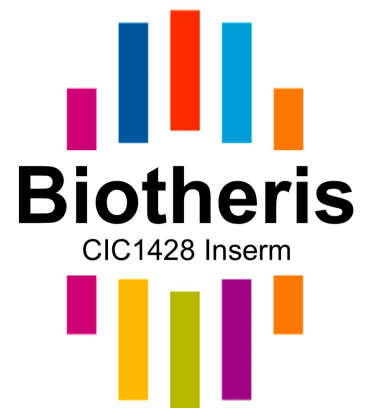


Intratumoral immunotherapy: The role of IR



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

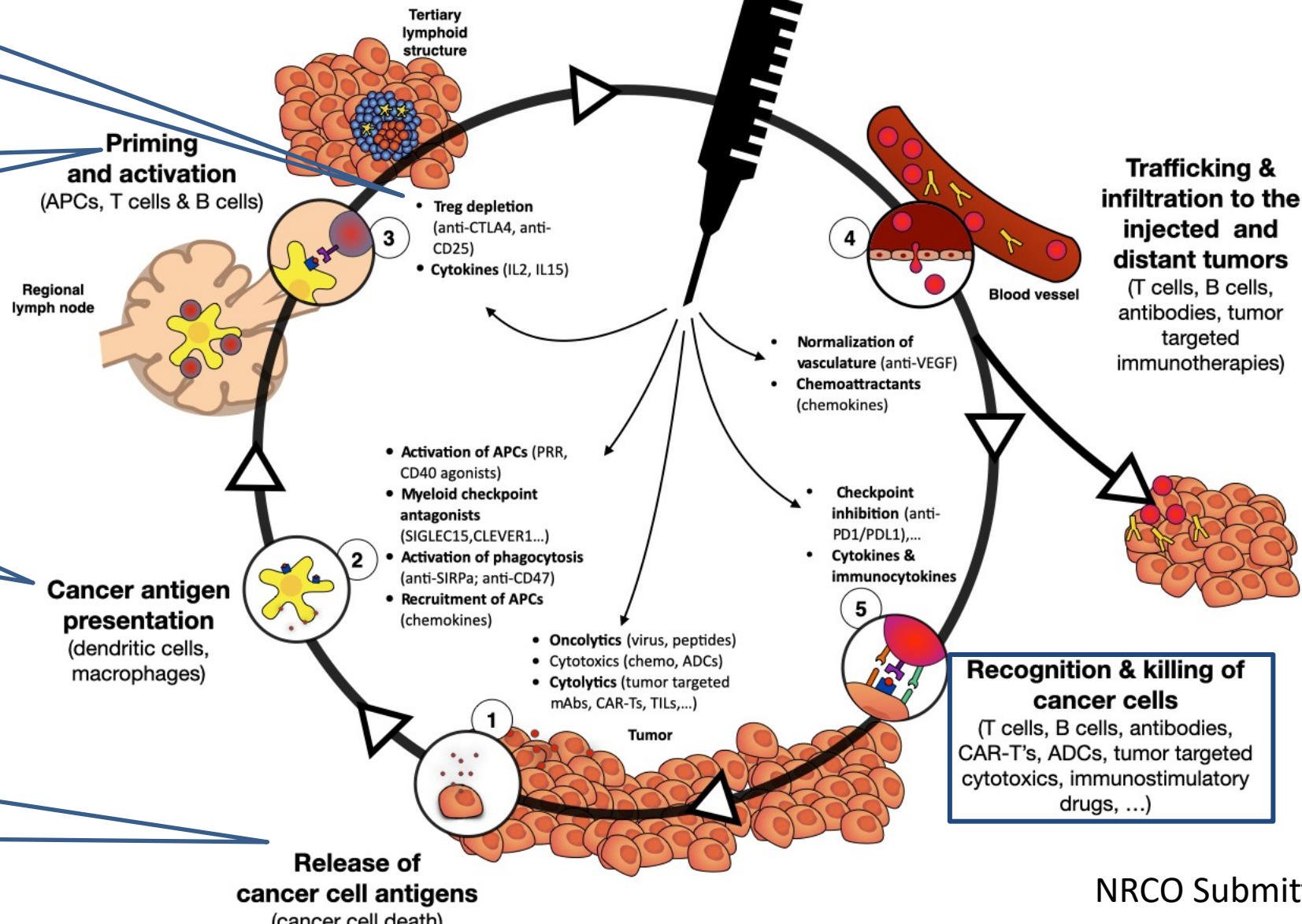
Tumor antigen release

- Oncolytic virus
- Tumor targeting mAbs
- Chemotherapy

Radiation therapy

- Thermal ablation (RFA, MWA, CRA)
- TACE
- SIRT

Boosting the intratumoral cancer immunity cycle

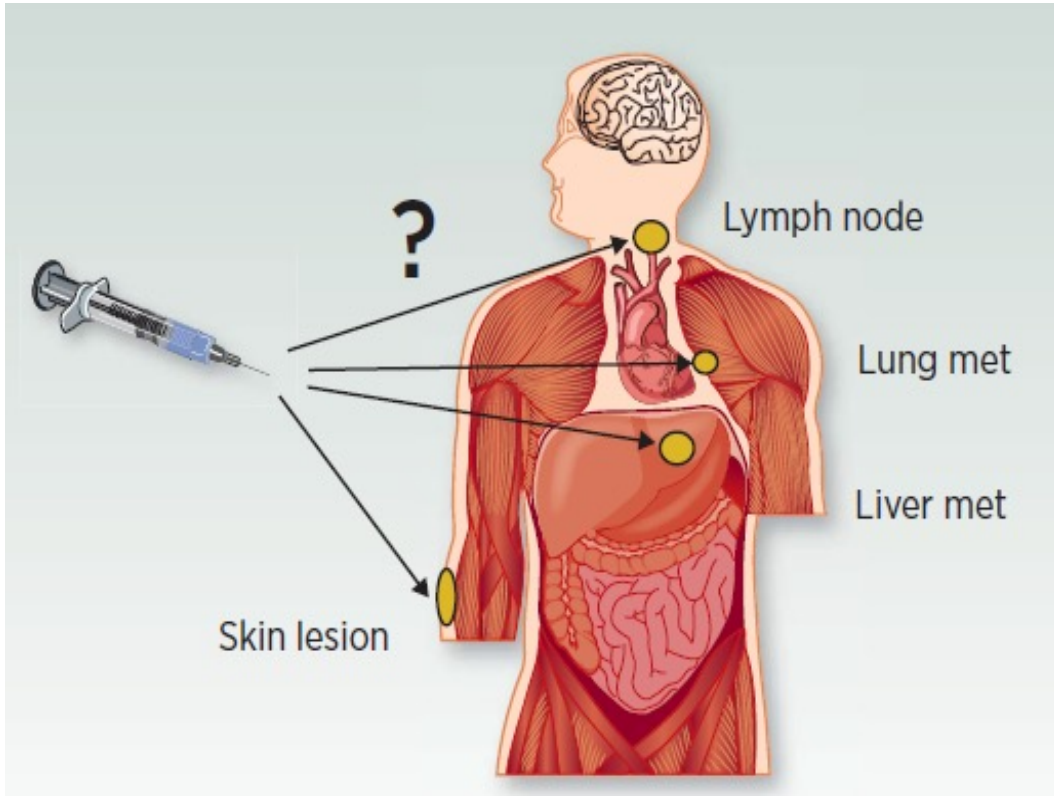


HIT-IT: Actual Challenges

- ◆ Target
- ◆ Dose
- ◆ Regimen
- ◆ Efficacy Assessment
- ◆ PK/PD
- ◆ Trial Designs, MTDs & DLTs

Are some tumor sites better than others to generate anti-tumour response in non injected sites ?

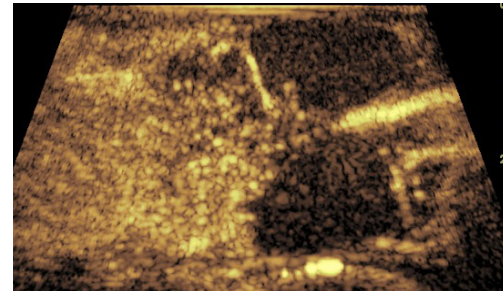
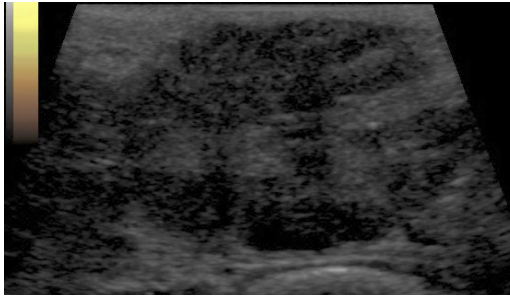
Prioritization ?



Organ* (puncture risk score)

- 1 - Skin / sub-cutaneous tumor or lymphnodes
- 2 - Bone / soft tissue
- 3-4 - Liver / Adrenal / Kidney / Deep lymph nodes (retroperitoneal, iliac, ...)
- 3-4 - Peritoneal / Pelvic
- 5 - Lung
- 8 - Deep mediastinal

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



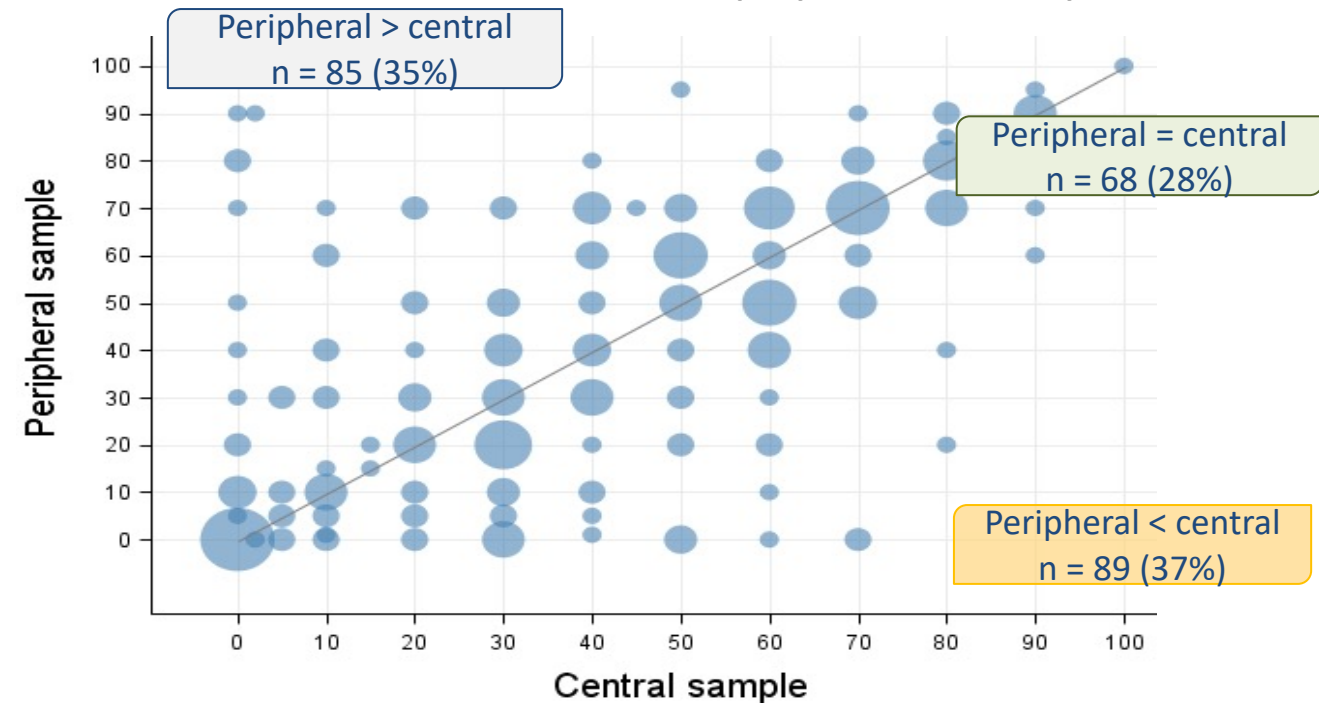
Contrats Enhanced US

Original Research

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



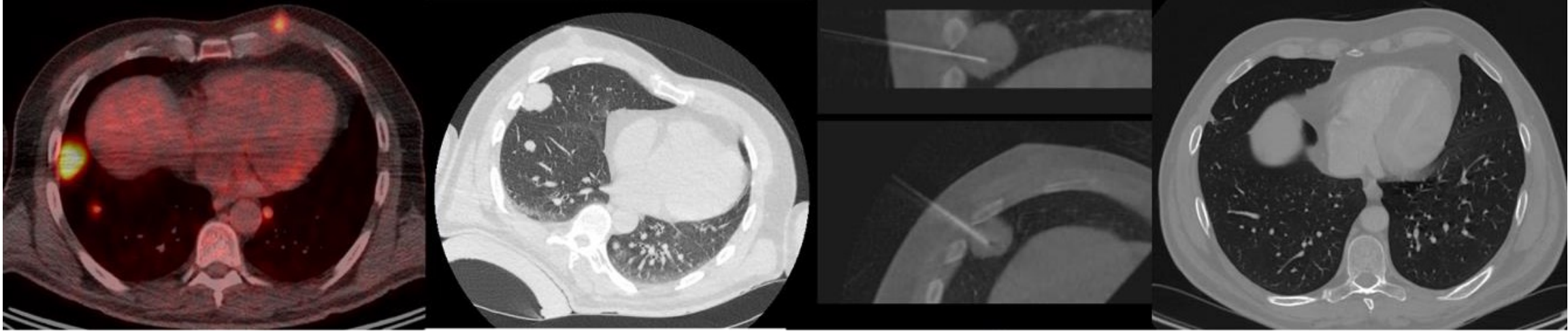
Tumor biopsy cellularity



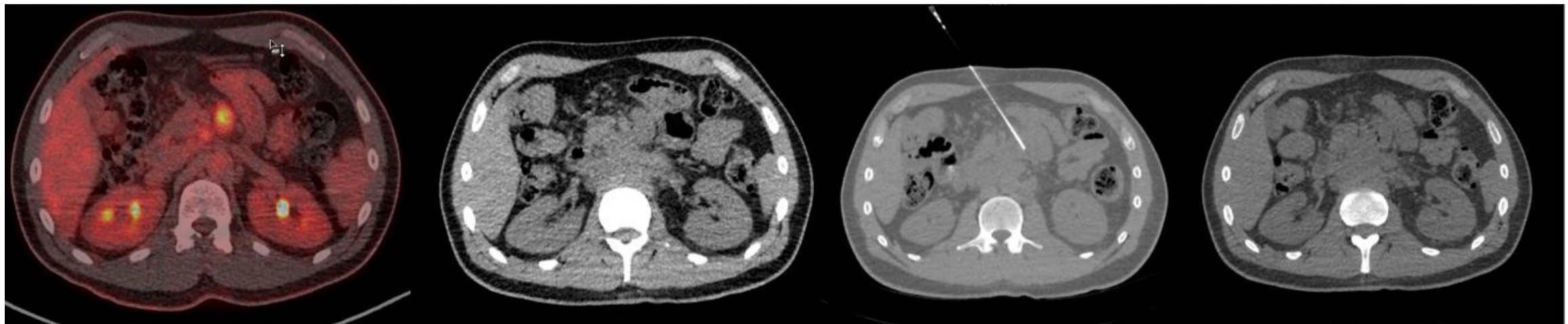
(Tacher V, Ledley MC, Hollebecque A, Soria JC, de Baère T. EJC 2016, 59 : 79-89)

Examples of local administration of immunotherapies using interventional radiology

55 years old man with a metastatic melanoma. A sub-pleural lung metastasis was injected under CT-scan guidance.



30 years old patient with a metastatic melanoma, with deep gastro-coeliac lymph nodes, included in a HIT-IT trial. Injection was made using a 22G needle under CT-scan guidance.

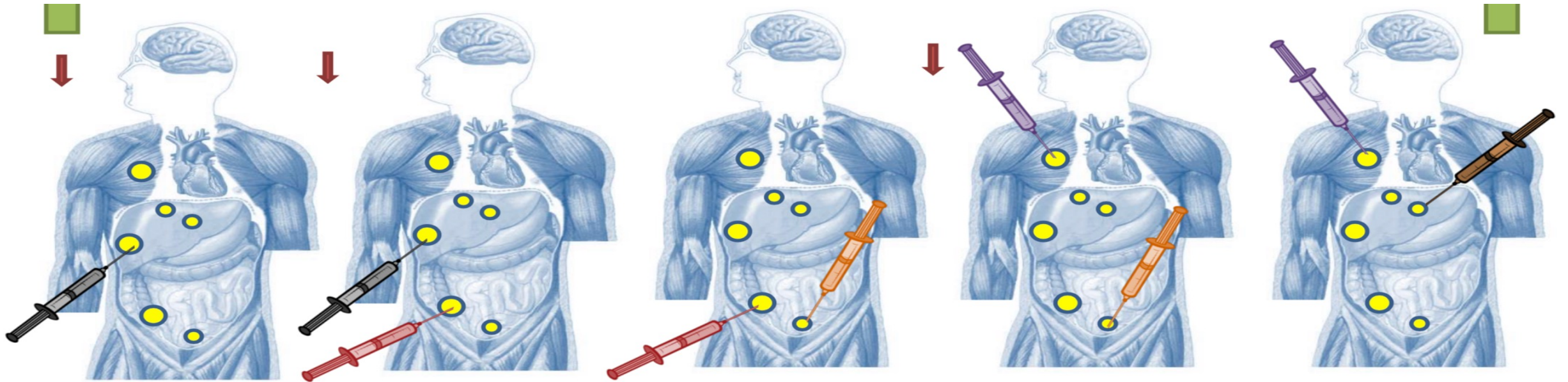


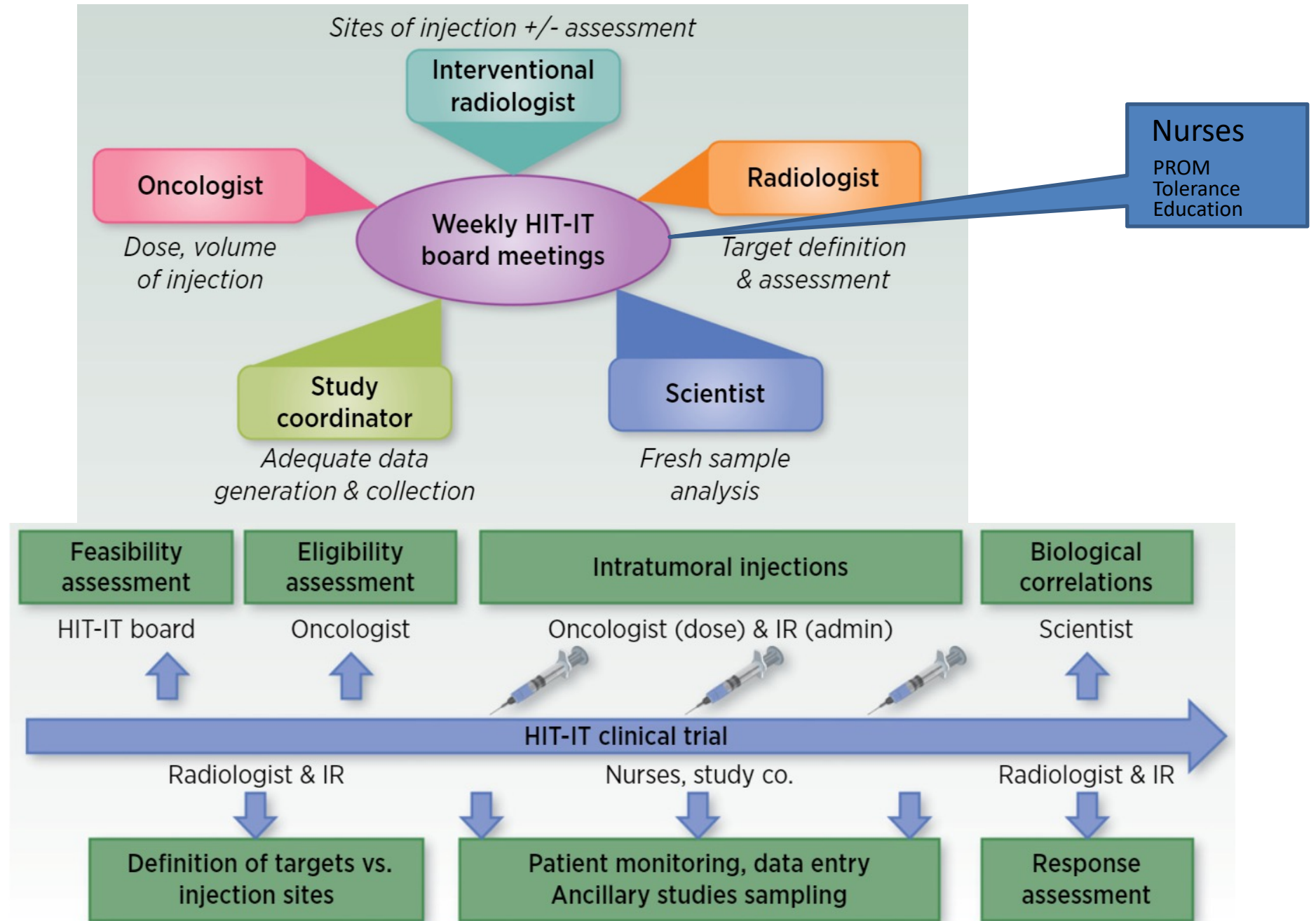
Regimen ?

Repeat injection(s) in one or several target

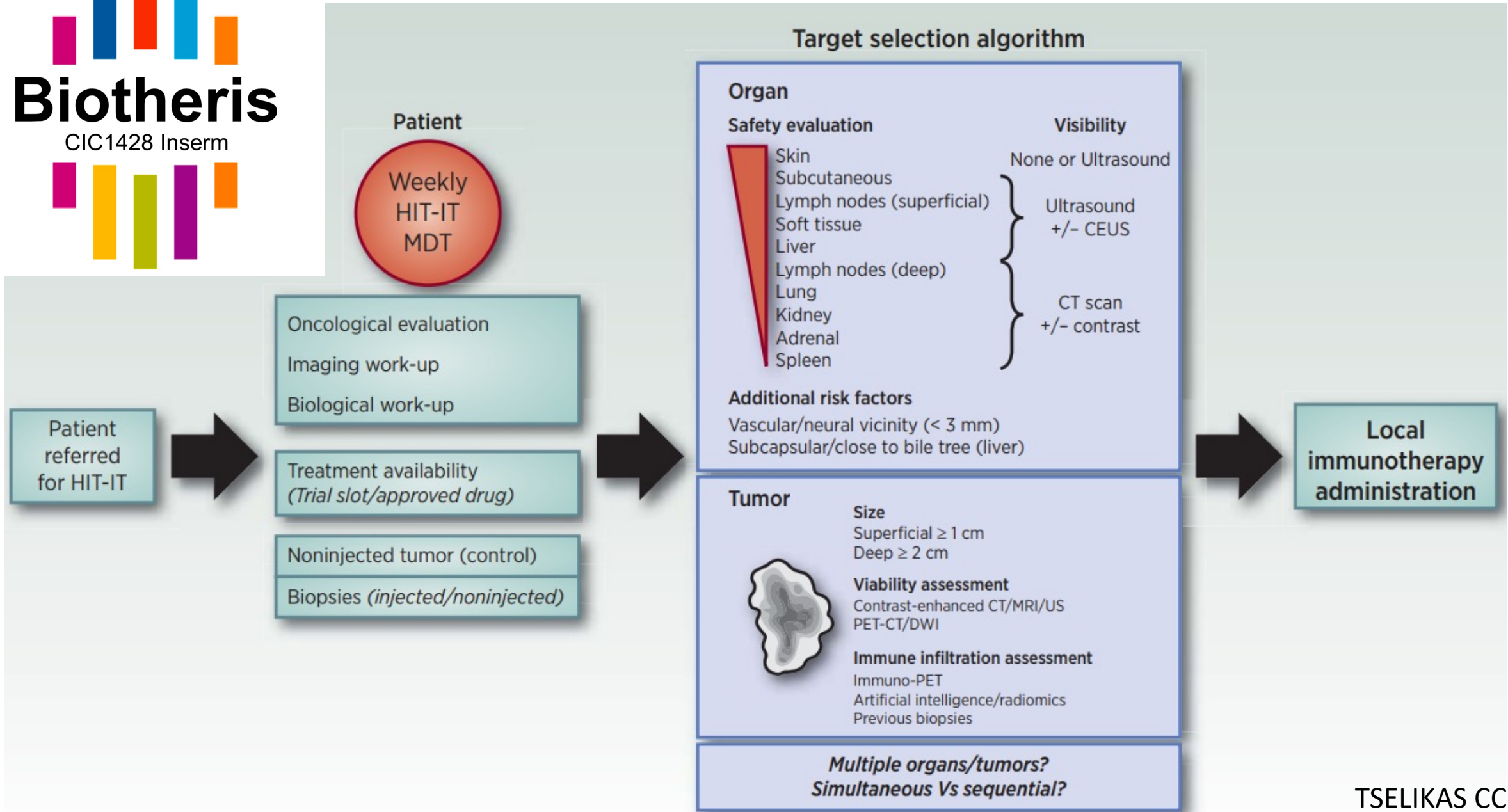
New lesion when complete enestic response ?

Injection of a different target at each cycle ?



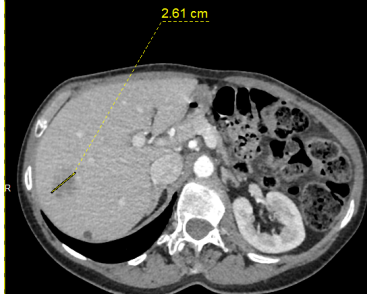


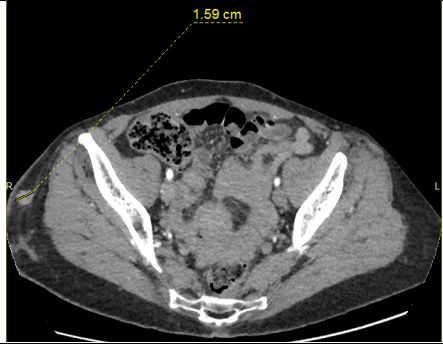
Target selection algorithm for patients referred for local immunotherapy treatment



Baseline

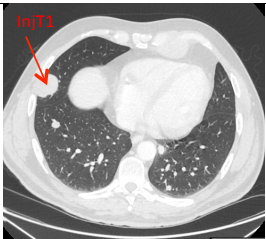
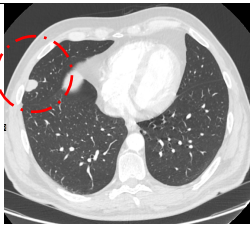
HIT IT Tumor Board CR BASELINE	
Date: 20-11-2018	
Présents : Radiologues interventionnels : ☒ Pr DE BAERE, ☒ Dr TSELIKAS, ☐ Dr MOULIN Radiologues : ☒ Dr AMMARI Oncologues : ☐ Dr MARABELLE, ☒ Dr CHAMPIAT Dermatologues : ☐ Dr ROUTIER ARC : ☐ Mme AUBRUN, ☒ Mme BENANNOUNE, ☐ Mme BODIN, ☐ Mme BOUSSELAHENE, ☐ Mme DZIRI, ☒ Mme FARHANE, ☐ Mme GOUISSEM, ☐ Mr HOUSSAIN, ☒ Mme ROY	
	Type histologique Mélanome Protocole : ILLUMINATE
Né le : 12/03/1956 - 62 ans Identifiant : 2018 02 238 GT Date TDM baseline 16/11/2018 C1J1 prévu le 23/11/2018	

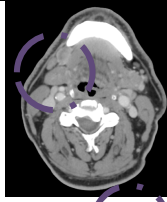
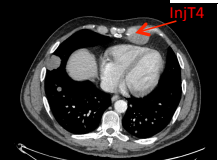
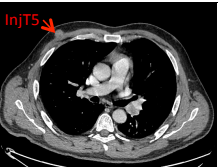
Lésion(s) injectée(s) ou injectable(s) :		
Lésion injectable		Baseline 16/11/2018
InjT1 : hépatique	Injected ☒ non ☐ yes le : Biopsied: ☒ no ☐ yes le :	
InjT2 : Ganglion inguinal droit	Injected ☒ non ☐ yes le : Biopsied: ☒ no ☐ yes le :	

InjT3 : Sous cutanée hanche droite	Injected ☒ non ☐ yes le : Biopsied: ☒ no ☐ yes le :	
Target for non injected evaluation : Cf TDM 16/11/2018 C1 : lung LUL Image : 91 size : 15 mm C2 : LN Carena Image : 133 size : 25 mm C3 : lung LLL Image : 206 size : 15 mm C4 : LN Right Obturator Image : 434 size : 25 mm Non target lesions : Cf TDM 16/11/2018 Lung nodules, LNs		
Avis du Staff du 20/11/2018 : Treatment 23/11/2018, First injection : InjT1		

Follow-up

HIT IT Tumor Board CR Evaluation	
Date: 20-11-2018	
Présents : Radiologues interventionnels : ☒ Pr DE BAERE, ☒ Dr TSELIKAS, ☐ Dr MOULIN Radiologues : ☒ Dr AMMARI Oncologues : ☐ Dr MARABELLE, ☒ Dr CHAMPIAT Dermatologues : ☐ Dr ROUTIER ARC : ☐ Mme AUBRUN, ☒ Mme BENANNOUNE, ☐ Mme BODIN, ☐ Mme BOUSSELAHENE, ☐ Mme DZIRI, ☒ Mme FARHANE, ☐ Mme GOUISSEM, ☐ Mr HOUSSAIN, ☒ Mme ROY	
Patient Nom: XXXXXXXXXX Prénom: Fabien Né le : 19-02-1970 Identifiant : 2018-12281 FX Date TDM 11/09/2018 C1J1 le 5/10/2018 TDM évaluation 15/11/2018	Type histologique Mélanome Protocole : NIVIPIT

Lesion(s) injectée(s) ou injectable(s) :			
Lésion injectable		Baseline : 11/09/2018	Evaluation Date : 15/11/2018
InjT1 : nodule RML	Injected ☐ no ☒ yes le : 5/10/18 Biopsied: ☒ no ☐ yes le :		
InjT2 : Cutaneous nodule	Injected ☐ no ☒ yes le : 5/10/18 26/10/18 Biopsied: Injected ☐ no ☒ yes le : 5/10/18		

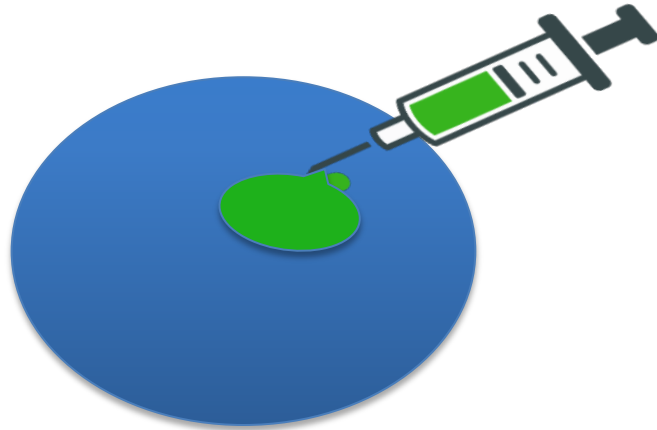
InjT3 : lésion right sub mandibular	Injectée ☒ no ☐ yes le : 16/11/18 Biopsied: ☒ no ☐ yes le :		
InjT4 : lésion pariétale antérieure gauche	Injectée ☒ no ☐ yes le : Biopsiée: ☒ no ☐ yes le :		
InjT5 : lésion mammaire droite	Injectée ☒ no ☐ yes le : Biopsiée: ☒ no ☐ yes le :		
Avis staff du 20/11/2018 : réponse on injected and nopr-injected 7/12/2018, injection of InjT1 et InjT3 are subjected			

Dose ? Volume ?

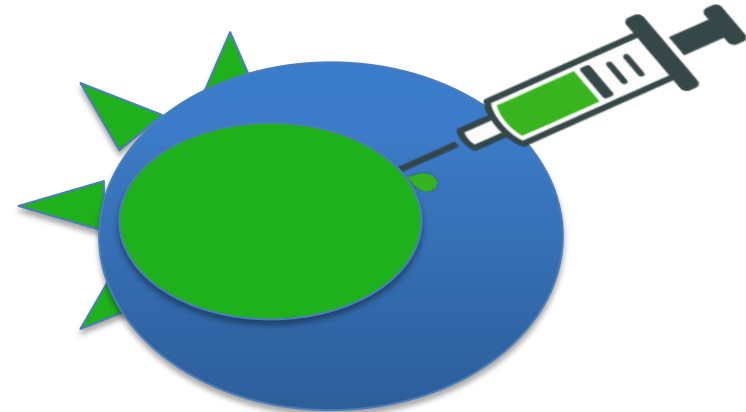
Dose :

X mg / kg of body weight ? Y mg/cm of tumor ?

Volume injected ? ratio of tumor size to volume of drug injected ?

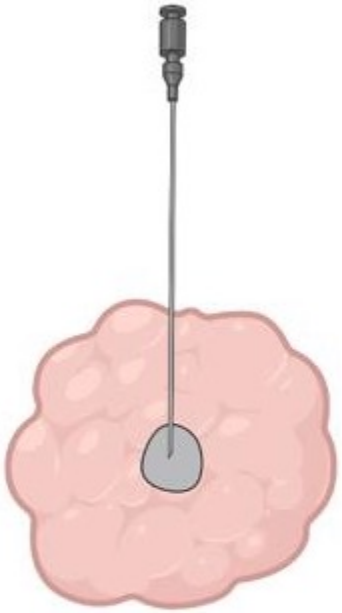


High concentration

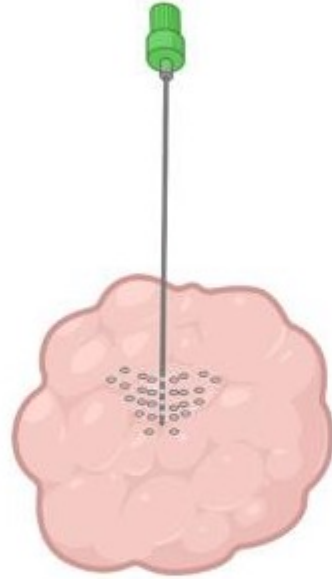


Low concentration

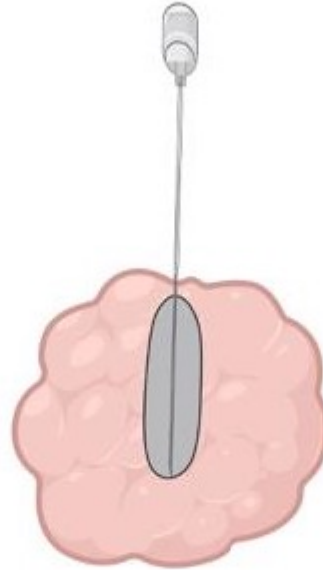
Devices for direct intratumoral immunotherapy



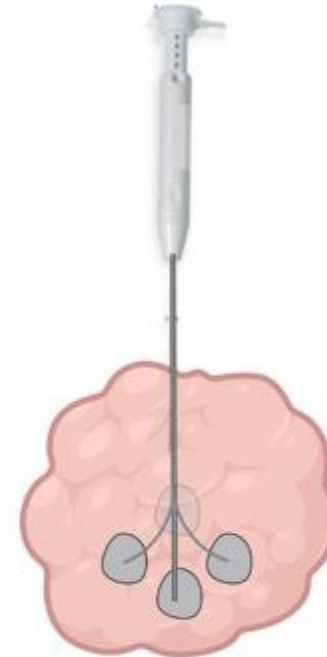
**Straight
Chiba needle
18-27G**



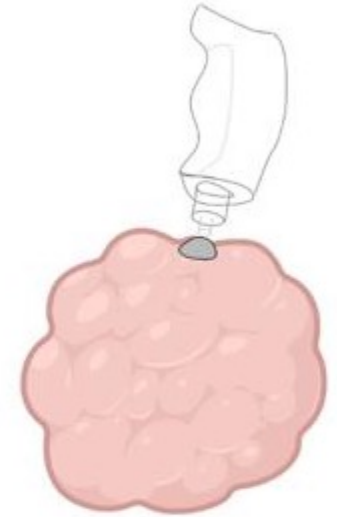
**Multiperforated
ProFusion
19-25G**



**Microporous catheter
Twin Star
27G**



**Multi-tine needle
QuadraFuse
18G**



**Jet Injector
Actranza™ Lab
Needle free**

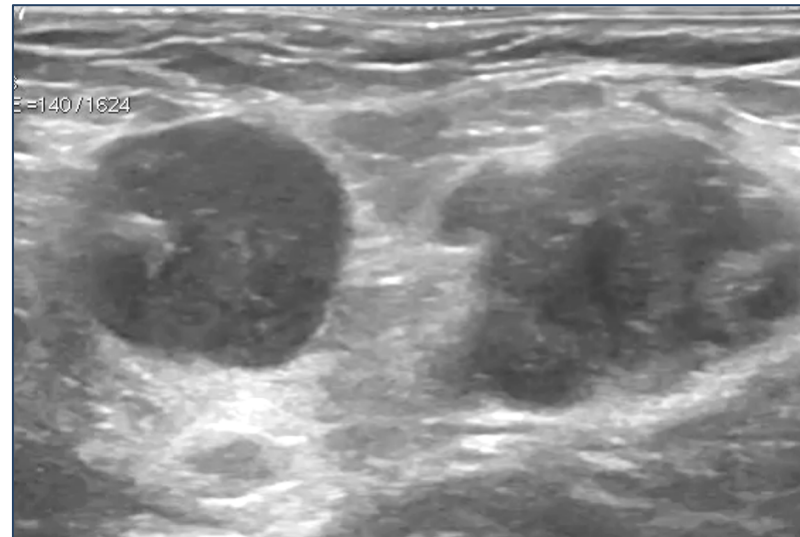
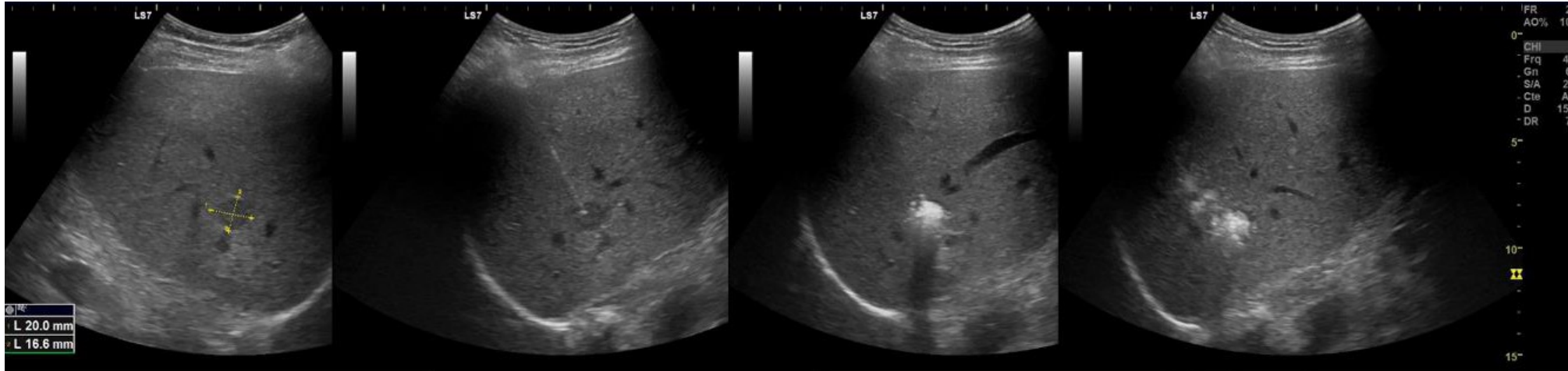
- Drug delivery assessment

US hardly allows for evaluation of treatment "diffusion"

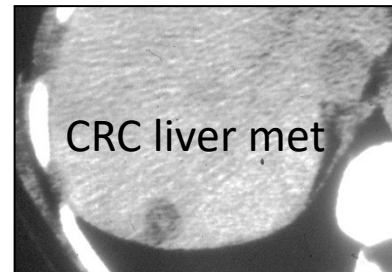
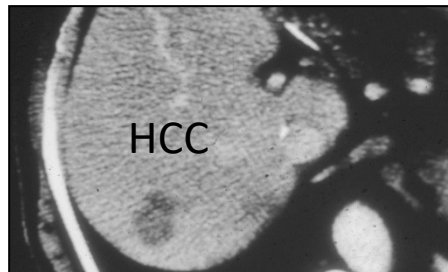
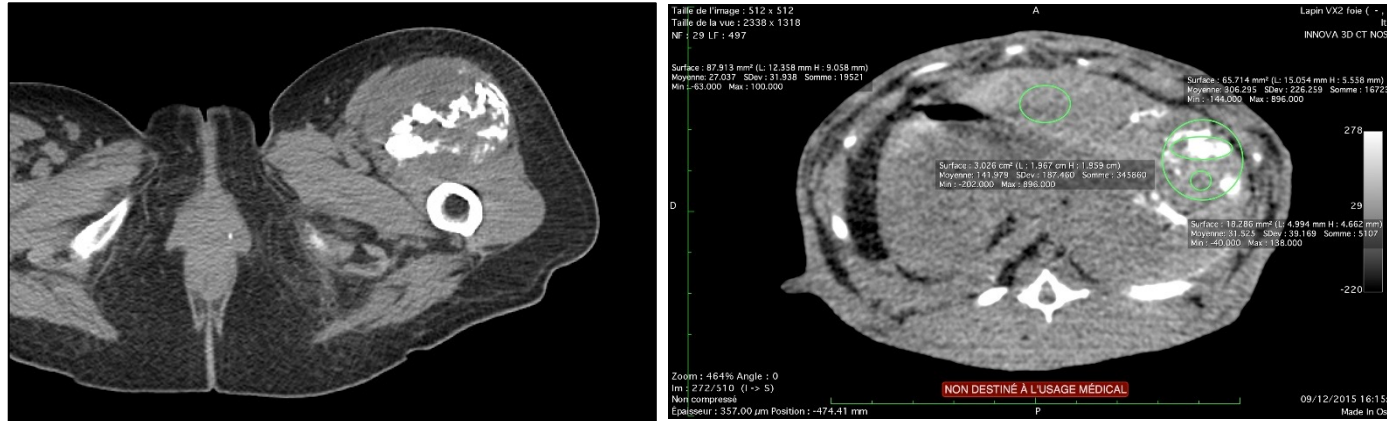
local administration of immunotherapies using interventional radiology

60-year old-patient, with colorectal cancer liver metastasis.

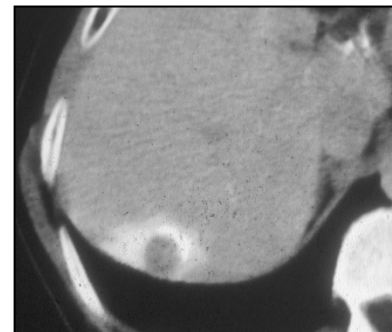
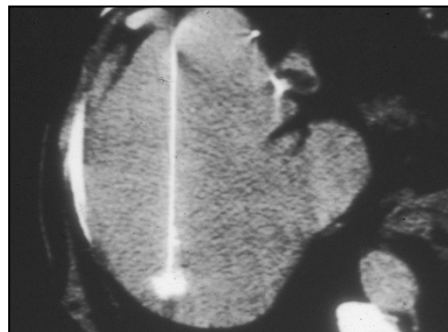
Ultrasound guided injection with a 22G needle.



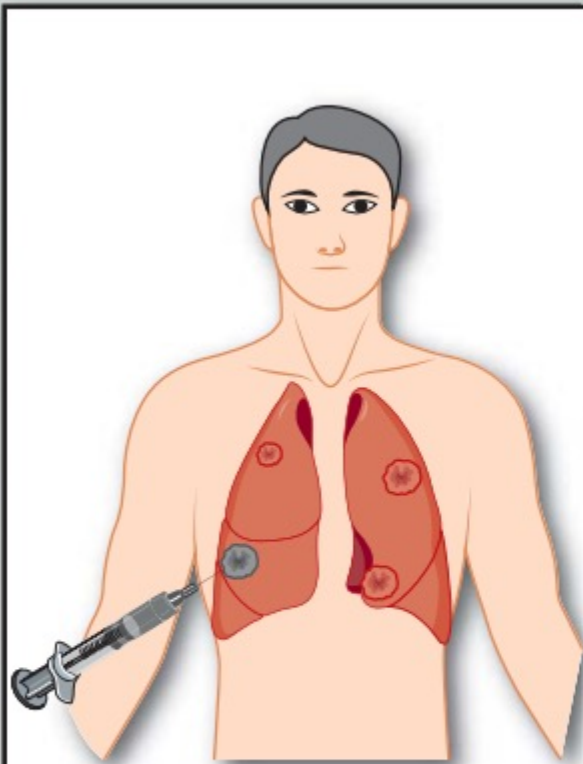
- **Drug delivery assessment**
CT allows for volumetric evaluation of treatment "diffusion"
as far as the compound injected is radio-opaque



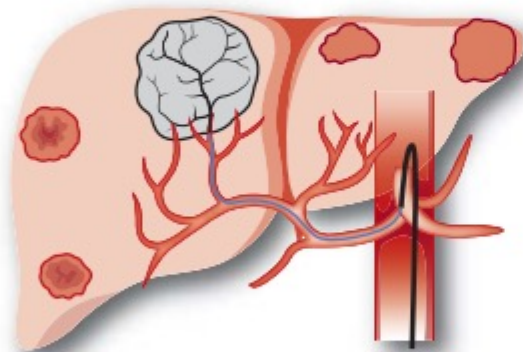
IT injection of chemotherapy + contrast medium



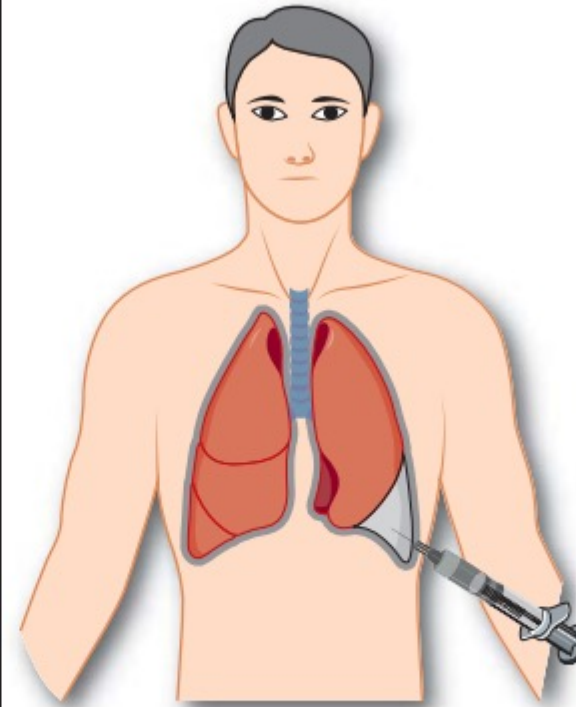
potential administration routes for local immunotherapy



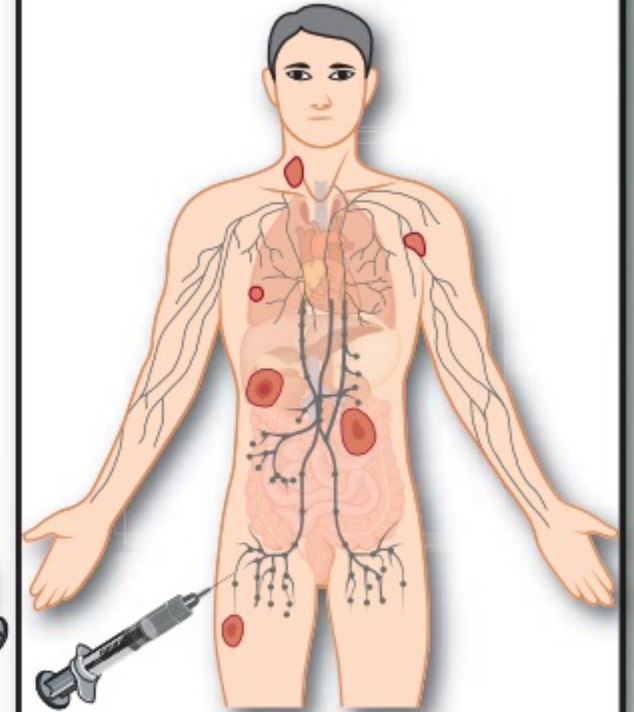
Percutaneous



Intra-arterial



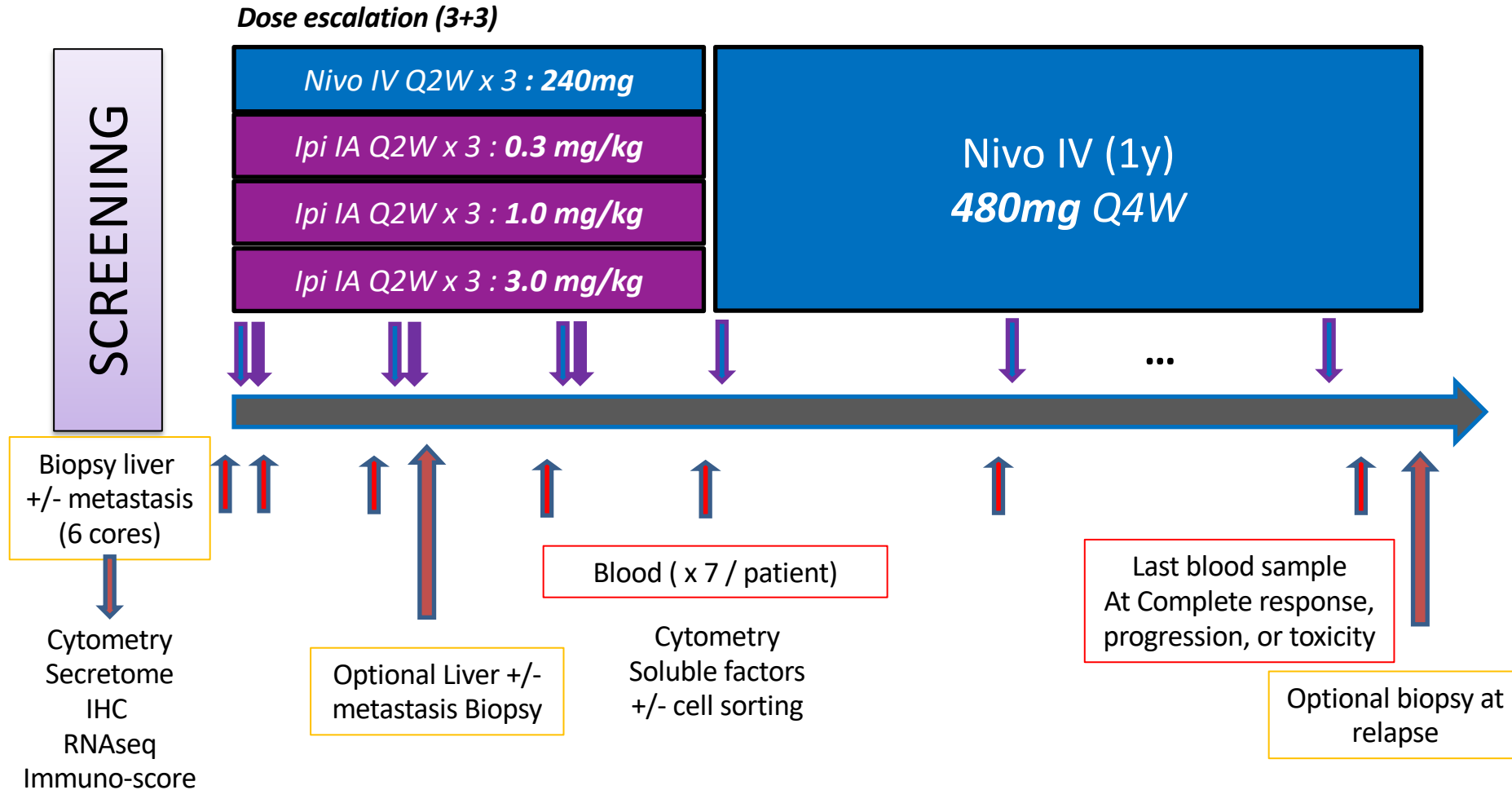
Intracavitary



Lymphatic

*Hepatic **I**pilimumab Intra-**A**rterally and **N**ivolumab Intra**V**enously for advanced HCC*

HIPANIV study scheme



Pickering emulsions with ethiodized oil and nanoparticles for slow release of intratumoral anti-CTLA4 immune checkpoint antibodies

JITC 2020

Lambros Tselikas^{1,2}, Thierry de Baere,¹ Thomas Isoardo,² Sandrine Susini,² Karine Ser-Le Roux,³ Mélanie Polrot,³ Julien Adam,⁴ Mathieu Rouanne,² Laurence Zitvogel,⁵ Laurence Moine,⁶ Frédéric Deschamps,¹ Aurélien Marabelle^{2,7}

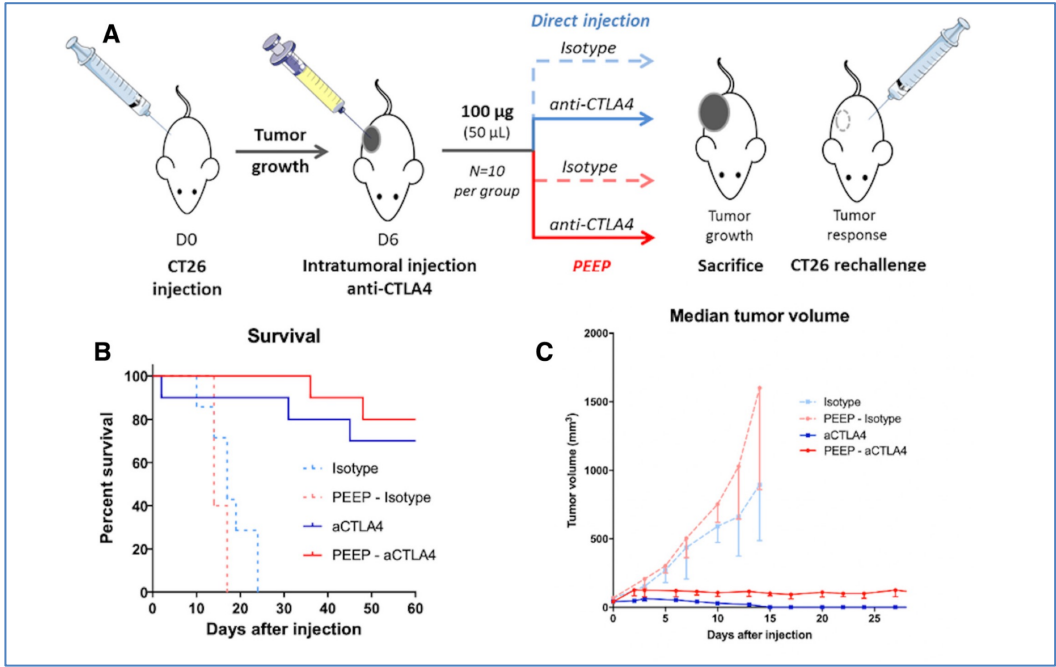
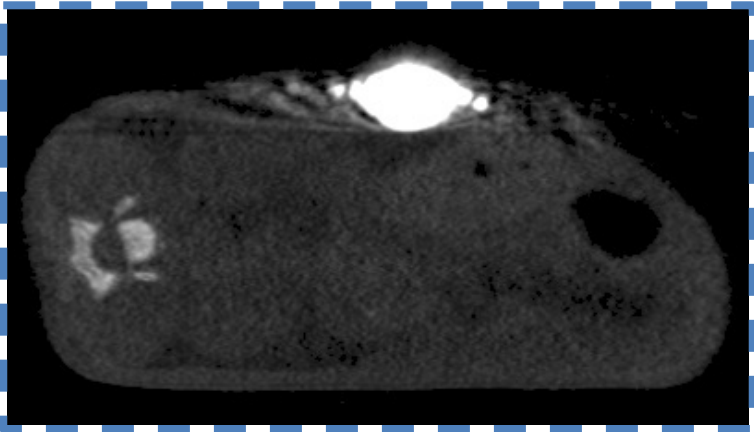
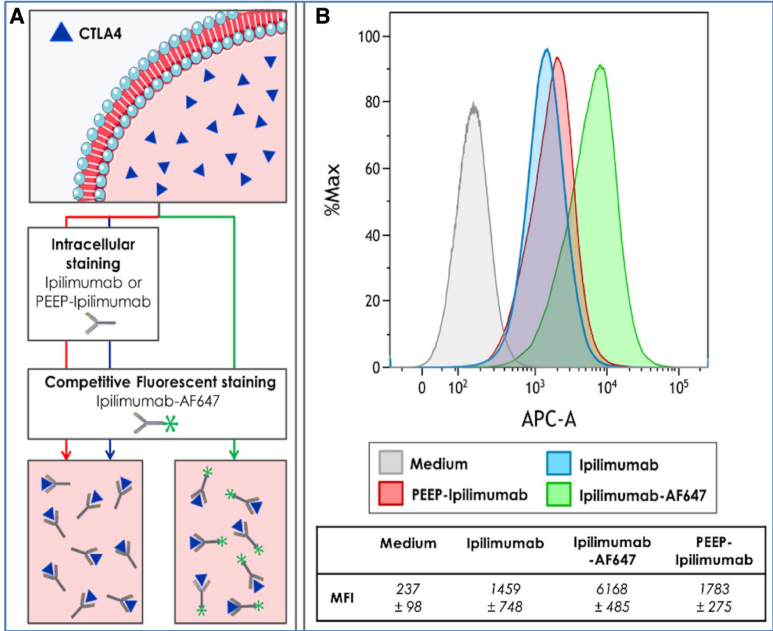
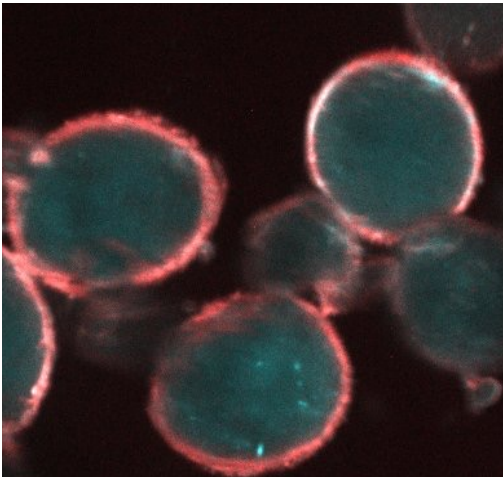
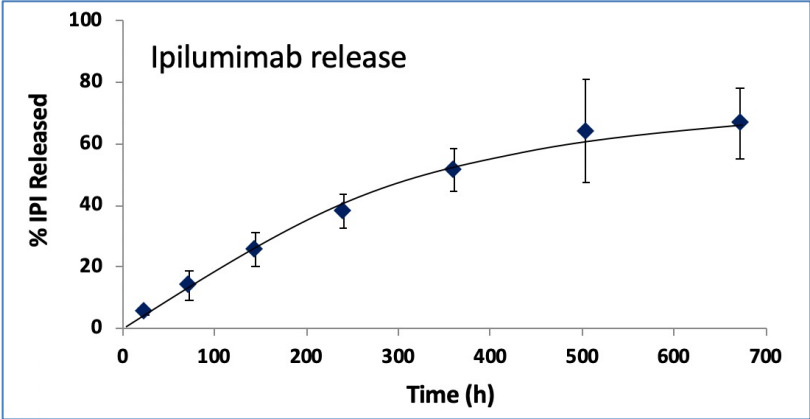
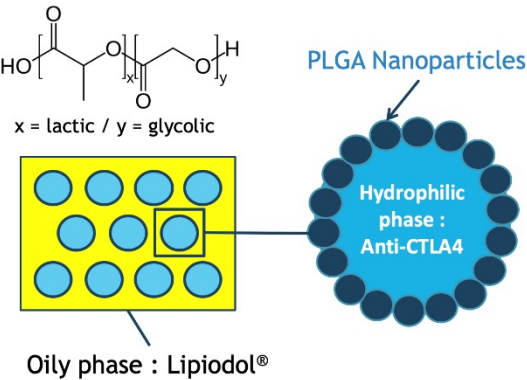
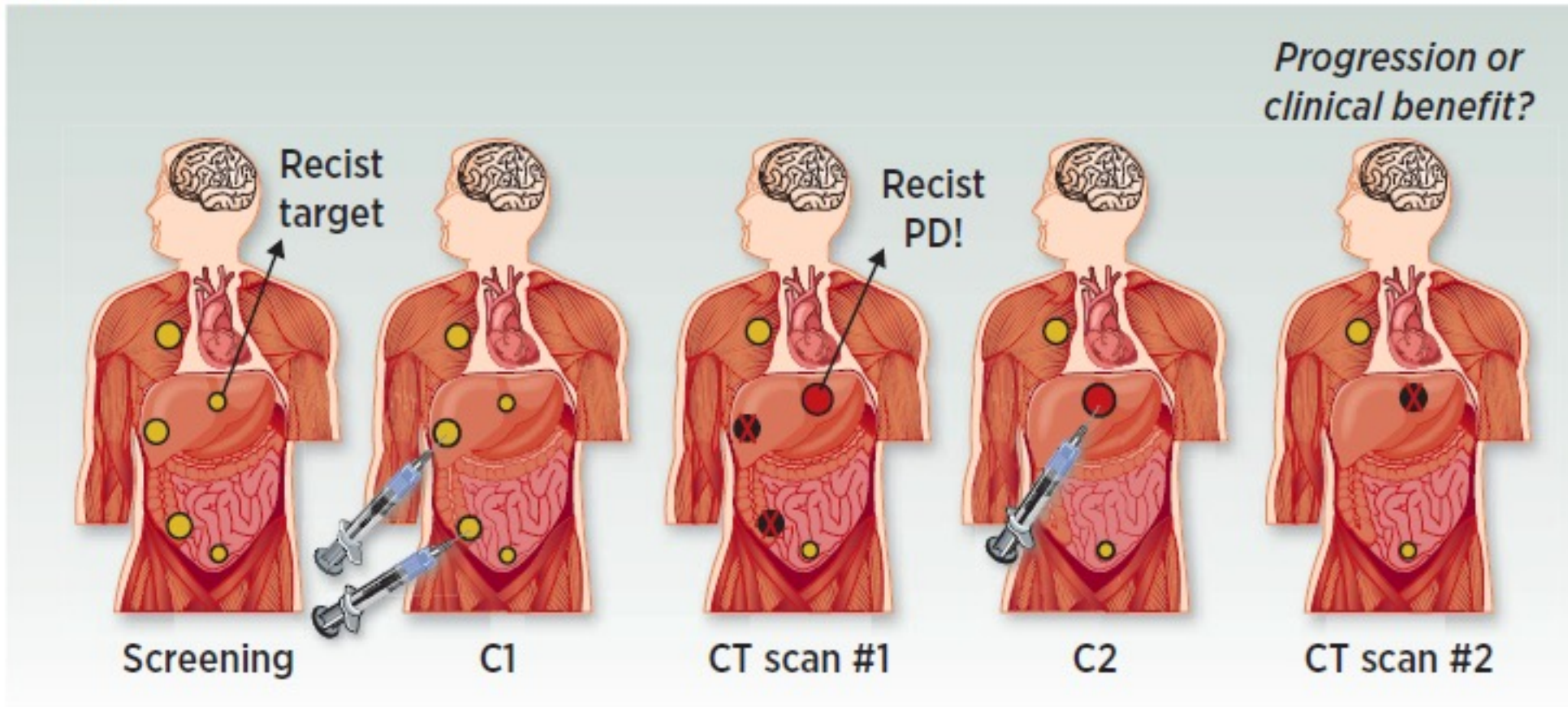


Illustration of a clinical case with objective clinical benefit which would not be captured by RECIST1.1 radiological criteria assessment.

Figure 5:

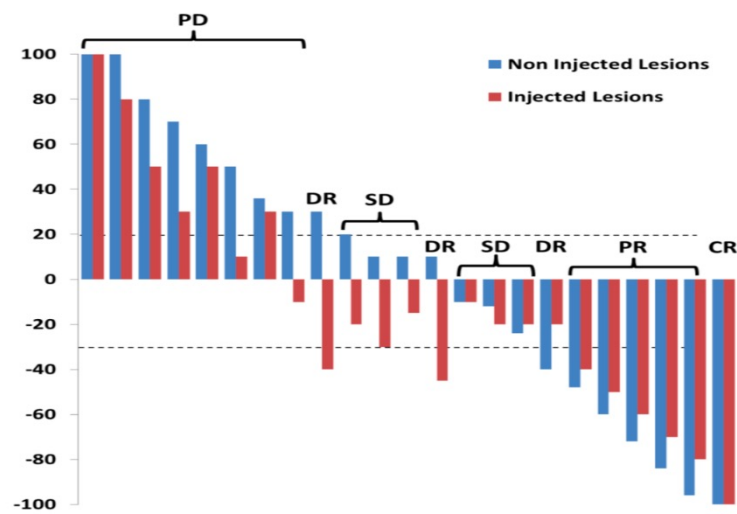


Starting the fight in the tumor:
expert recommendations for the development
of human intratumoral immunotherapy (HIT-IT)

A. Marabelle^{1*}, R. Andtbacka², K. Harrington³, I. Melero⁴, R. Leidner⁵, T. de Baere⁶, C. Robert⁷,
P. A. Ascierto⁸, J.-F. Baurain⁹, M. Imperiale¹⁰, S. Rahimian¹¹, D. Tersago¹², E. Klumper¹³, M. Hendriks¹⁴,
R. Kumar¹⁵, M. Stern¹⁶, K. Öhrling¹⁷, C. Massacesi¹⁸, I. Tchakov¹⁹, A. Tse²⁰, J.-Y. Douillard²¹, J. Tabernero²²,
J. Haanen²³ & J. Brody²⁴

(Ann Oncol. 2018;29:2163-2174)

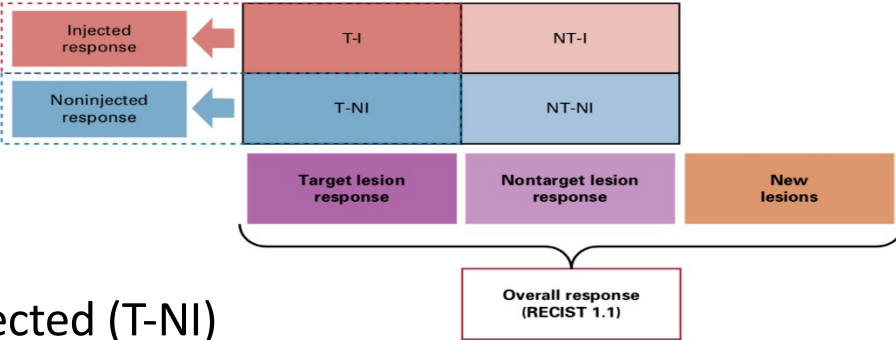
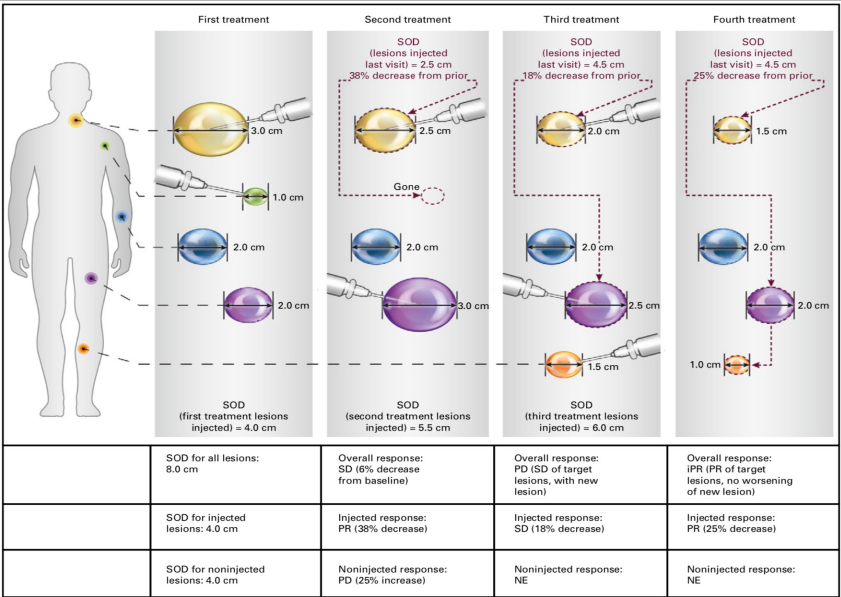
Waterfall Plots for HIT-IT



target injected (T-I)
nontarget injected (NT-I)

Response Criteria for Intratumoral
Immunotherapy in Solid Tumors: itRECIST

Gregory V. Goldmacher, MD, PhD, MBA¹; Anuradha D. Khilnani, MD¹; Robert H. I. Andtbacka, MD²; Jason J. Luke, MD³;
F. Stephen Hodi, MD⁴; Aurelien Marabelle, MD, PhD⁵; Kevin Harrington, MBBS, PhD⁶; Andrea Perrone, MD¹; Archie Tse, MD, PhD⁷;
David C. Madoff, MD⁸; and Lawrence H. Schwartz, MD⁹ (JCO. 2020; 38,23 : 2667)



target noninjected (T-NI)
non- target noninjected (NT-NI)

Interventional radiology for local immunotherapies techniques, perspectives and challenges

INTERVENTIONAL RADIOLOGY FOR LOCAL IMMUNO-ONCOLOGY		
Already available	Work in progress	To develop
Accurate targeting (almost any organ)	Drug distribution evaluation	Drug deposition quantification
Safe pathway	Specific material for local administration	Real time functional imaging
Real (or almost) time per procedural imaging	Alternative routes (other than direct percutaneous intratumoral)	Bed-side immune infiltration quantification (on biopsies)
Sequential, multitarget tissue sampling	Target tagging for tracking over time	IR local treatments and local immunotherapies

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

A. Marabelle^{1*}, R. Andtbacka², K. Harrington³, I. Melero⁴, R. Leidner⁵, T. de Baere⁶, C. Robert⁷,
P. A. Ascierto⁸, J.-F. Baurain⁹, M. Imperiale¹⁰, S. Rahimian¹¹, D. Tersago¹², E. Klumper¹³, M. Hendriks¹⁴,
R. Kumar¹⁵, M. Stern¹⁶, K. Öhrling¹⁷, C. Massacesi¹⁸, I. Tchakov¹⁹, A. Tse²⁰, J.-Y. Douillard²¹, J. Tabernero²²,
J. Haanen²³ & J. Brody²⁴

Annals of Oncology

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

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

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

Anenestic Lesion
(not injected)

Enestic Lesion
(injected)

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

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.*

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

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

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.

Thank you

