Introduction to Intratumoral Therapy

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SITC 2019

Gustave Roussy Immunotherapy Program
Get a GRIP on Cancer

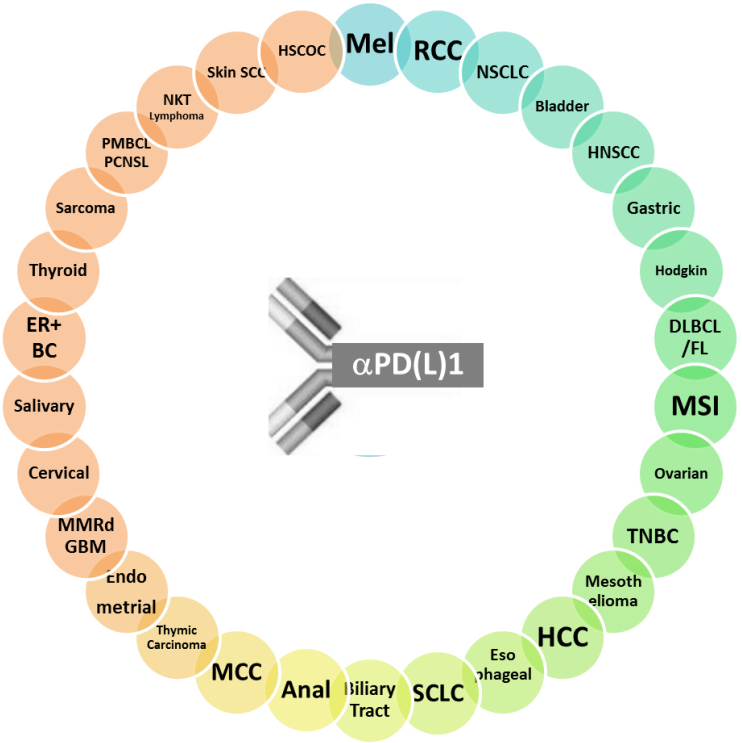
DISCLOSURES - *OVER THE LAST 5 YEARS (2014-2019)*

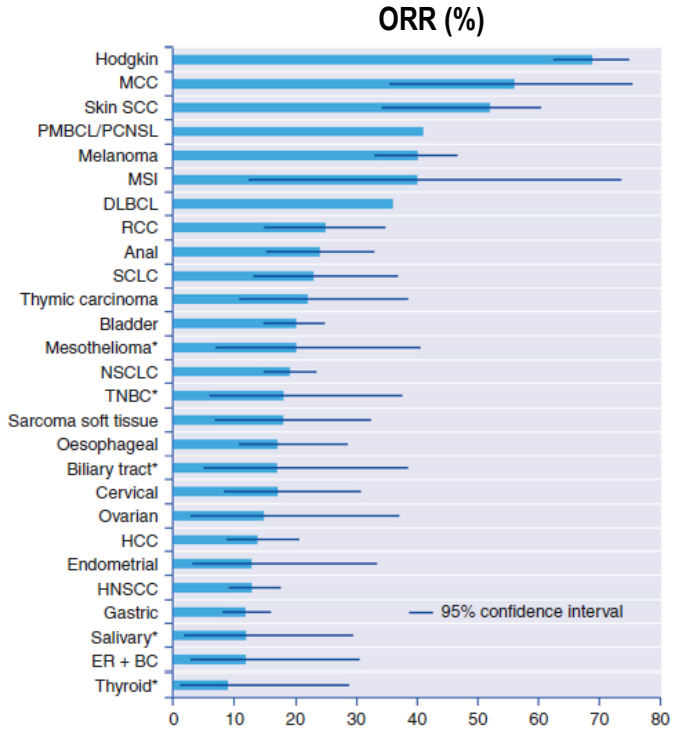
INSTITUTIONAL LINKS: Principal Investigator of Clinical Trials from the following companies: Roche/Genentech, BMS, Merck (MSD), Pfizer, Lytix pharma, Eisai, Astra Zeneca/Medimmune, Tesaro, Chugai, OSE immunotherapeutics, SOTIO, Molecular Partners. **Principal Investigator of the following academic trials**: ACSE NIVOLUMAB/NCT03012581 (funding INCa, Ligue contre le Cancer & BMS; sponsor Unicancer), ISI-JX/NCT02977156 (funding Transgene; sponsor Leon Berard Cancer Center), NIVIPIT/NCT02857569 (funding BMS; sponsor Gustave Roussy), PEMBIB/NCT02856425 (funding Boehringer Ingelheim; sponsor Gustave Roussy). **Sub-Investigator of Clinical Trials sponsored by the following companies:** Aduro Biotech, Agios Pharmaceuticals, Amgen, Argen-X Bvba, Arno Therapeutics, Astex Pharmaceuticals, Astra Zeneca, Aveo, Bayer Healthcare Ag, Bbb Technologies Bv, Beigene, Bioalliance Pharma, Biontech Ag, Blueprint Medicines, Boehringer Ingelheim, Bristol Myers Squibb, Ca, Celgene Corporation, Chugai Pharmaceutical Co., Clovis Oncology, Daiichi Sankyo, Debiopharm S.A., Eisai, Exelixis, Forma, Gamamabs, Genentech, Inc., Gilead Sciences, Inc, Glaxosmithkline, Glenmark Pharmaceuticals, H3 Biomedicine, Inc, Hoffmann La Roche Ag, Incyte Corporation, Innate Pharma, Iris Servier, Janssen , Kura Oncology, Kyowa Kirin Pharm, Lilly, Loxo Oncology, Lytix Biopharma As, Medimmune, Menarini Ricerche, Merck Sharp & Dohme Chibret, Merrimack Pharmaceuticals, Merus, Millennium Pharmaceuticals, Nanobiotix, Nektar Therapeutics, Novartis Pharma, Octimet Oncology Nv, Oncoethix, Oncomed, Oncopeptides, Onyx Therapeutics, Orion Pharma, Oryzon Genomics, Pfizer, Pharma Mar, Pierre Fabre , Rigontec Gmbh, Roche, Sanofi Aventis, Sierra Oncology, Taiho Pharma, Tesaro, Inc, Tioma Therapeutics, Inc., Xencor. **Gustave Roussy Research Grants** : Astrazeneca, BMS, Boehringer Ingelheim, Janssen Cilag, Merck, Novartis, Pfizer, Roche, Sanofi. **Non-Financial Support (drug supply to Gustave Roussy sponsored trials):** Astra Zeneca, Bayer, BMS, Boehringer Ingelheim, Johnson & Johnson, Lilly, Medimmune, Merck serono, NH TherAGuiX, Pfizer, Roche

PERSONAL LINKS: Member of Clinical Trial Scientific Committee: NCT02528357 (GSK), NCT03334617 (Astra Zeneca). **Member of Data Safety and Monitoring Board:** NCT02423863 (Oncovir, Inc.). **Scientific Advisory Boards :** Innate Pharma, Merck Serono, eTheRNA, Lytix pharma, Kyowa Kirin Pharma, Bayer, Novartis, BMS, Symphogen, Genmab, Amgen, Biothera, Nektar, GSK, Oncovir, Pfizer, Seattle Genetics, Flexus Bio, Roche/Genentech, OSE immunotherapeutics, Transgene, Gritstone, Merck (MSD), Cerenis, Protagen, Partner Therapeutics, Servier, Sanofi, Pierre Fabre, Molecular Partners, Medicxi.

Teaching/Speaker Bureau activities: Roche/Genentech, BMS, Merck (MSD), Merck Serono, Astra Zeneca/Medimmune, Amgen, Sanofi. **Scientific & Medical Consulting :** Roche, Pierre Fabre, Onxeo, EISAI, Bayer, Genticel, Rigontec, Daichii Sankyo, Imaxio, Sanofi, BioNTech, Corvus, GLG, Deerfield, Guidepoint Global, Edimark, System Analytics, imCheck, Sotio, Bioncotech, Molecular Partners, Pillar Partners, Boehringer Ingelheim, T3 Pharma. **Non-Financial Support (travel expenses):** Astra Zeneca, BMS, Merck (MSD), Roche. **Co-Founder & Share Holder:** PEGASCY SAS (Gustave Roussy Spin Off for Drug Repositioning). **Patent Issued (not licensed yet)**: "Humanized and Chimeric Monoclonal Antibodies to CD81", Stanford Office of Technology Licensing, 3000 El Camino Real, Bldg. 5, Suite 300, Palo Alto, CA 94306-2100. U.S. Application Serial No. 62/351,054. **Pre-Clinical and Clinical Research Grants (Institutional Funding):** Merus, BMS, Boehringer Ingelheim, Transgene, Fondation MSD Avenir. **Member of the following scholar societies**: European Society for Medical Oncology (ESMO), American Society for Clinical Oncology (ASCO), American Association for Cancer Research (AACR), European Academy for Tumor Immunology (EATI). Founder and president of the French society for Immunotherapy of Cancer (FITC). Member of the board of the Immuno-Oncology Group at the French Network of Comprehensive Cancer Centers (Unicancer). Member of the working group on rheumatic adverse events induced by cancer immunotherapies of the European League Against Rhumatoid Arthritis (EULAR). **Supervisory Board Member** of the Gustave Roussy Foundation. **Member of the Steering Committee** of the Immuno-Oncology Task Force at Unicancer. **Member of the Editorial Boards** of the European Journal of Cancer and ESMO IO Tech

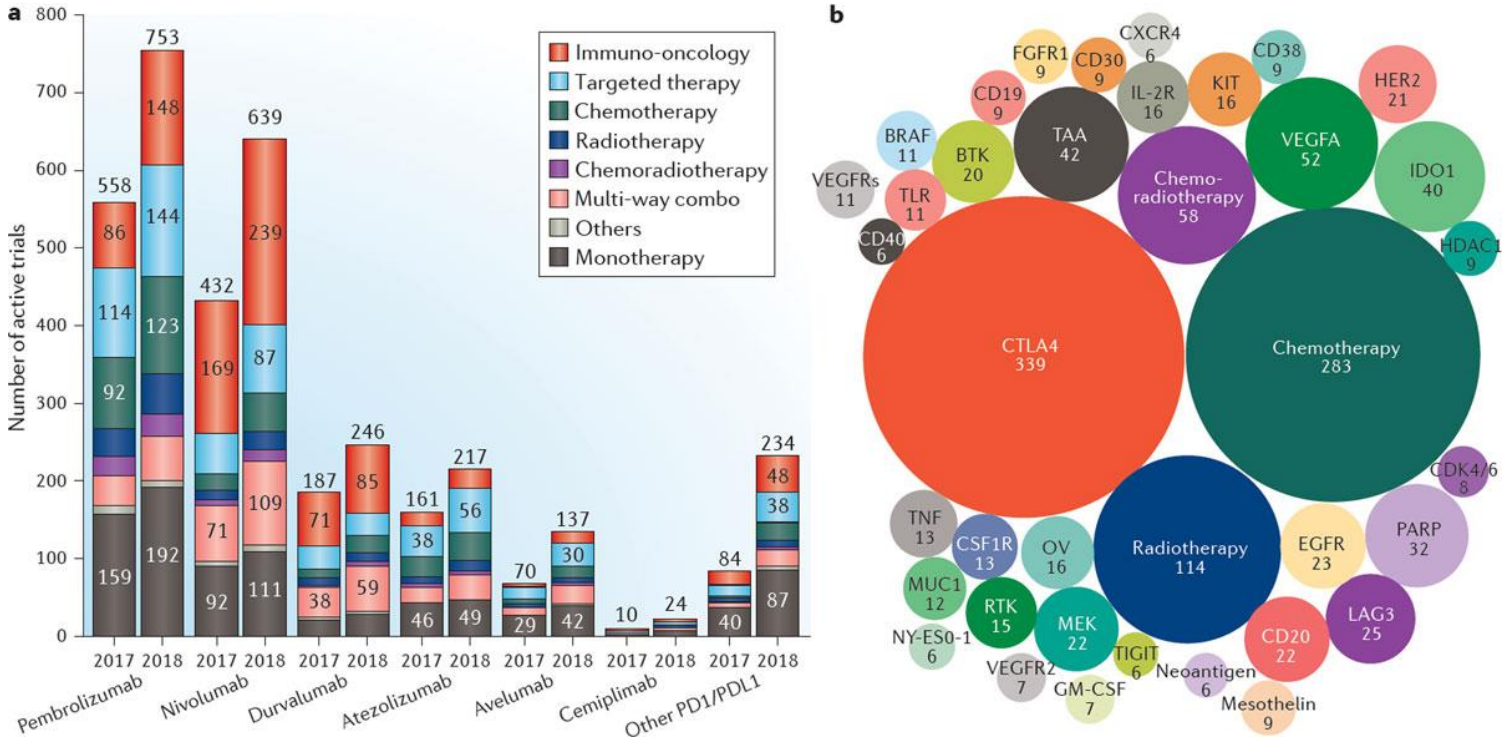
Cancers with Sensitivity to PD(L)1 Blockade: « PD-lomas »





Hirsch L, Zitvogel L, Eggermont A, Marabelle A. Br J Cancer 2019;120:3–5.

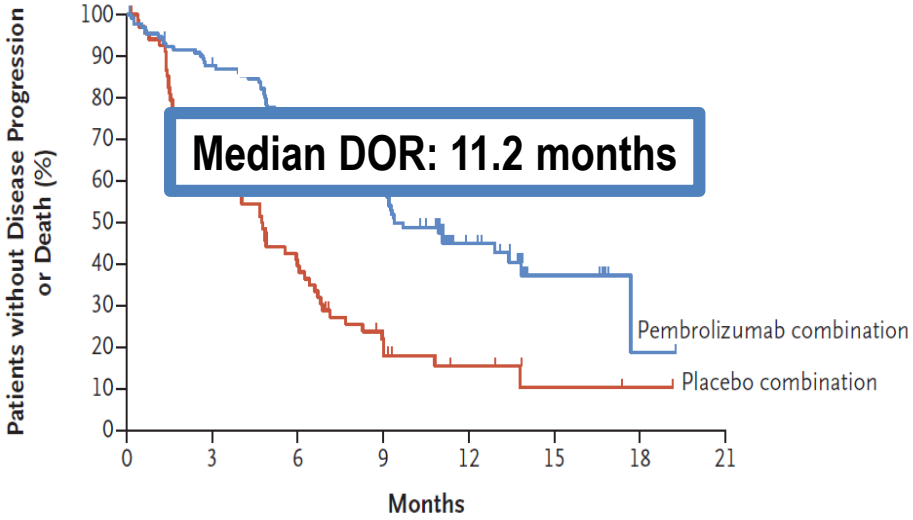
Clinical Trial Landscape for PD1/PDL1 Immune Checkpoint Blockade



Tang J, et al. Nat Rev Drug Discov 2018;17:854.

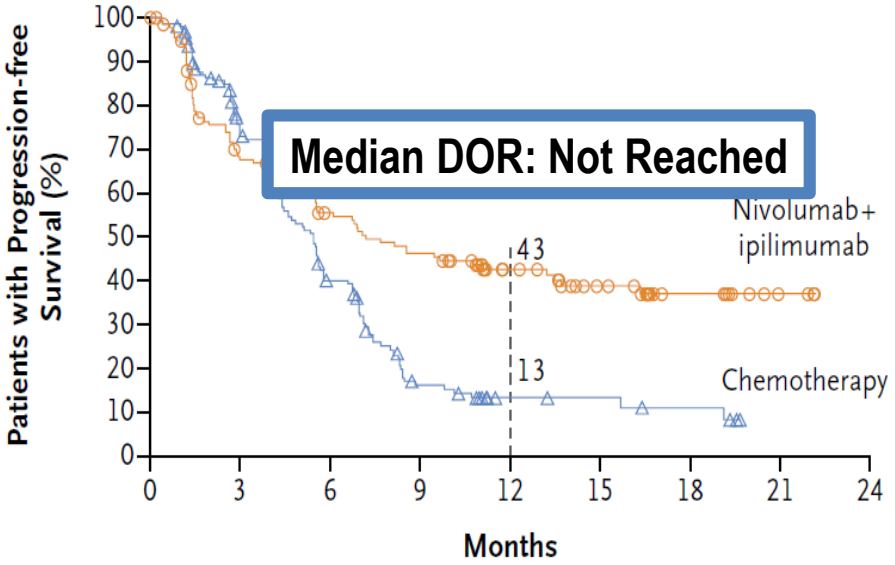
ANTI-PD1 COMBOS FOR I-O NAIVE NSCLC PATIENTS

+CHEMO



Gandhi L., et al. (2018). N. Engl. J. Med. *378*, 2078–2092.

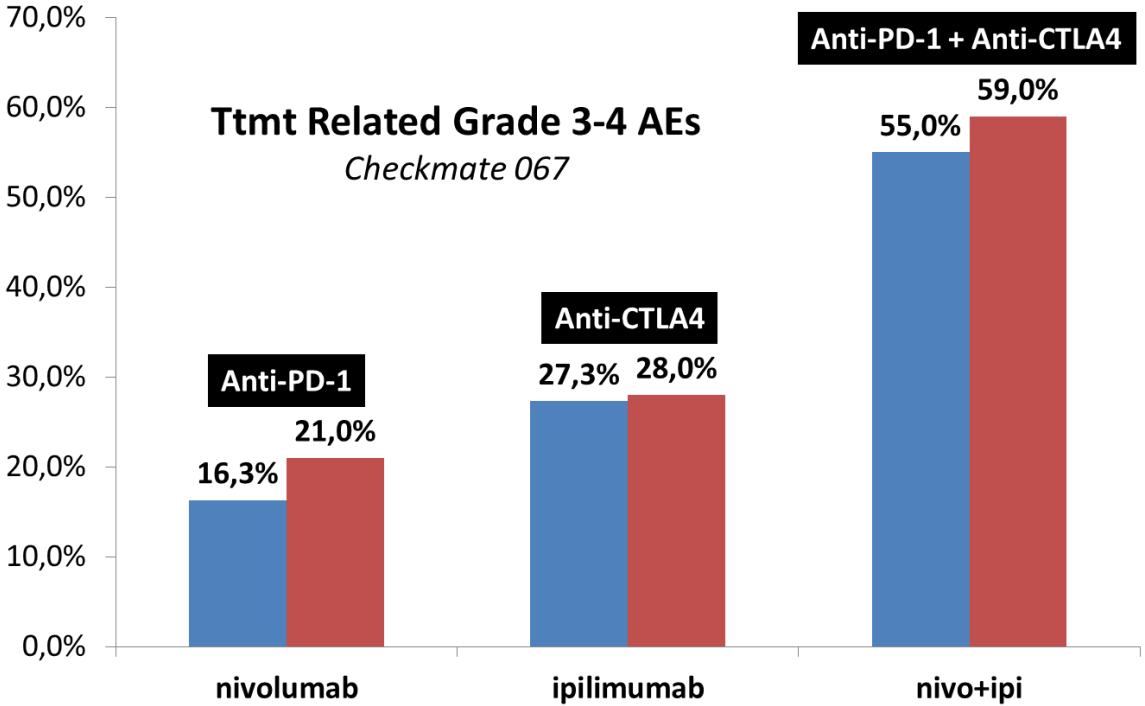
+ANTI-CTLA-4



Hellmann M.D., et al. (2018). N. Engl. J. Med. *378*, 2093–2104.

Limit = Immune Related Adverse Events

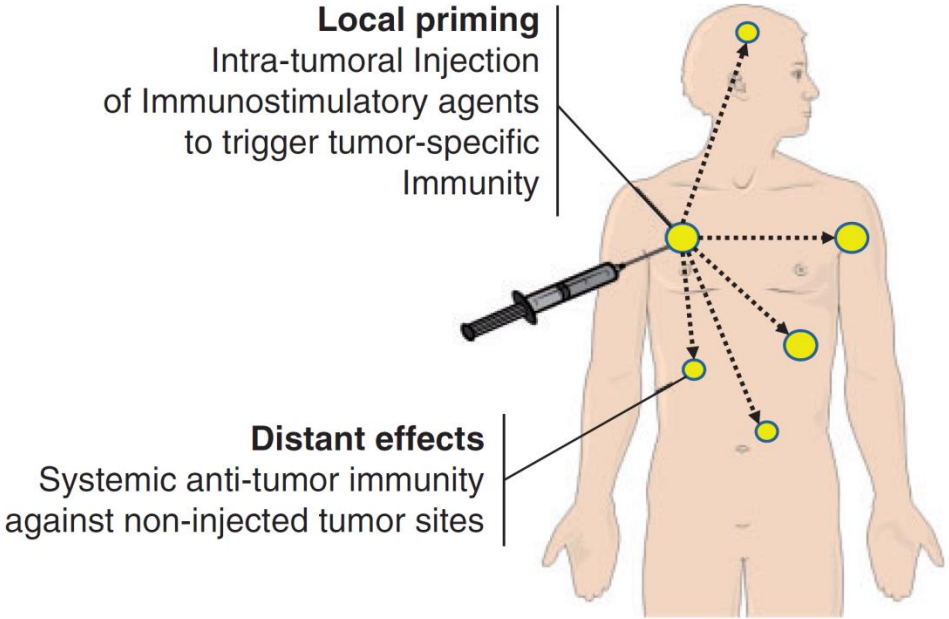
On-target / *Off-tumor* Effects



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

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

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

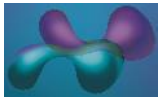


Marabelle, A. et al. (2017). Ann. Oncol. 28, xii33-xii43.

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

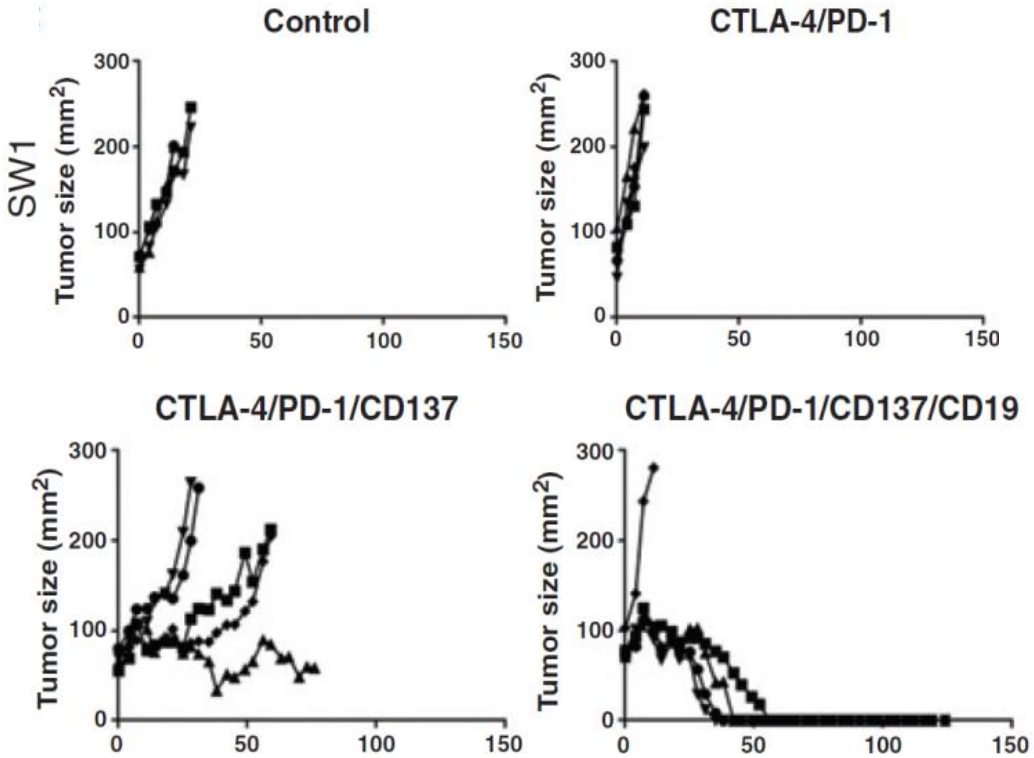
Marabelle, A., Tselikas, L., de Baere, T., and Houot, R. (2017). Ann. Oncol. *28*, xii33-xii43.



Cancer as a +/- Unstable Equilibrium

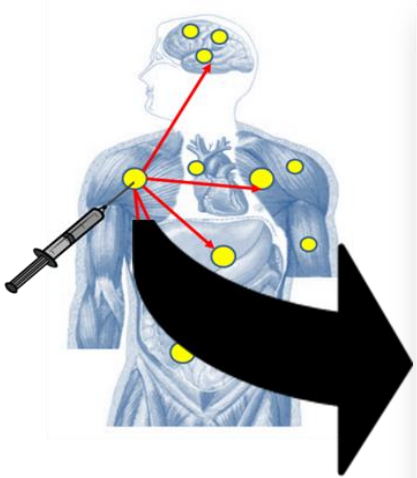
Cracking the Code of Intratumoral Immune Tolerance

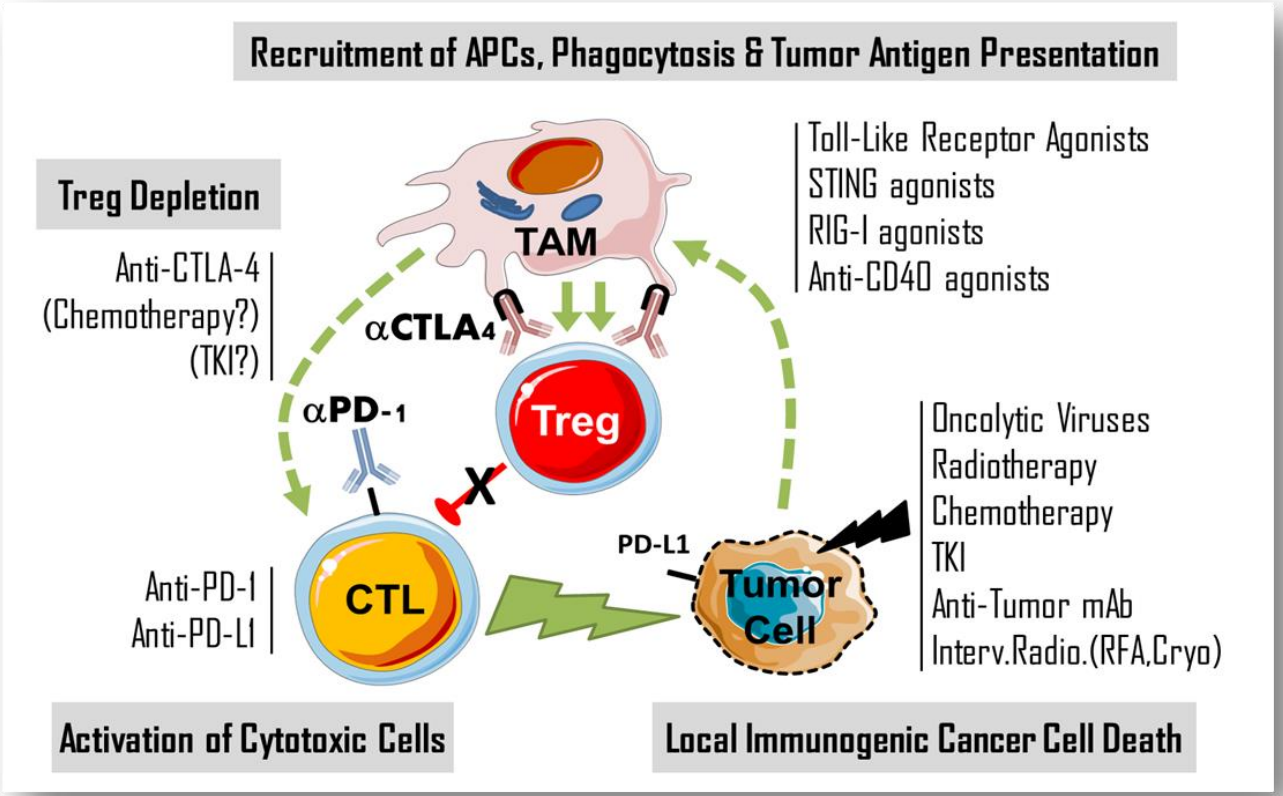
Intratumor Injections



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

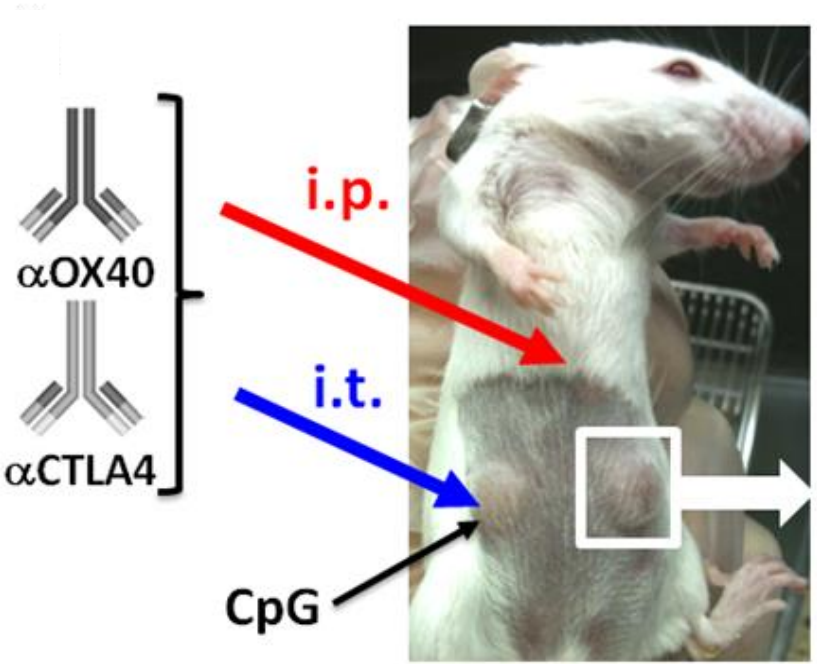
Potential Combinations for *In situ Priming* of Anti-Tumor Immunity

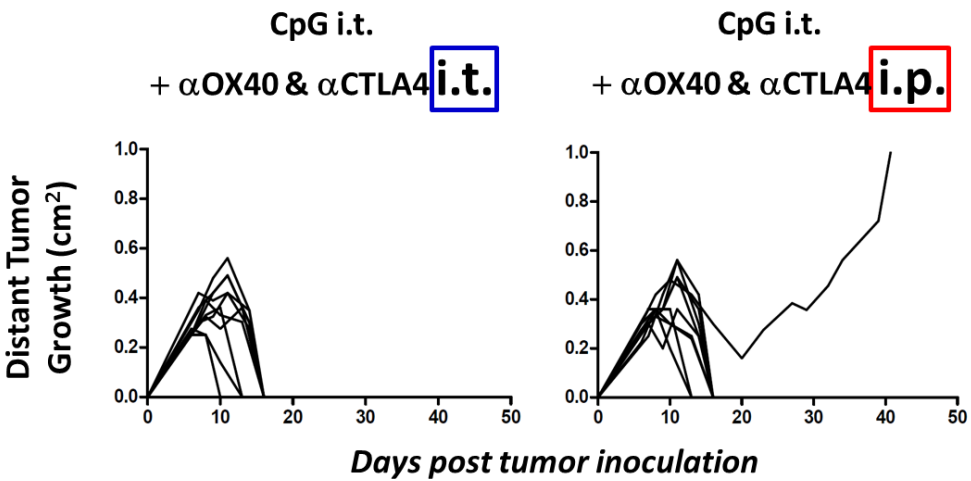




Marabelle, A., Tselikas, L., de Baere, T., and Houot, R. (2017). Ann. Oncol. *28*, xii33-xii43.

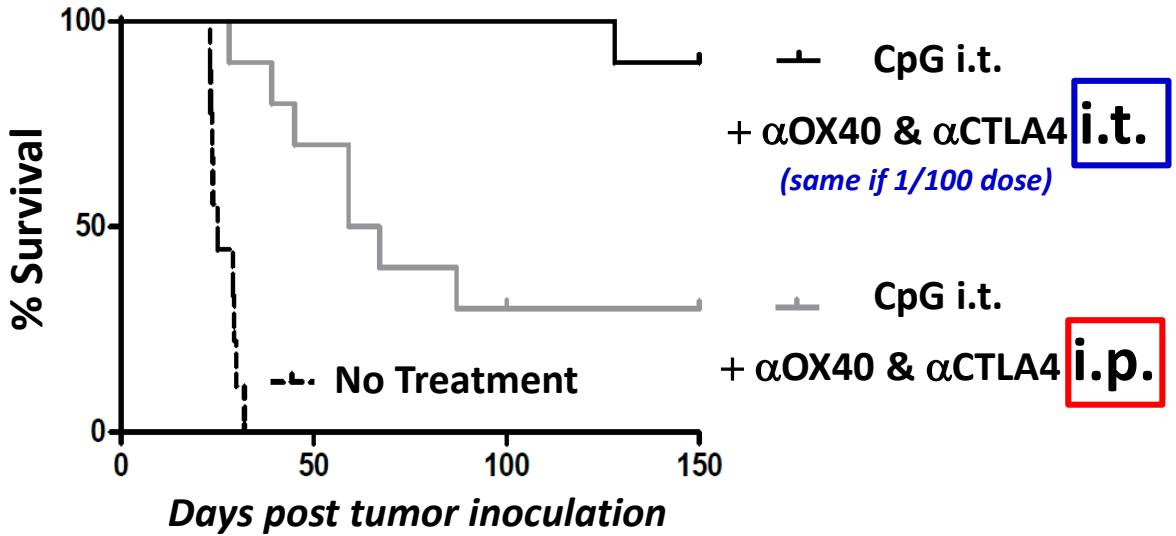
Systemic vs Local Immunomodulation: Effect on Contra-Lateral Tumor Growth





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

Intra-tumoral immunomodulation
Works better than Systemic immunomodulation



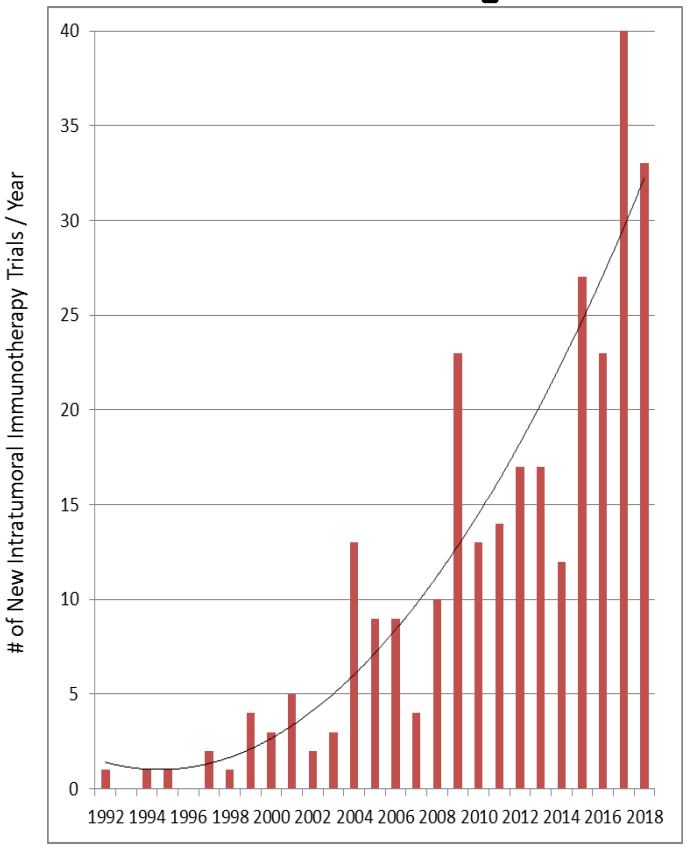
Marabelle A, et al. J Clin Invest 2013; Jun 3; 123:2447–63.

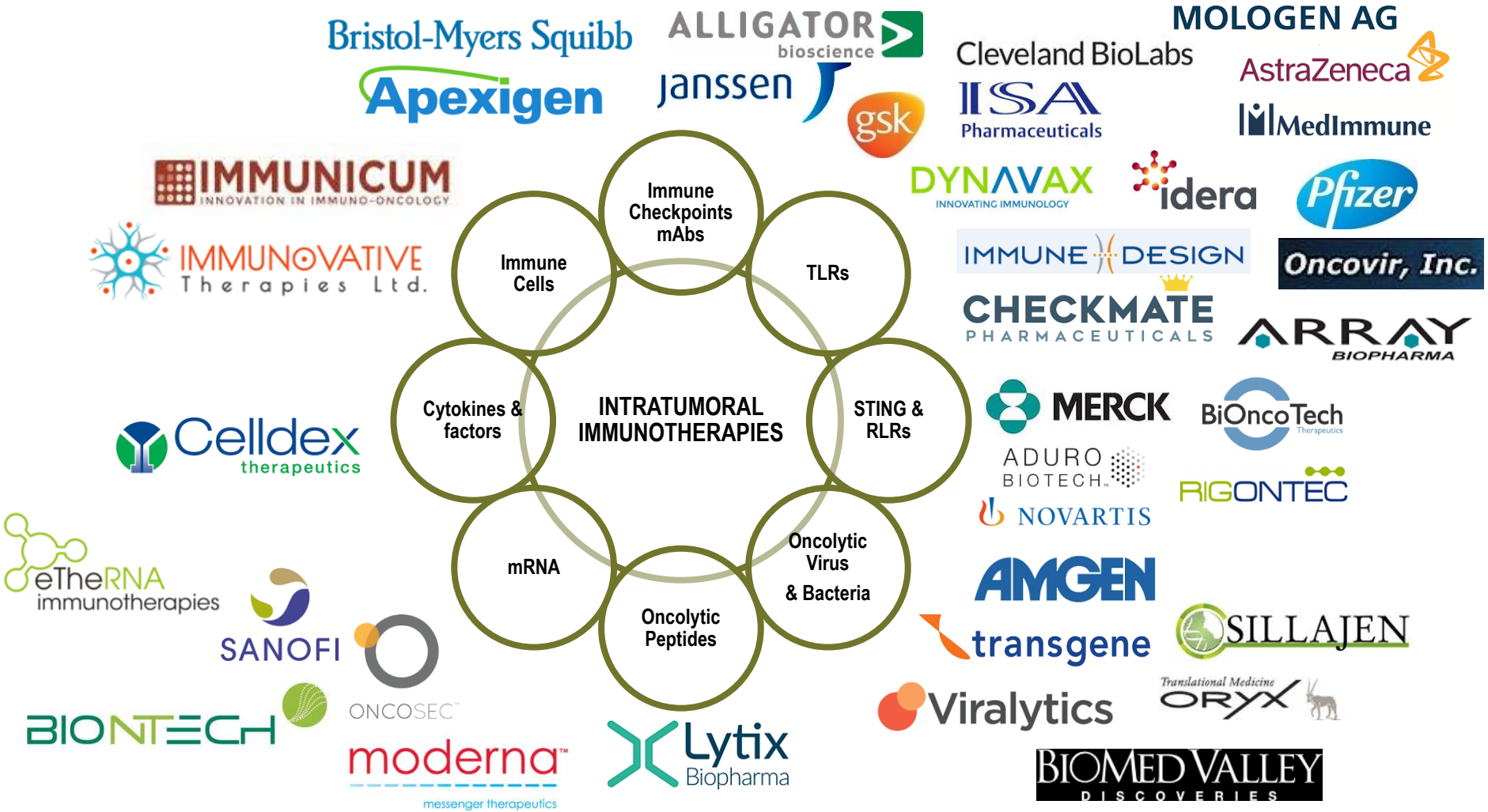
HIT-IT: Usual Skepticism

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

Number of New Intratumoral Immunotherapy Trials / Year

(clinicaltrials.gov)

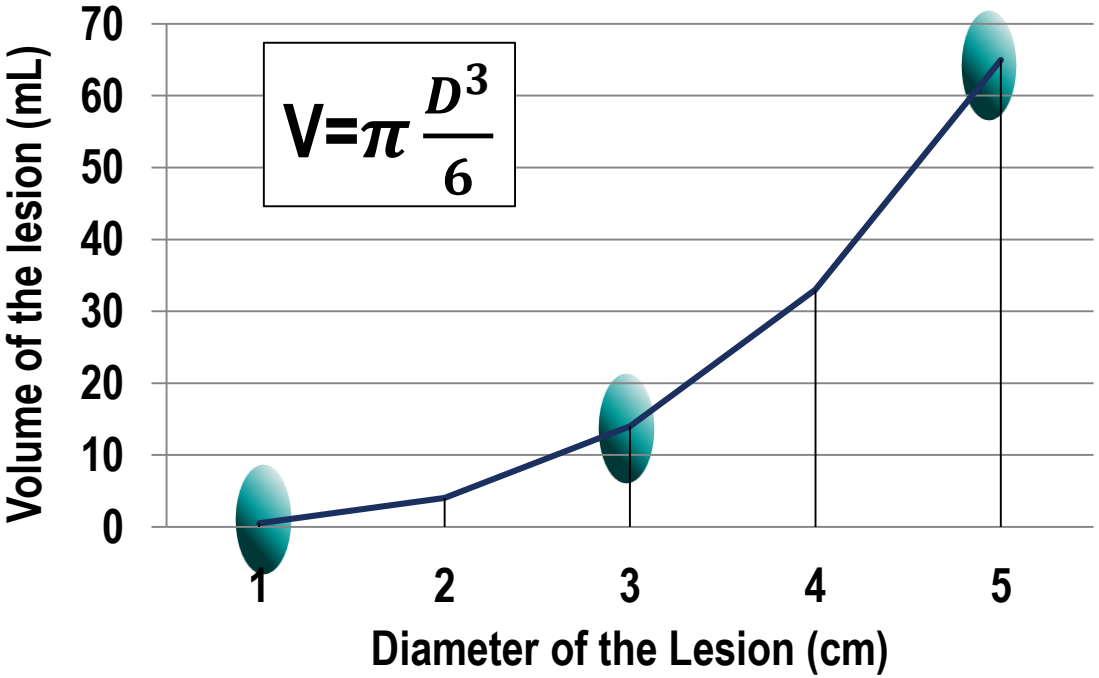


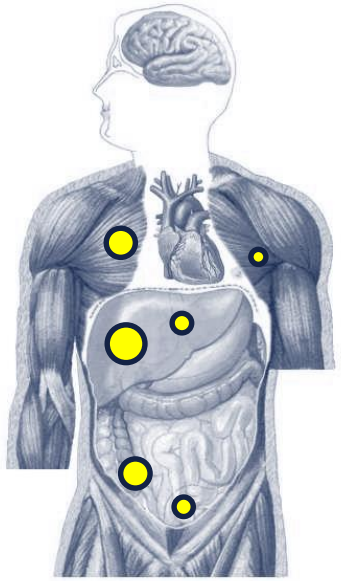

Bristol-Myers Squibb
Apexigen
ALLIGATOR bioscience
Janssen
gsk
MOLOGEN AG
Cleveland BioLabs
ISA Pharmaceuticals
AstraZeneca
MedImmune
IMMUNICUM
INNOVATION IN IMMUNO-ONCOLOGY
IMMUNOVATIVE Therapies Ltd.
DYNAVAX
INNOVATING IMMUNOLOGY
idera
Pfizer
IMMUNE DESIGN
Oncovir, Inc.
CHECKMATE PHARMACEUTICALS
ARRAY BIOPHARMA
Immune Checkpoints mAbs
TLRs
Immune Cells
Cytokines & factors
INTRATUMORAL IMMUNOTHERAPIES
STING & RLRs
mRNA
Oncolytic Virus & Bacteria
Oncolytic Peptides
Celldex therapeutics
MERCK
BiOncoTech Therapeutics
ADURO BIOTECH
RIGONTEC
NOVARTIS
eTheRNA immunotherapies
SANOFI
AMGEN
transgene
SILLAJEN
BIONTECH
ONCOSEC
moderna
messenger therapeutics
Lytix Biopharma
Viralytics
Translational Medicine ORYX
BIOMED VALLEY DISCOVERIES

HIT-IT: Actual Challenges

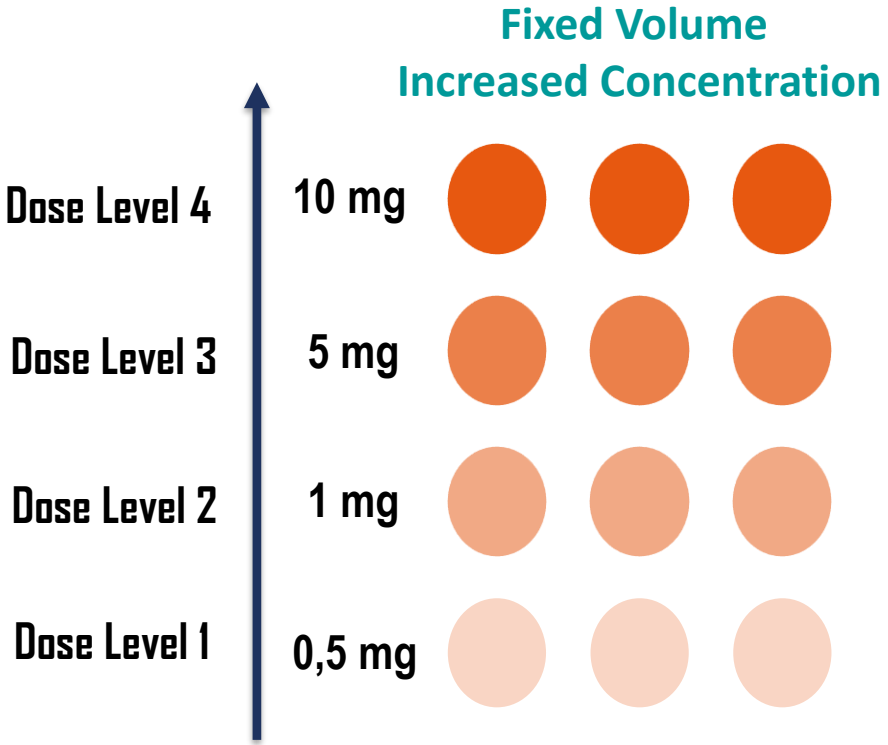
- Dose
- Regimen
- Efficacy Assessment
- PK/PD
- Trial Designs, MTDs & DLTs

How Do We Determine the Right Dose for HIT-IT ?

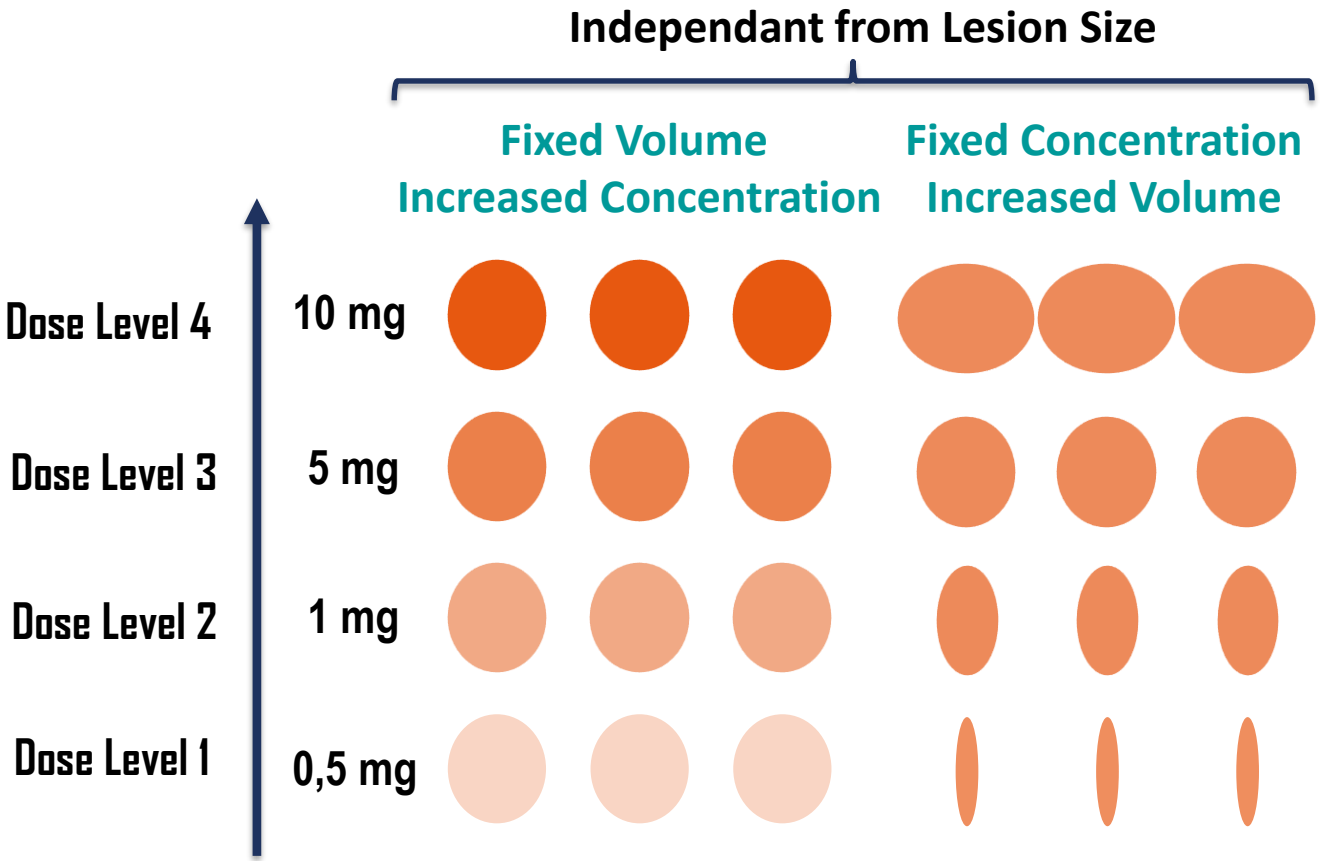




How Do We Determine the Right Dose for HIT-IT ?



How Do We Determine the Right Dose for HIT-IT ?



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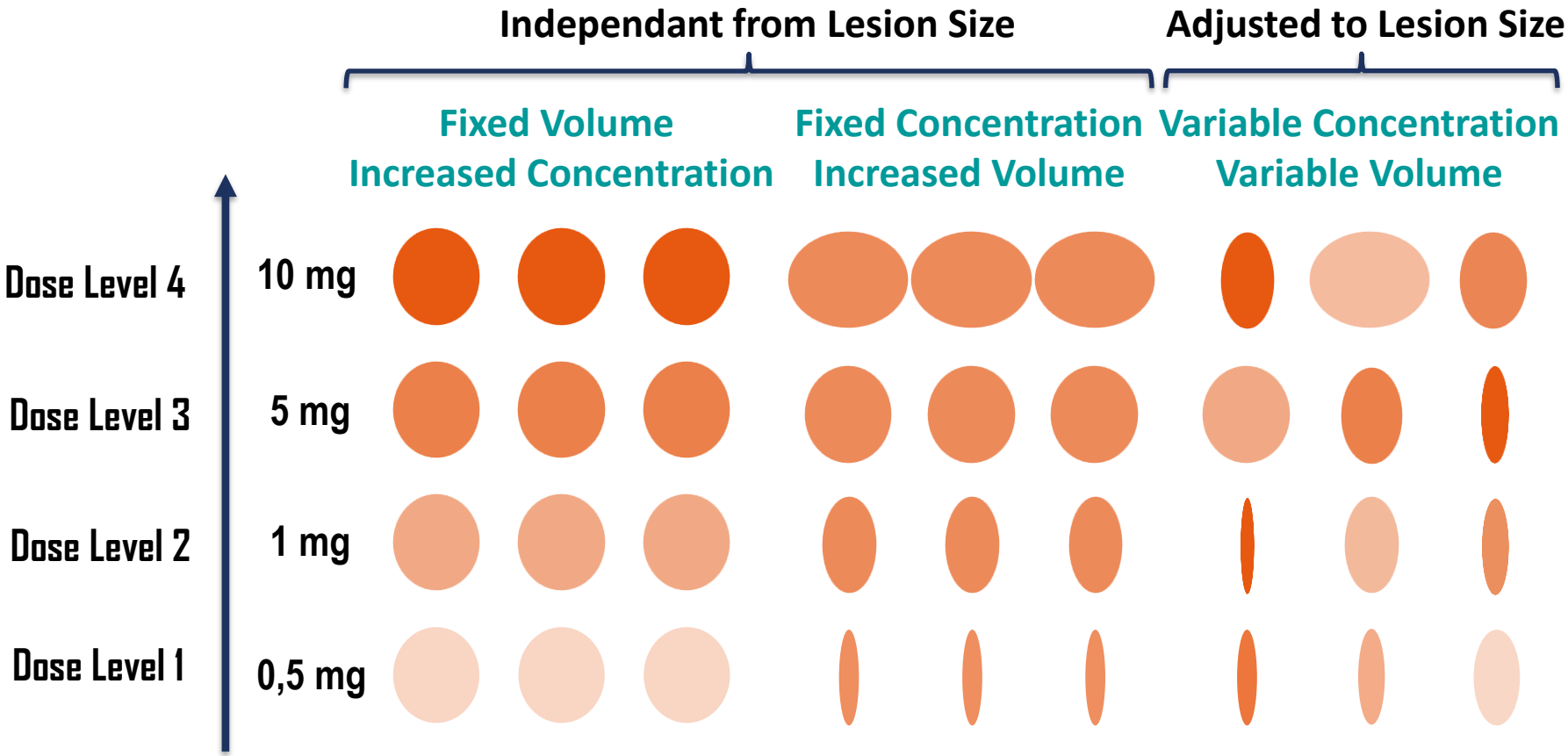


Trial Designs, MTDs & DLTs

- **Dose escalation to reach MTD or Optimal Biological Dose ?** ➔ ***how do you define OBD??***
- **PD is key !** ➔***How much PD data can you get out of a 3+3 design?***
- **Are Grade 3/4 dose-related, lesion-related or patient related (DLTs)?** ➔ ***Better define DLT criteria***

Which Regimen for HIT-IT ?

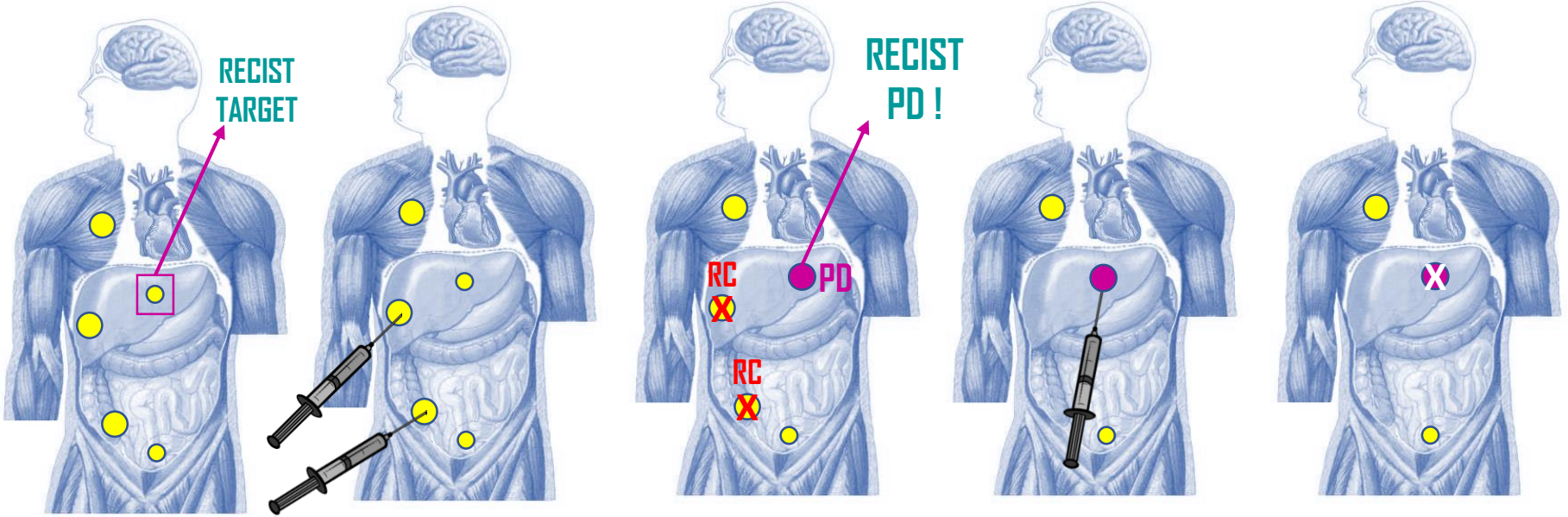
- **Q2W/Q3W regimen: based on recovery for white blood cells & PK**
- ***During an infection, the immune system is not working one day every 3 weeks***
- **Half life & PD effects: rather short with agonists**
- **Tachyphylaxia over time +/- ADAs**

PK/PD: what does matter ? What dose matters ?

- PK: who cares if low systemic doses ?
- PK vs local bioavailability (*tumor or draining LN?*)
- PD+++: target expression & target engagement

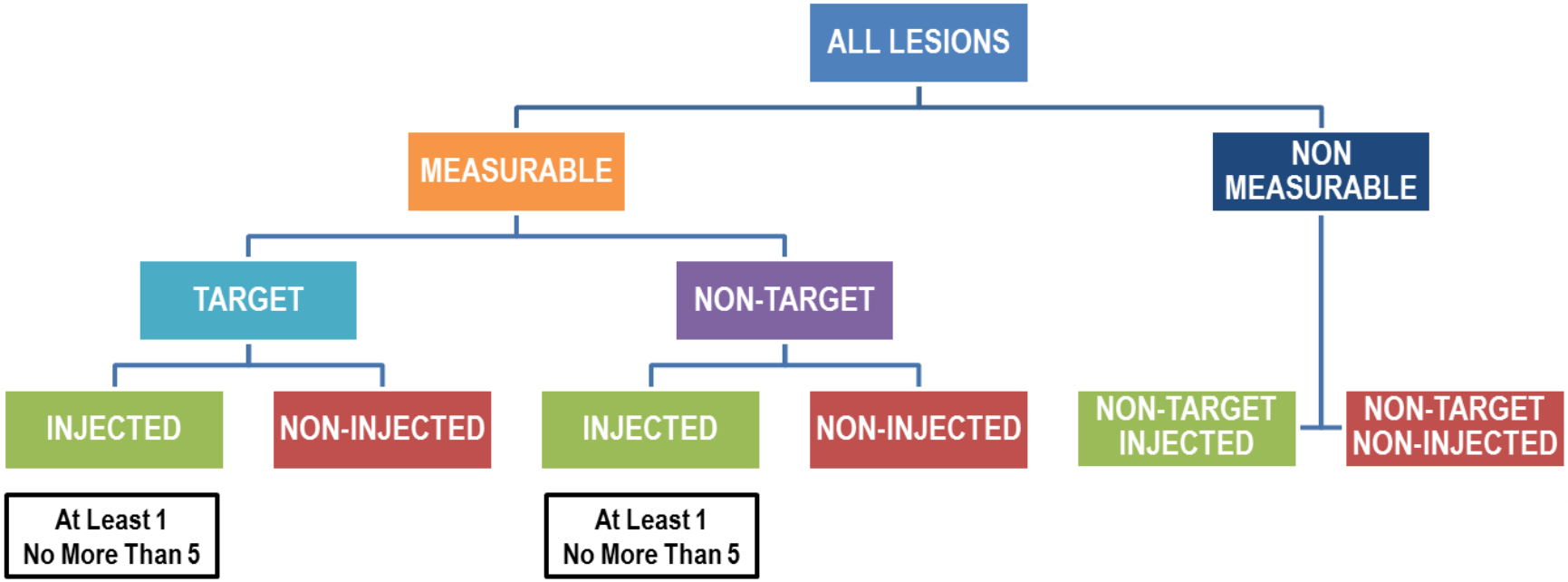
Imaging Assessment Criteria: RECIST is not Adapted to HIT-IT

Clinical Benefit ?



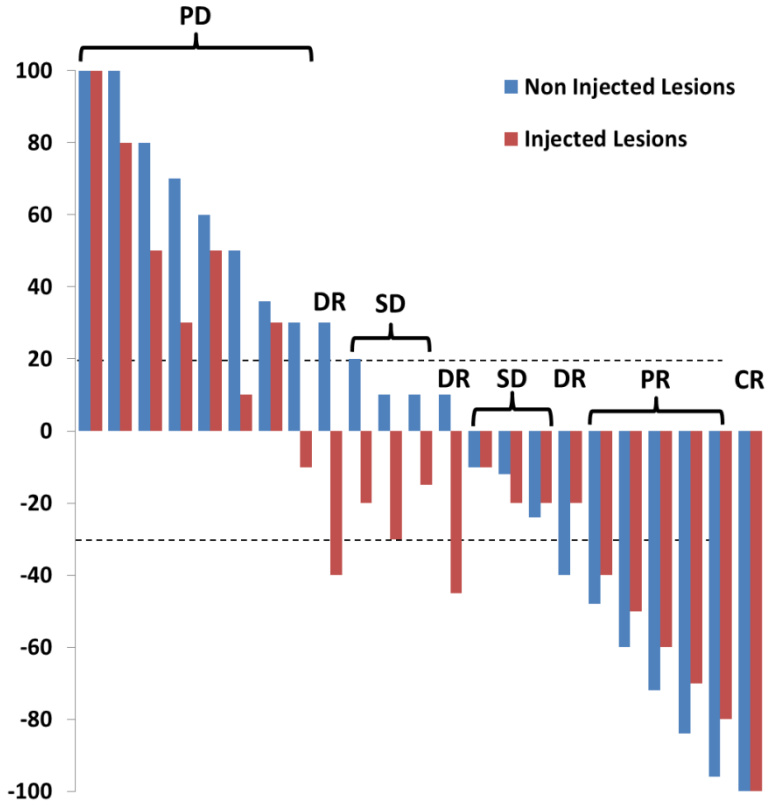
Screening C1 CT-Scan #1 C2 CT-Scan #2

Intra Tumoral RECIST (itRECIST)



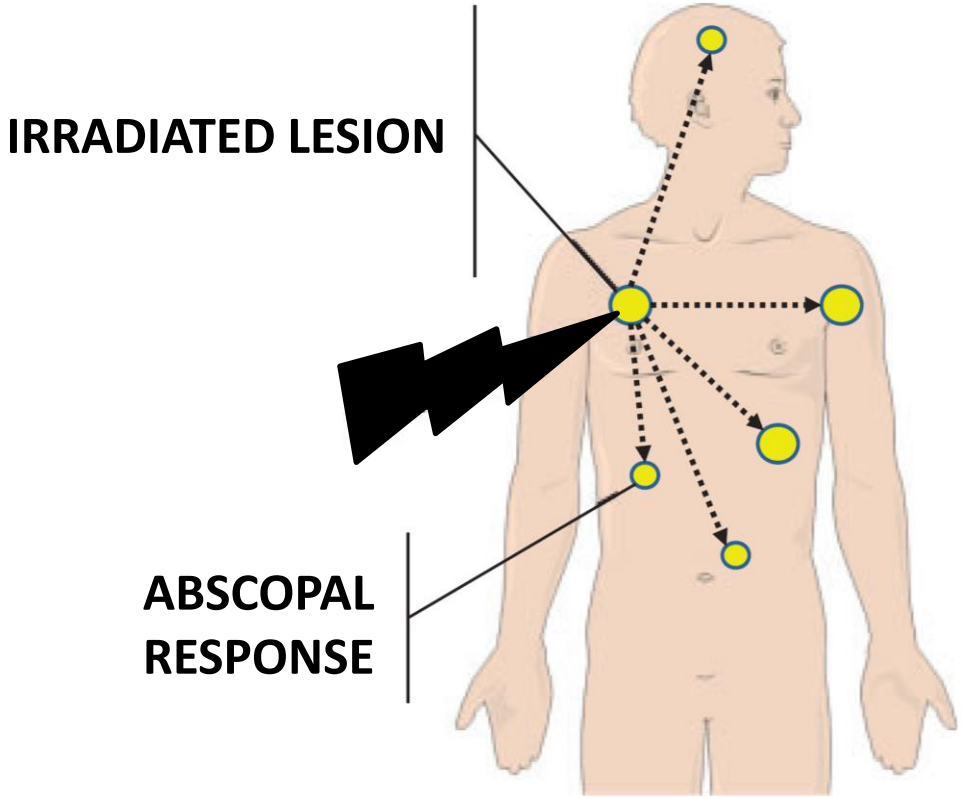
Goldmacher G et al. Consensus Manuscript in Preparation

Waterfall Plots for HIT-IT

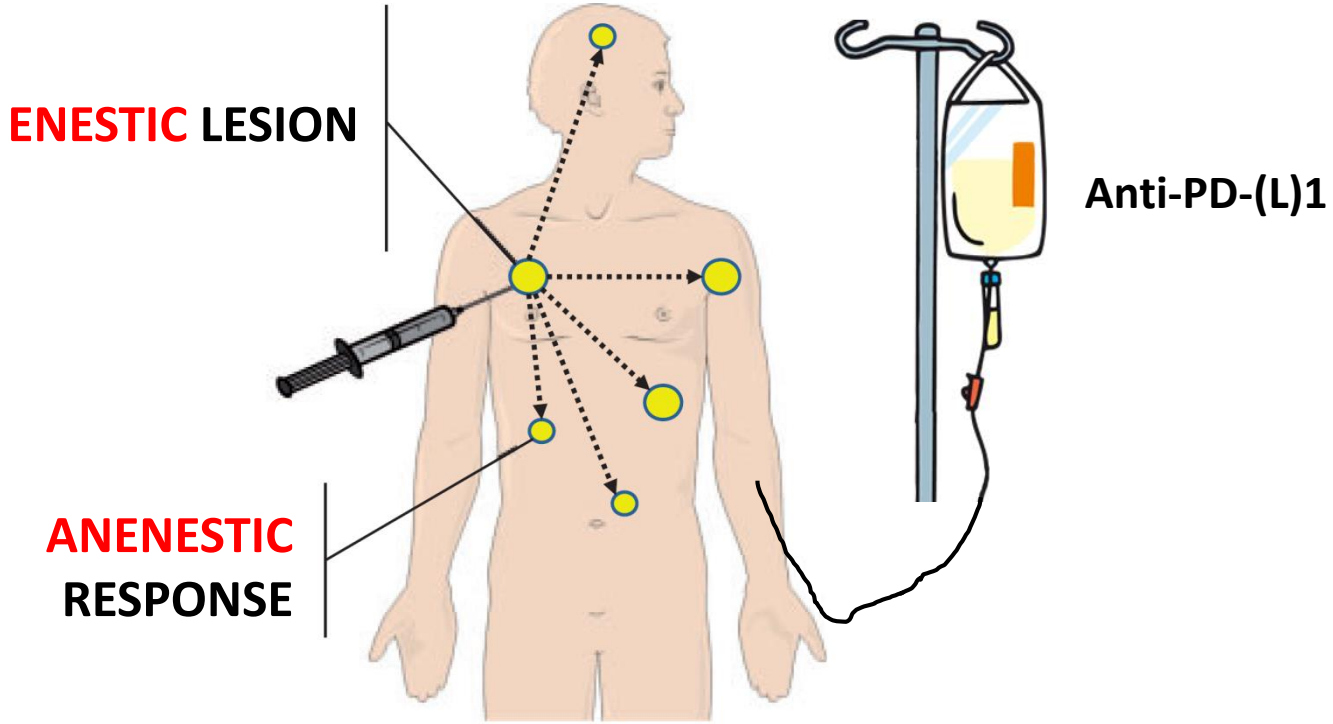


Marabelle A, et al Ann Oncol. 2018;29:2163–74

ABSCOPAL = IRRADIATION

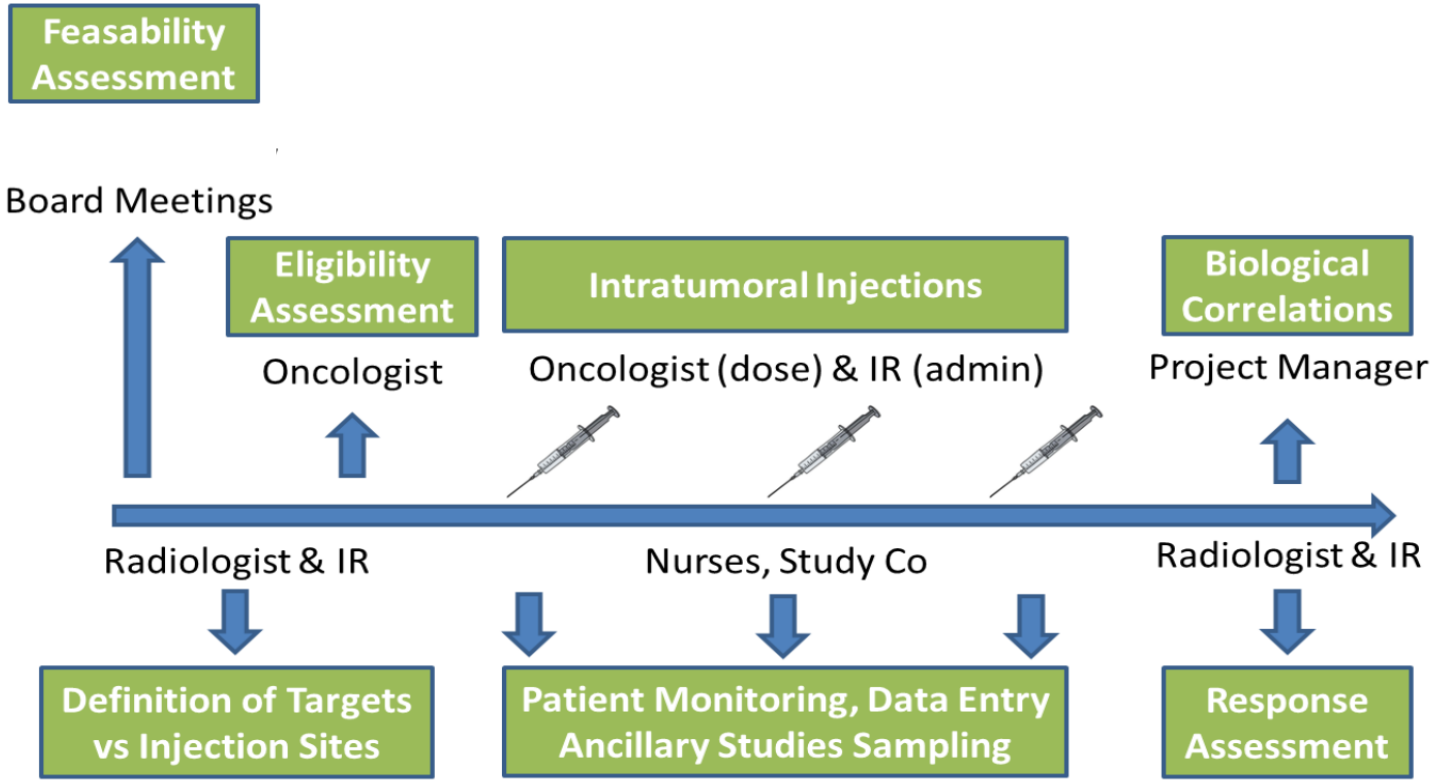


ENESTIC (*injected*) vs ANENESTIC (*non-injected*)



Marabelle A, et al Ann Oncol. 2018;29:2163–74

Logistics for Intratumoral Immunotherapies



Dedicated Board Meetings for Intratumoral Immunotherapy

Interventional Radiologist

Sites of Injection +/- assessment

Oncologist

Dose, Volume

Radiologist

Target Definition & Assessment

Study Coordinator

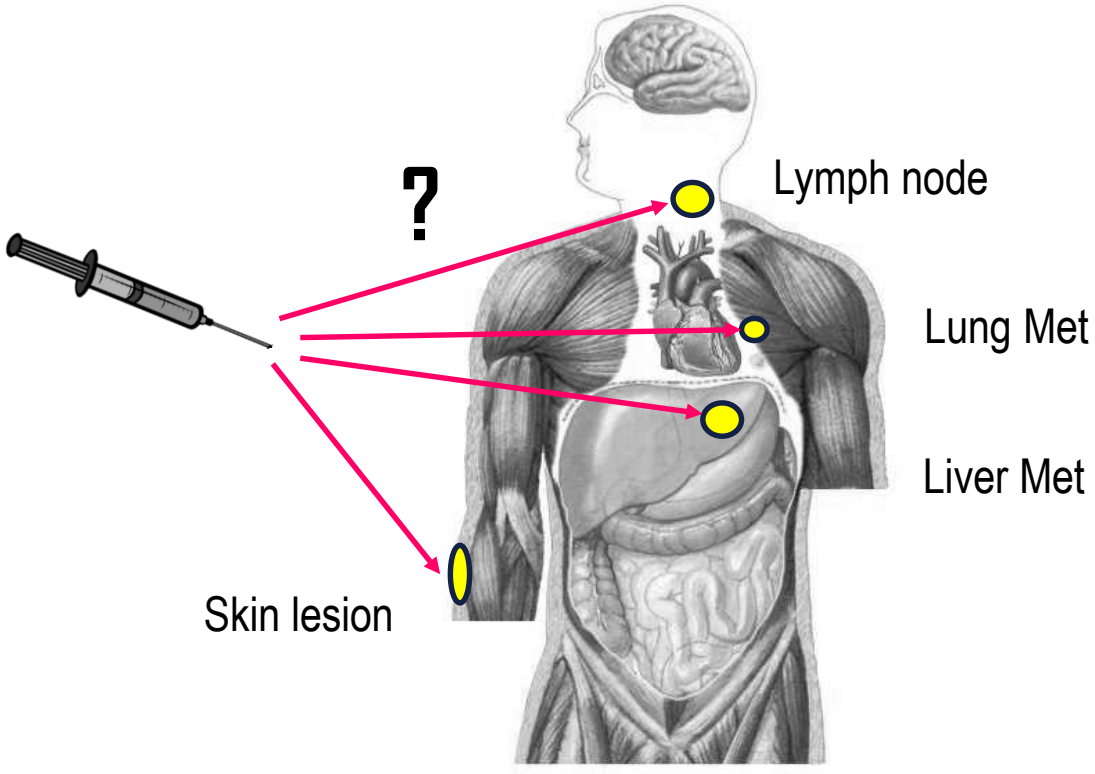
Data Collection in CRF

Scientist

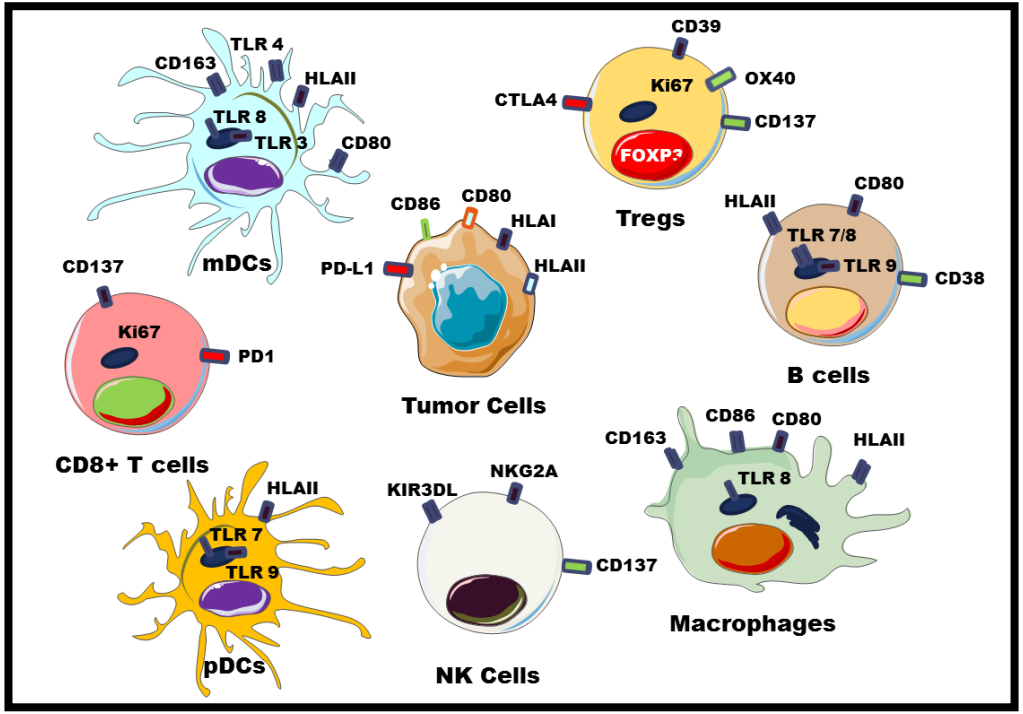
Fresh Sample Analysis

Current Clinical & Scientific Questions for HIT-IT

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



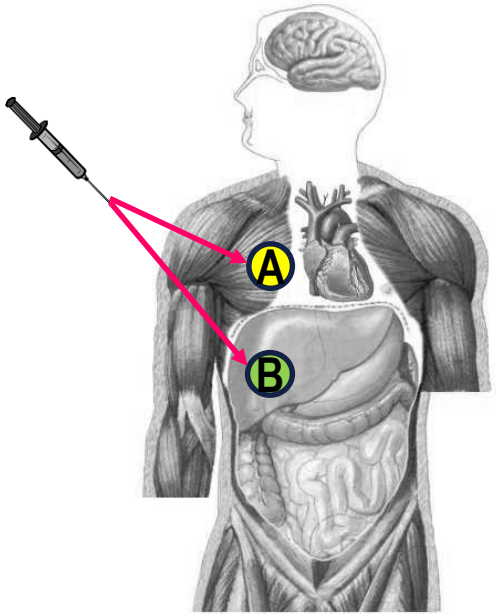
Are pre-existing immune infiltrates predictive for efficacy or can you inflame a cold tumor ?



Adapted from Shekarian T, et al. Pattern Recognition Receptors: Immune Targets to Enhance Cancer Immunotherapy. Ann Oncol 2017;28:1756–66.

Is concomitant treatment of several lesions better than sequential ?

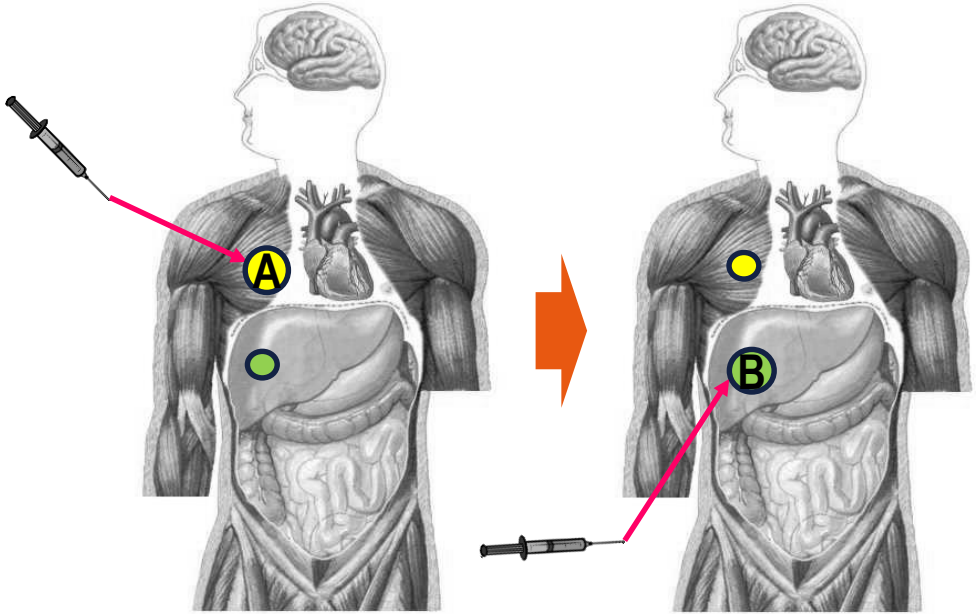
A+B



C1D1

or

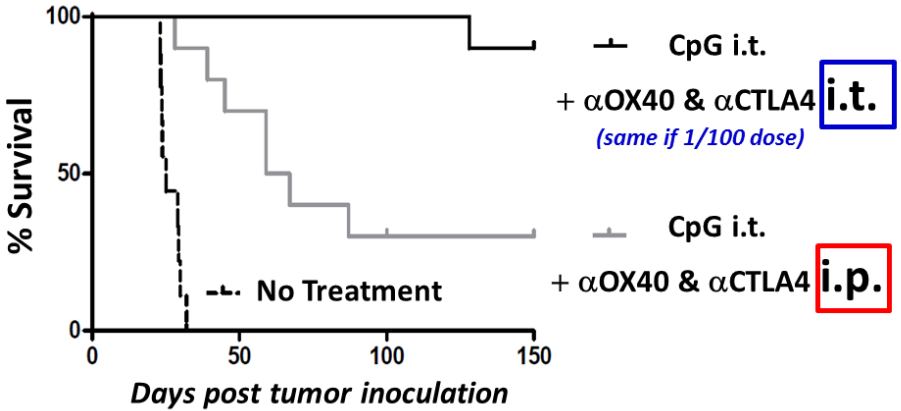
A➔B



C1D1 C2D1

Prime-Boost?

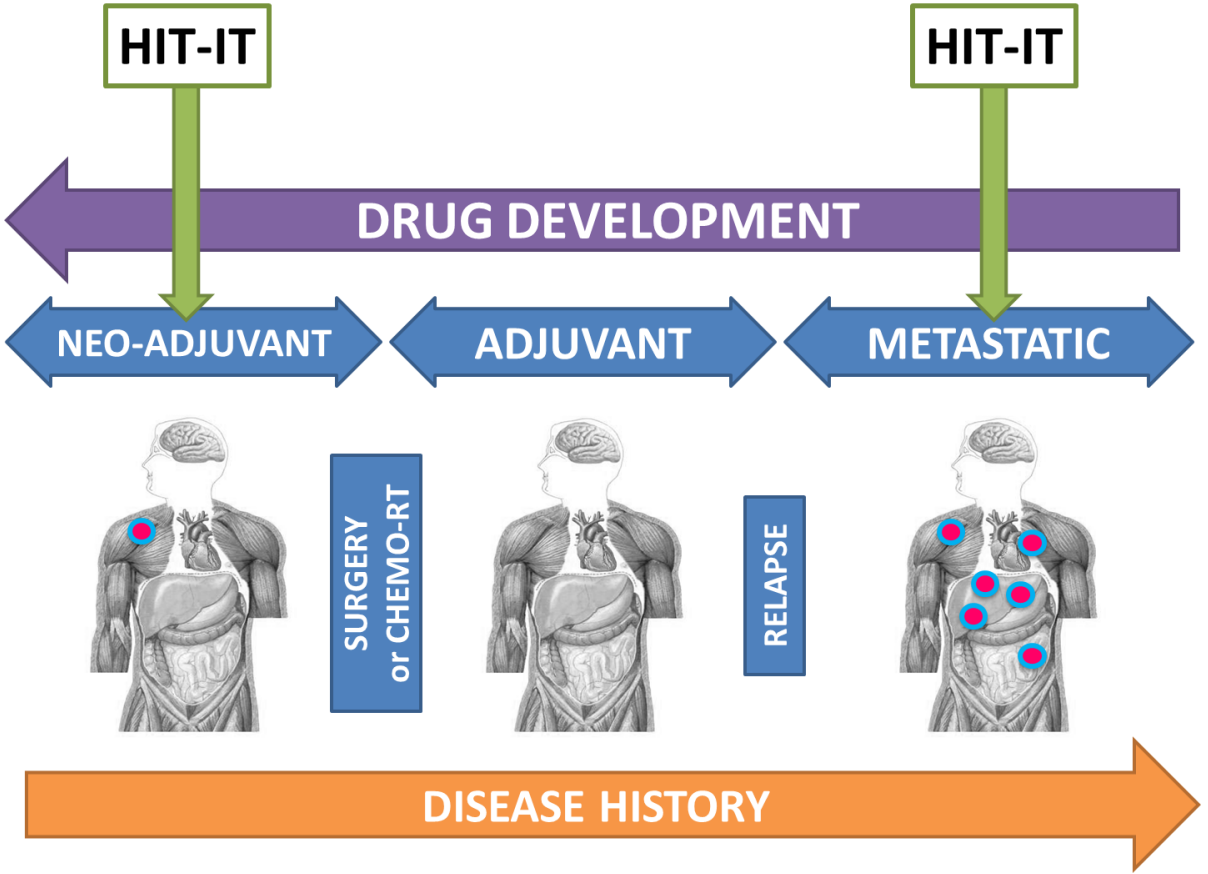
Is HIT-IT generating a better memory anti-tumor immunity than systemic therapy ?



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

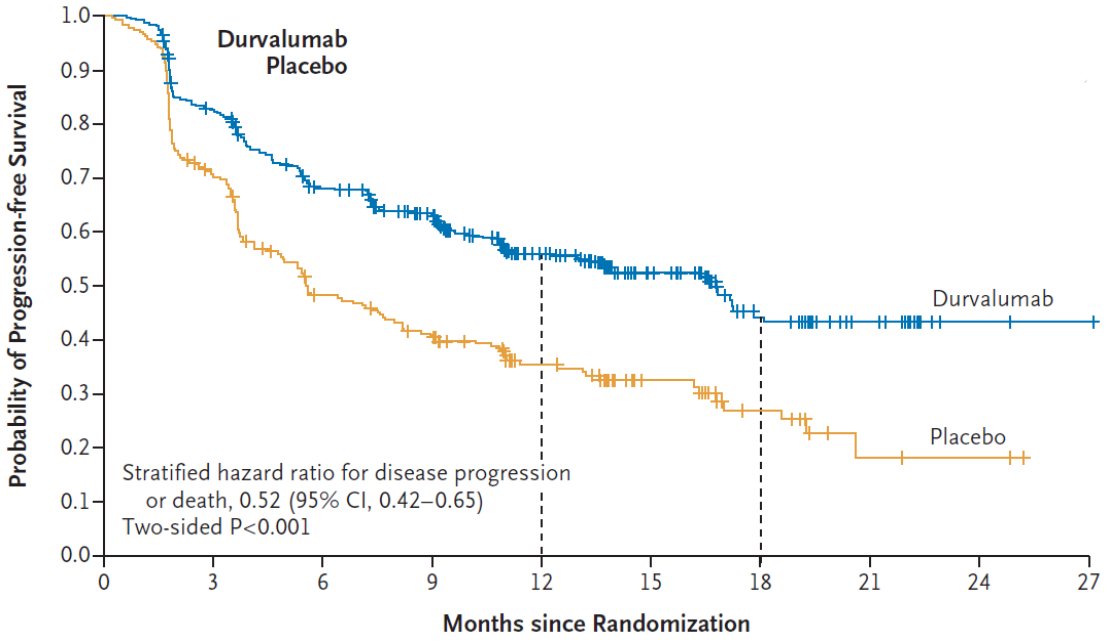
Surrogate markers for Clinical Assessment ?

Pioneer What Could Become the Next Standard of Care



Neo-Adjuvant IT vs Adjuvant IV

NEO-ADJUVANT IO



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

Take Home Messages

- Local priming to trigger systemic responses
- Immunization agnostic from target : *Universal* rather than personalized cancer vaccine
- Safety allowing multiple combinations
- Multiple sites for prime boosting & address cancer heterogeneity
- Pre/On-treatment biological explorations to better understand variability of anti-cancer immune responses

Needs Dedicated Staff & Resources
for Clinical Implementation & Research Performance

DITEP
Drug Development Department

TEAMWORK MAKES THE DREAM WORK

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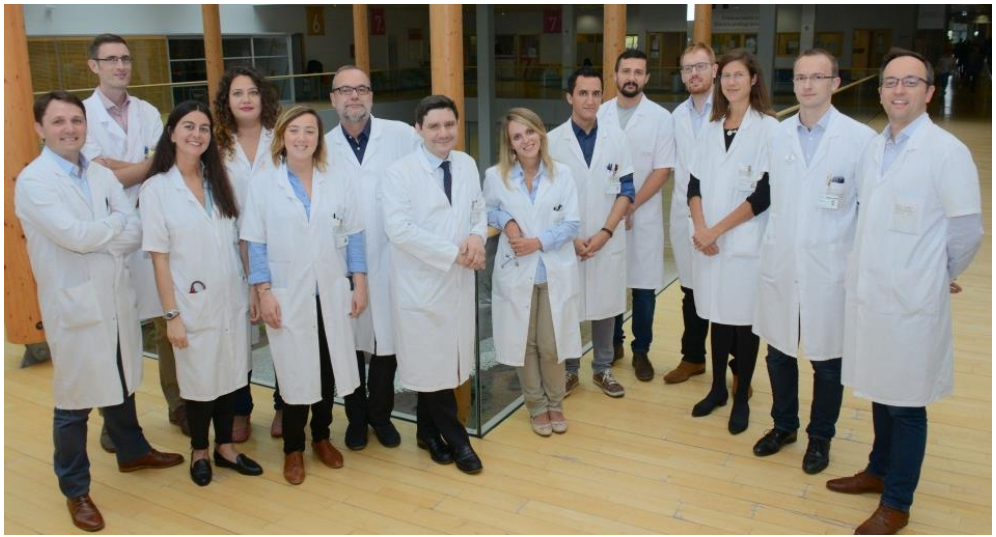

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