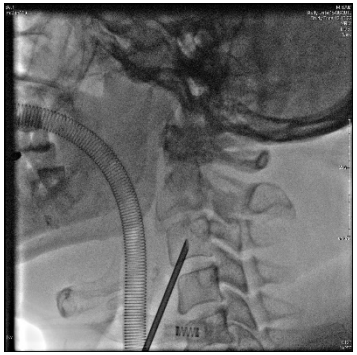
1. **Intratumoral**
   - Image guidance (US, CT, CEUS…)
   - Size of the target
   - Organ
   - Needle caliber

2. **Immunotherapy** (virus, peptide, PRRs agonist , immune checkpoint, modified immune cells…)
   - Target(s)
     - Prioritization
     - Enestic* (injected) vs. anenestic° (non-injected) ~~Abscopal~~
   - Injection
     - Volume / Concentration
     - Monitoring / Visibility
     - Delivery platform

* From “énesi,” which means “injection” in Greek

Marabelle A, et al. *Ann Oncol*. 2018;29(11):2163-2174.

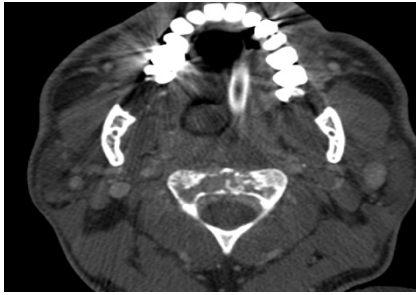
Which Organ? Safety

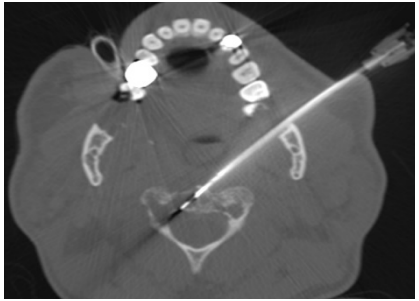


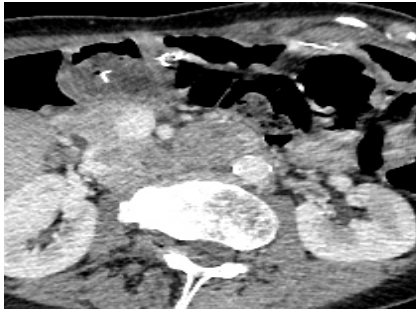
Organ* (puncture risk score)

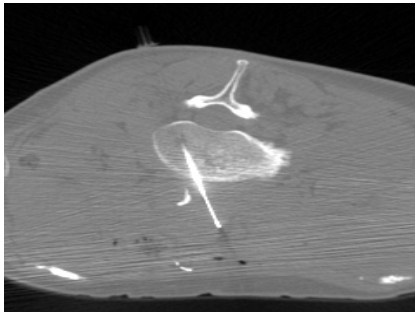
1	- Skin / subcutaneous tumor or lymphnodes
2	- Bone / soft tissue
3-4	- Liver / adrenal / kidney / deep lymph nodes (retroperitoneal, illiac…)
3-4	- Peritoneal / Pelvic
5	- Lung
8	- Deep mediastinal

Repeated injections!!!









* Hollow organ & endoluminal approach excluded (bronchus, esophagus, stomach, colon, bladder).

Organ* (puncture risk score)

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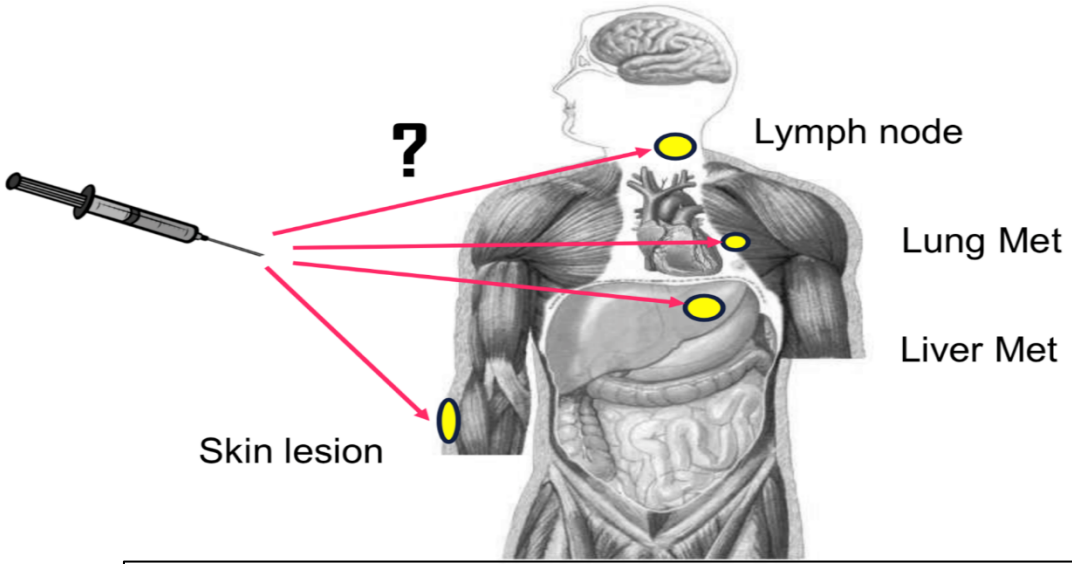
3-4	- Peritoneal / Pelvic
5	- Lung
8	- Deep mediastinal

AWG N°	Diam. mm.	Area mm²
16	1,290	1,3100
17	1,150	1,0400
18	1,024	0,8230
19	0,912	0,6530
20	0,812	0,5190
21	0,723	0,4120
22	0,644	0,3250
23	0,573	0,2590
24	0,511	0,2050
25	0,455	0,1630
26	0,405	0,1280

*Hollow organ & endoluminal approach excluded (bronchus, esophagus, stomach, colon, bladder).

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



How to prioritize according to possible benefit of HIT-IT

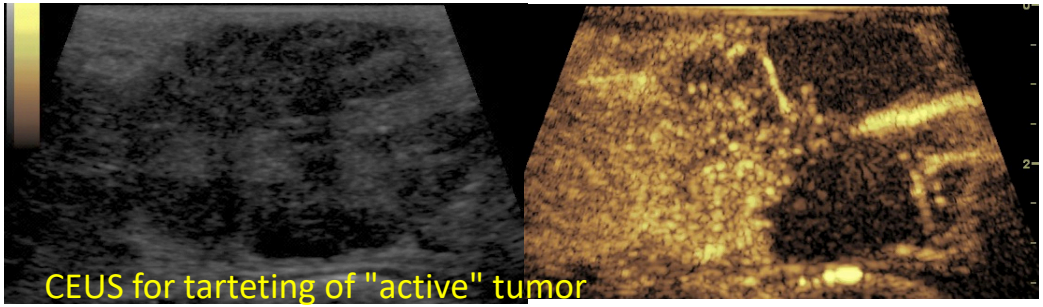
- one organ vs. another?
- large lesions vs. small lesions?
- newly occurred lesions?

Targeting the active tumor and not the necrotic part of the lesion

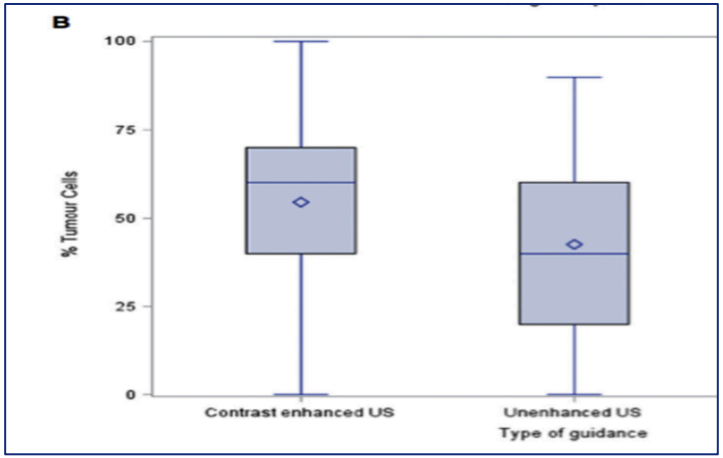
European Journal of Cancer 59 (2016) 79–89
Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.ejcancer.com
ELSEVIER
EJC

Original Research

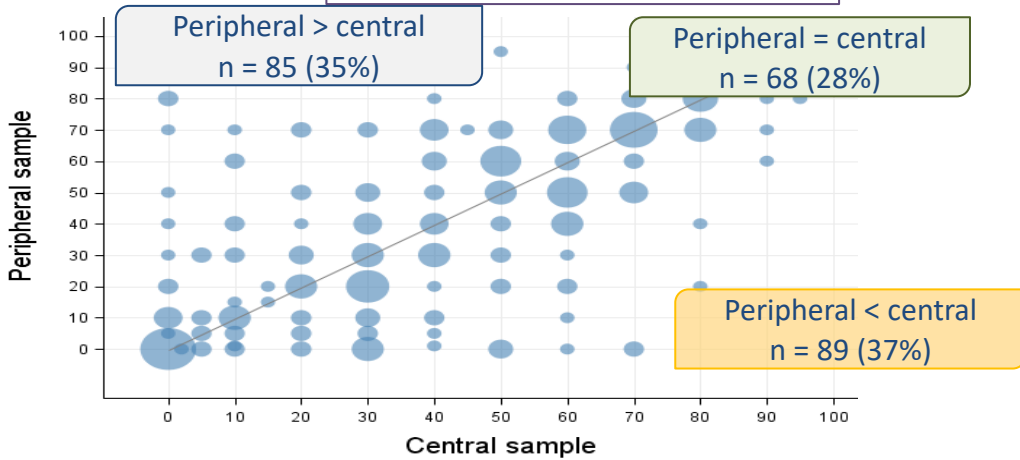
Factors associated with success of image-guided tumour biopsies: Results from a prospective molecular triage study (MOSCATO-01)



Doppler US
Contrast-Enhanced US

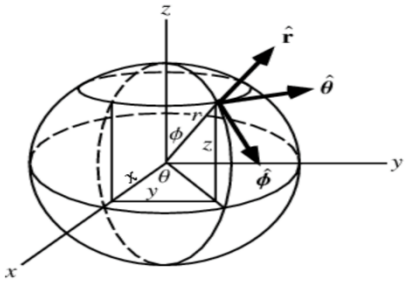


Tumor biopsy cellularity



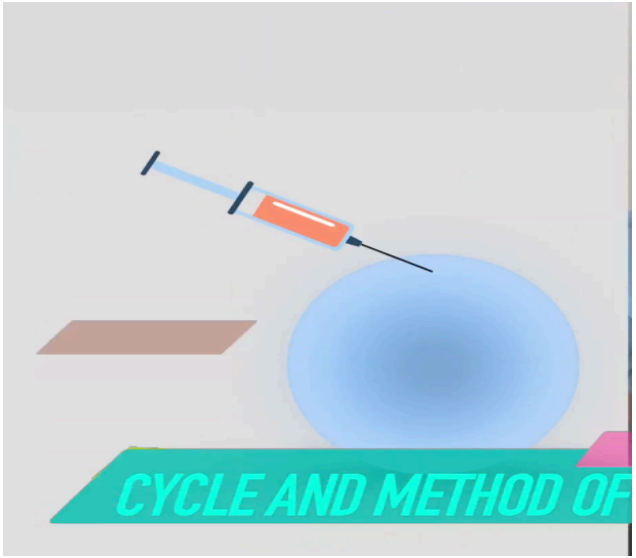
Tacher V, et al. Presented at: EJC 2016; 59:79-89)

How / Where to Inject?

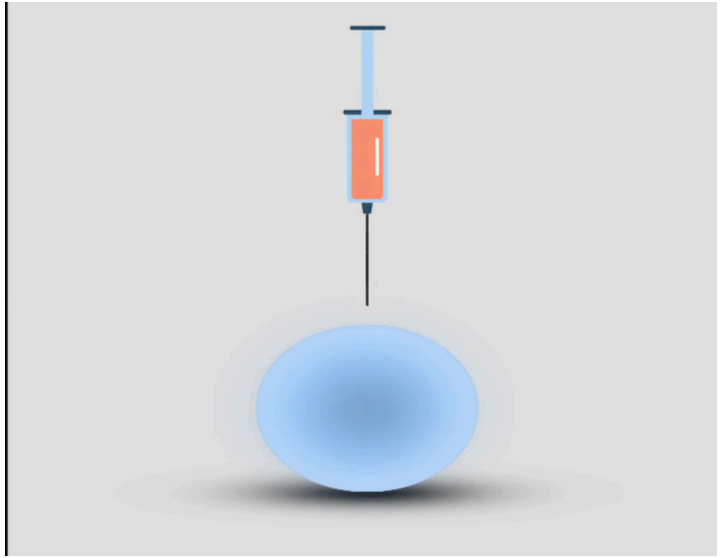


To cover the all tumor volume (the all volume of active tumor)

Sequential Injection



Radial Injection



SPECIAL ARTICLE

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

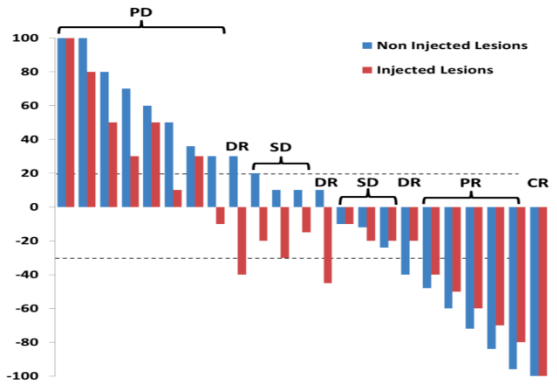
A. Marabelle[1*], R. Andtbacka[2], K. Harrington[3], I. Melero[4], R. Leidner[5], T. de Baere[6], C. Robert[7], P. A. Ascierto[8], J.-F. Baurain[9], M. Imperiale[10], S. Rahimian[11], D. Tersago[12], E. Klumper[13], M. Hendriks[14], R. Kumar[15], M. Stern[16], K. Öhrling[17], C. Massacesi[18], I. Tchakov[19], A. Tse[20], J.-Y. Douillard[21], J. Tabernero[22], J. Haanen[23] & J. Brody[24]

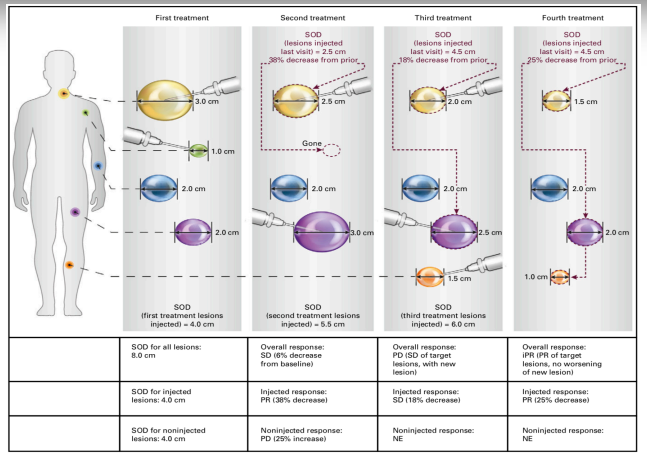
review ar

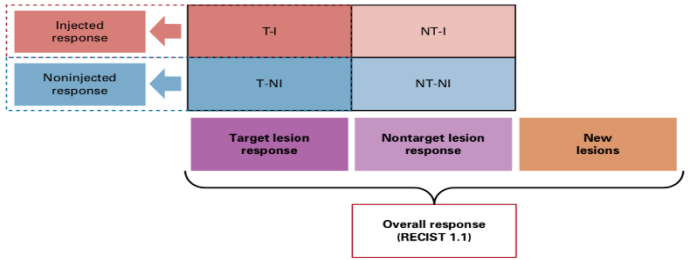
Response Criteria for Intratumoral Immunotherapy in Solid Tumors: itRECIST

Gregory V. Goldmacher, MD, PhD, MBA[1]; Anuradha D. Khilnani, MD[1]; Robert H. I. Andtbacka, MD[2]; Jason J. Luke, MD[3]; F. Stephen Hodi, MD[4]; Aurelien Marabelle, MD, PhD[5]; Kevin Harrington, MBBS, PhD[6]; Andrea Perrone, MD[1]; Archie Tse, MD, PhD[7]; David C. Madoff, MD[8]; and Lawrence H. Schwartz, MD[9]

Waterfall Plots for HIT-IT







Marabelle A, et al. *Ann Oncol.* 2018;29:2163-2174. Goldmacher GV, et al. *JCO.* 2020; 38,23:2667.

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

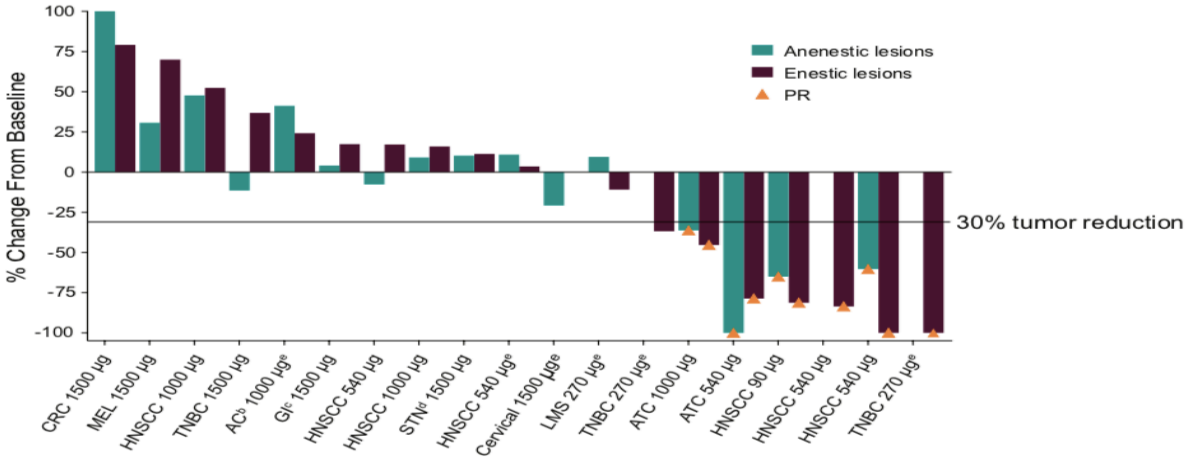
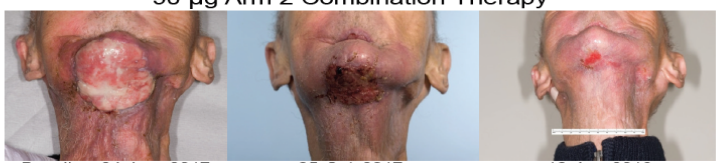


Figure 4. Tumor Images in Selected Patients With Partial Responses

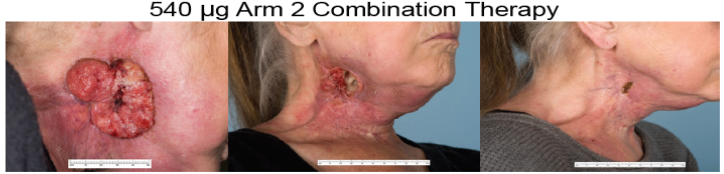
A. HNSCC[a]

90 µg Arm 2 Combination Therapy



Baseline: 24-Aug-2017 | 05-Oct-2017 | 10-Jan-2018

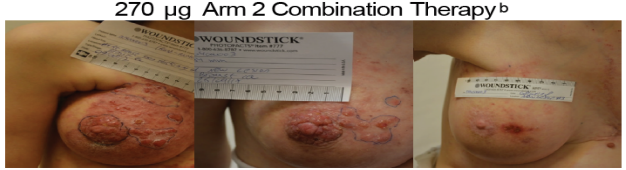
540 µg Arm 2 Combination Therapy



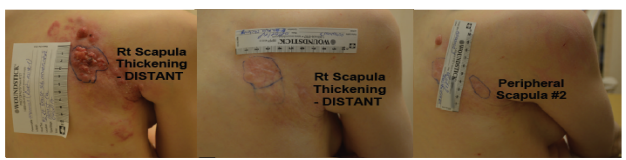
Baseline: 26-Sept-2017 | 10-Oct-2017 | 11-Jan-2018

B. TNBC (BRCA2 Mutant)[a]

270 µg Arm 2 Combination Therapy[b]



Baseline: 09-Aug-2017 | 25-Sep-2017 | 08-Jan-2018



Baseline: 09-Aug-2017 | 08-Jan-2018 | 08-Jan-2018

[a]Tumor lesions in images reflect injected (enestic) lesions.

[a]Injected (enestic) lesions, upper panels; noninjected (anenestic) lesions, lower panels. [b]Crossover patient to 270 µg Arm 2 combination therapy from 90 µg Arm 1 monotherapy

- Distant / Non-injected / Abscopal / Non-Enestic Effect is demonstrated in precilinical and clinical studies: *In-Situ Vaccination*

- HIT-IT can reverse immunoresistance to checkpoint inhibitors, but best compound, best combination is unknown

- When chemotherapy is used as an immunomodulator, systemic delivery of chemotherapy can be questionned

- HIT-IT is opening questions on:
  - Target (accesibility, safety…)
  - Delivery (dose, regimen, flow, pressure, monitoring…)
  - Evaluation (PK, PD, iRecist, Hit-IT Recist...)

- Nobody can deliver better than IRs

Thank You