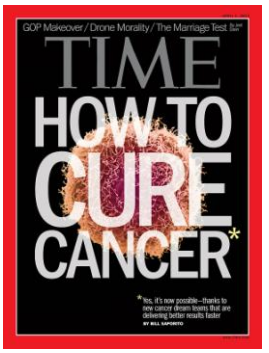
THERANOSTICS IN NUCLEAR MEDICINE

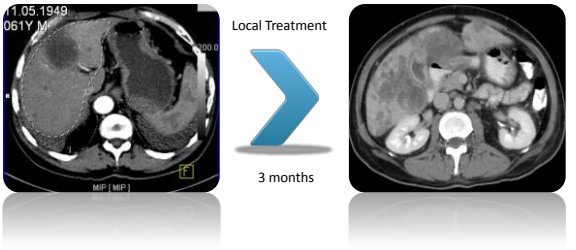
Prof. Dr. Niklaus G. Schaefer, MD

The promise of modern medicine

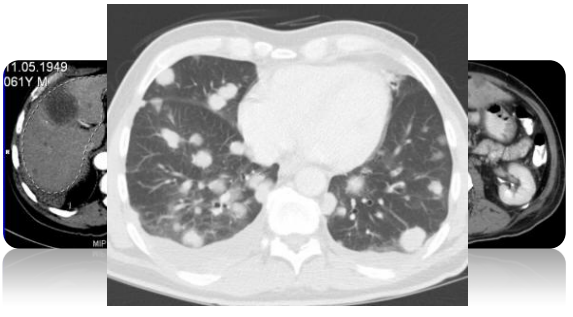


Fiction or Reality ?

Pancreatic Cancer

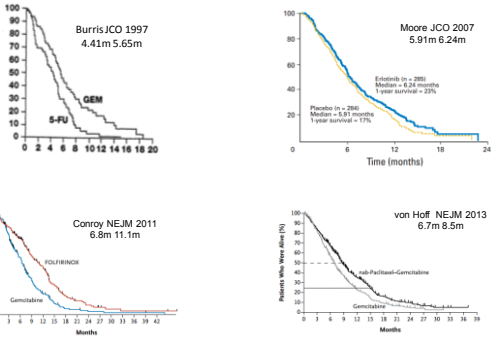


And that is reality !



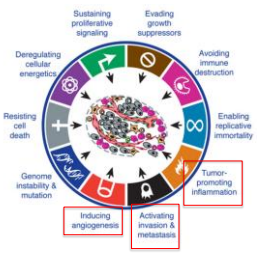
3 months later

Where do we stand today ?



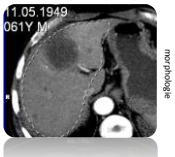
What is the problem ?

Hallmarks of Cancer

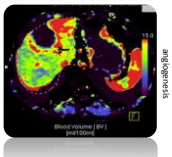


Hallmarks of Cancer (adapted), Hanahan et Weinberg, Cell 2011

Visualisation #1

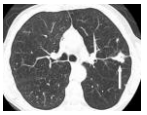


Visualisation #2



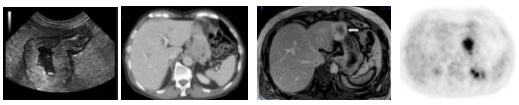
How can we detect cancer ?

EXTERNAL Source
MORPHOLOGY



Internal Source
FUNCTION

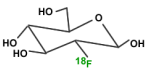
Tracer
what is the difference in tracers

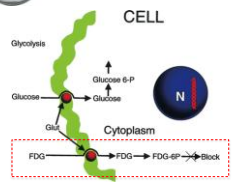


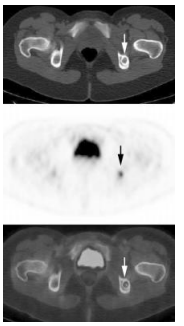
Forme d'imagerie	Concentrations du contraste (mol/kg kg)
Sonographie (US)	10^{-3}
Tomodensitométrie (CT)	10^{-3}
Résonance magnétique (IRM)	10^{-5}
Chimiotherapie	10^{-5}
Scintigraphie	10^{-12} (piko)
Positron Emission Tomographie (TEP)	10^{-12} (piko)

What is the current principle

Fluor-18– Deoxyglucose = FDG
Demi-vie : 110 minutes, injection i.V.

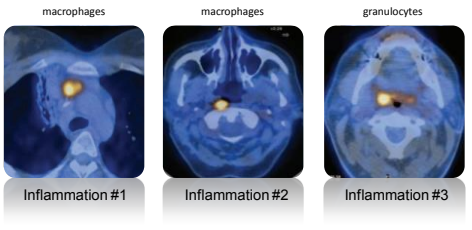






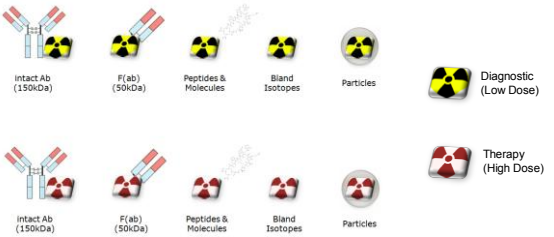
Schaefer et al. Radiology 2004

FDG - PET
what is the problem ?

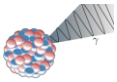


Schaefer et al. Radiology 2007

Evolution of Tracers
(Evolution of Theranostics)

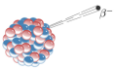


Theragnostics Paradigma



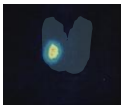
Diagnostic

e.g. Jod-123



Therapy

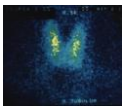
e.g. Jod-131



Adenoma of the Thyroid
Hyperthyroidism
Scintigraphy

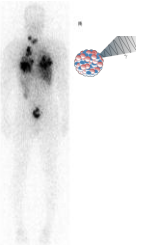
24.8 x (Autonomie-)Volumen [ml] x Herddosis [Gy]

mITU [%] x HWZ [d]

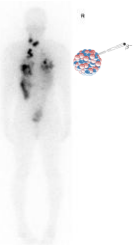


Complete Restoration
Scintigraphy

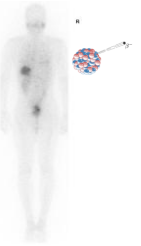
Thyroid Cancer



Iodine-123
80MBq



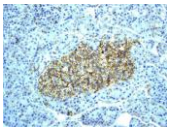
Iodine-131
7400 MBq
1st Cycle



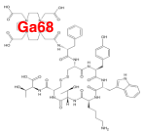
Iodine-131
7400 MBq
2nd Cycle

Somatostatin Analogs

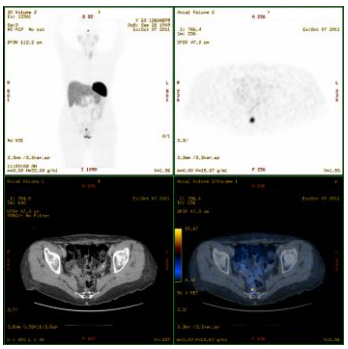
Neuroendocrine Tumors



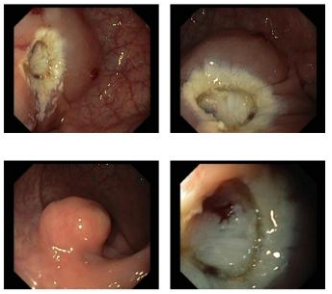
SSTR2R +++
Neuroendocrine Tumor



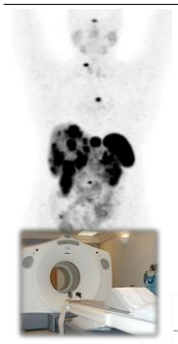
Ga - DOTATATE



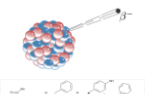
Colonoscopie

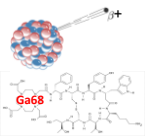


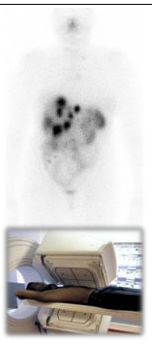
Ga68/Lu177 DOTATATE



Ga68 DOTATATE



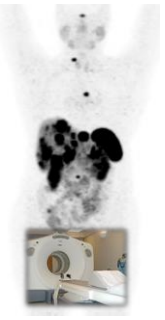




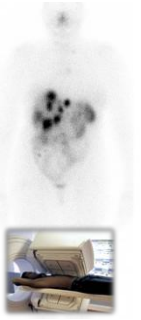
Lu 177 DOTATATE

Ga68/Lu177 DOTATATE

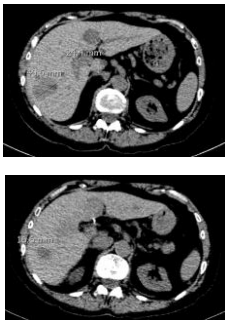
Patient Example



Ga68 DOTATATE



Lu 177 DOTATATE



Lu177 - DOTATATE

Aim	Evaluate the efficacy and safety of ^{177}Lu-Dotatate + SSAs (symptoms control) compared to Octreotide LAR 60mg (off-label use)[1] in patients with inoperable, somatostatin receptor positive, midgut NET, progressive under Octreotide LAR 30mg (label use)
Design	International, multicenter, randomized, comparator-controlled, parallel-group

Treatment and Assessments
Progression free survival (RECIST criteria) every 12 weeks

Dose 1 Dose 2 Dose 3 Dose 4

Baseline and Randomization

- n = 115: 4 administrations of 7.4 GBq of ^{177}Lu-Dotatate every 8 weeks + SSAs (symptoms control)
- n = 115: Octreotide LAR (high dose - 60mg every 4 weeks[1])

5 Years follow up

[1] FDA and EMA recommendation

Netter – 1 Trial

Lutetium – 177 DOTATATE

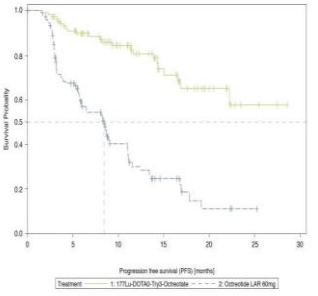
N = 229 (ITT)
Number of events: 90

- ^{177}Lu-Dotatate: 23
- Oct 60 mg LAR: 67

Hazard ratio: **0.21**
[0.129 – 0.338] **p < 0.0001**

79% reduction in the risk of disease progression/death

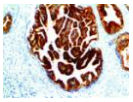
Estimated Median PFS in the Lu-DOTATATE arm
≈ 40 month



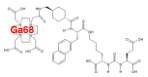
All progressions centrally confirmed and independently reviewed for eligibility (SAP)

Prostate Cancer

Gallium 68 PSMA



PSMA – R +++
Metastatic Prostate Cancer



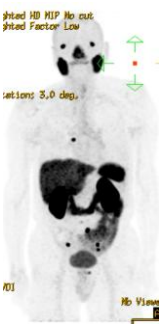
Ga68 PSMA

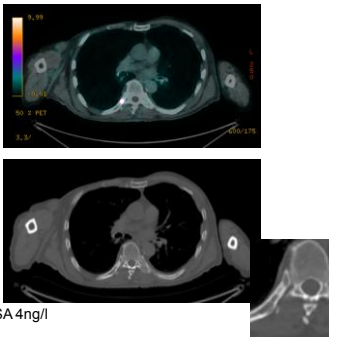
PET
Ga68 PSMA

PET
18F CHOLIN (Standard)

Gallium 68 PSMA-11

@ CHUV – Patient 1



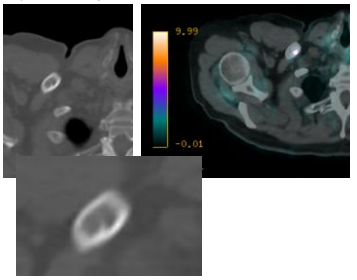


70y, PSA 4ng/l

Gallium 68 PSMA-11

@ CHUV – Patient 2

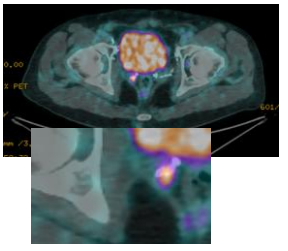
78y, PSA 1.1ng/l



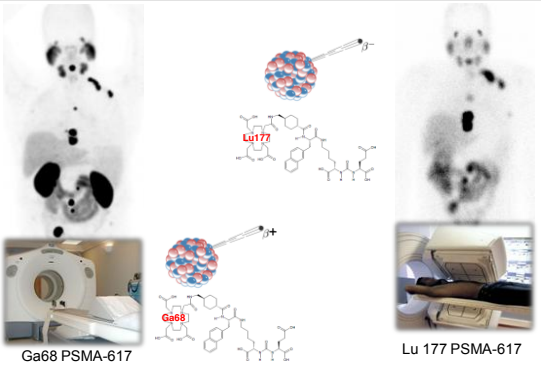
Gallium 68 PSMA-11

@ CHUV – Patient 3

64y, PSA 0.8ng/l



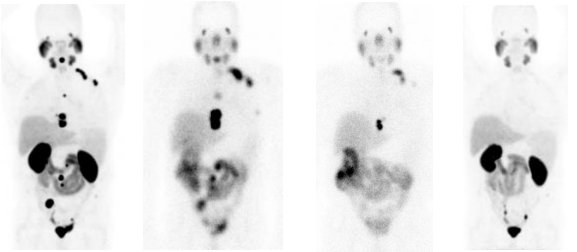
Ga68 / Lu177 PSMA - 617



Ga68 PSMA-617

Lu 177 PSMA-617

Ga68 / Lu177 PSMA - 617

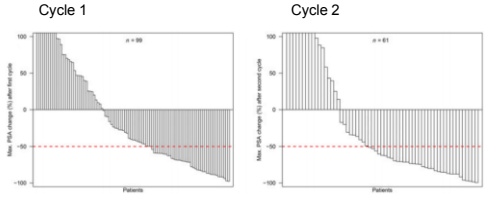


PET | Cycle #1 | Cycle #2 | PET

Haberkorn, Personal Communication 2014

Lutetium - 177 PSMA - 617

German Multicenter Trial



Rhabar et al. JNM 2017

Lu177 PSMA

Efficacy Meta - Analysis

	PSA fall >50%	CT (RECIST)	PSMA PET (EORTC)	Symptomatic response	Biochemical/ radiological PFS	Overall Survival
Zechmann 2014 et al.[39]	61% PD 14%	–	–	23% CR, 61% PR	Median BPFS 126 days (62–149)[3]	–
Ahmadzadehfar 2015 et al.[25]	50% PD 30%	–	–	–	–	–
Ahmadzadehfar 2016 et al.[1]	42% PD 21%	PR 40% SD 55% PD 5%	PR 80% SD 0% PD 20%	–	–	–
Kratochwil 2016 et al.[27]	43%–72%[1] PD 27%			–	–	–
Baum 2016 et al.[3]	59% PD 11%	PR 20%, SD 52%, PD 28%	PR 56% SD 8% PD 36%	33% PR	Median radiological PFS 13.7 months	Median not reached
Rahbar 2016 et al.[29]	31% PD 23%	–	–	–	–	–
Rahbar 2016 et al.[8]	32–50%[2] PD 20%	–	–	–	–	29.4 vs. 19.7 weeks
Heck 2016 et al.[6]	33% PD 32%	PR 11%, SD 56%, PD 33%	'integrated' CR 5%, SD 63%, PD 32%	14% CR, 42% PR	Median PFS 175 days (95% CI 35–315)	
Yadav 2016 et al.[42]	Mean Pre- and post 275/141 PD 20%		CR 33%, PR 50%, SD 17% (n = 6)	Analgesic score 2.5 reduced to 1.8	Median PFS 12 months	Median OS 15 months

Lu177 PSMA

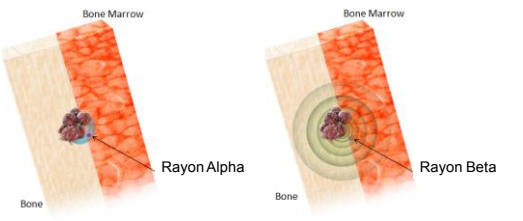
Toxicity Meta - Analysis

	Haematological toxicity (G2-3)			Non-haematological toxicity	
	Hb	WCC	Platelets	Salivary	Other
Zechmann 2014 et al.[39]	Below 'normal range' 75%	15%	10%	25%	Hypothyroidism 1/28, mucositis 1/28
Ahmadzadehfar 2015 et al.[25]	10%	10%	10%	20%	Fatigue 20%, nausea 20%
Ahmadzadehfar 2016 et al.[1]	25%	12%	0%	9%	Nausea 12%, fatigue 13–17%, hypogeusia 4%
Kratochwil 2016 et al.[27]	10%	7%	7%	7%	Fatigue G1, nausea G1
Baum 2016 et al.[3]	5% N/S changes[1]	9% N/S changes[1]	0%	4%	–
Rahbar 2016 et al.[8]	15% N/S changes	5.4%	3% N/S changes	9%	Nausea G1 1.4%
Rahbar 2016 et al.[29]	9–20%[2]	0–11%[2]	0%	15%	Nausea 14%, nil with routine antiemetic use
Heck 2016 et al.[6]	32% (G1-2)	Neutropenia 5%	25% (G1-2)	37%	Fatigue 25%, Anorexia 25%,
Yadav 2016 et al.[42]	6.5%	3%	0%	Nil reported	–

Fatigue and dry mouth appear most commonly. Haematological problems occur and can be significant in the group of men with borderline marrow function due to extensive bone metastases.

Dose Escalation

Alpha versus Beta Radiation

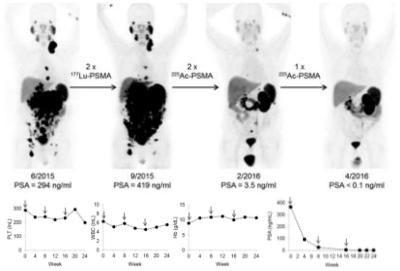


20 High | LET BM Toxcitiy | 1 Low

Rathke etal. JNM 2017

Lu177 PSMA

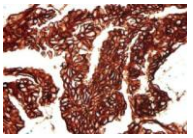
Actinium – 225 PSMA - 617



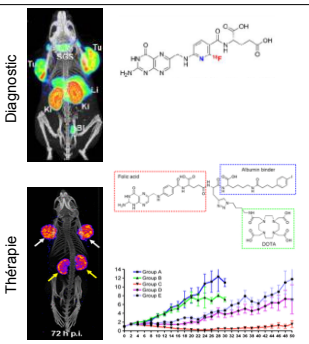
Kratochwil et al. JNM 2016

Ovarian Cancer

18F Aza Folate



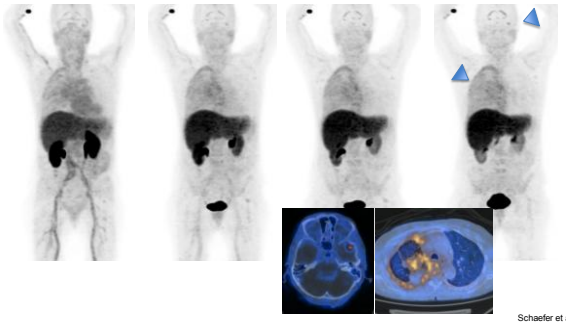
Immun-histochimie Folate Récepteur
Cancer des Ovaires



Reist T et al. Radiosynthesis and Preclinical Evaluation of 3'-Aza-2'-[18F]Fluorofolic Acid: A Novel PET Radiotracer for Folate Receptor Targeting. Bioconjug Chem. 2013
Müller C et al. 2.DOTA Conjugate with an Albumin-Binding Entity Enables the First Folic Acid-Targeted 177Lu-Radionuclide Tumor Therapy in Mice. J Nucl Med. 2013 Jan;54(1):124-31

18F Aza Folate

Phase 1, Patient #1



Schaefer et al.

18F Aza Folate

Dosimétrie, Patient #1

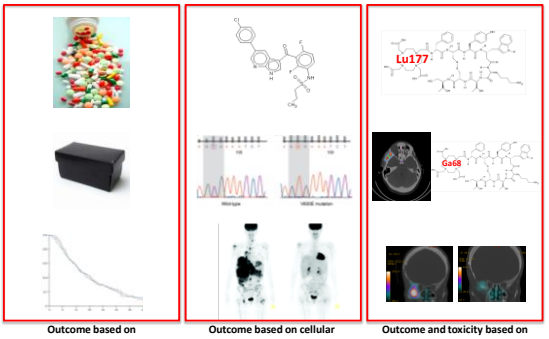
Organ Doses (mSv/MBq), Nuclide: F-18 (1.10E02 min), Adult Female
Calculated: 10.27.2015 at 03:16:10 CET

Target Organ	Alpha	Beta	Photon	Total	EDE Cont.	ED Cont.
Adrenals	0.00E000	3.96E-03	1.74E-02	2.14E-02	0.00E000	1.07E-04
Brain	0.00E000	7.21E-04	2.92E-03	3.64E-03	0.00E000	1.82E-05
Breasts	0.00E000	2.57E-03	6.62E-03	9.19E-03	1.38E-03	4.60E-04
Gallbladder Wall	0.00E000	5.63E-03	2.44E-02	3.01E-02	0.00E000	0.00E000
LLI Wall	0.00E000	5.42E-03	1.22E-02	1.76E-02	0.00E000	2.11E-03
Small Intestine	0.00E000	1.56E-02	1.39E-02	2.95E-02	0.00E000	1.48E-04
Stomach Wall	0.00E000	1.55E-02	1.63E-02	3.17E-02	1.90E-03	3.81E-03
ULI Wall	0.00E000	4.90E-03	1.52E-02	2.01E-02	0.00E000	1.01E-04
Heart Wall	0.00E000	5.72E-03	1.36E-02	1.94E-02	0.00E000	0.00E000
Kidneys	0.00E000	2.29E-02	1.90E-02	4.19E-02	2.51E-03	2.09E-04
Liver	0.00E000	6.26E-02	4.39E-02	1.07E-01	6.39E-03	5.33E-03
Lungs	0.00E000	1.28E-02	1.26E-02	2.54E-02	3.05E-03	3.05E-03
Muscle	0.00E000	3.71E-03	8.43E-03	1.21E-02	0.00E000	6.07E-05
Ovaries	0.00E000	2.57E-03	1.29E-02	1.54E-02	3.86E-03	3.09E-03
Pancreas	0.00E000	5.65E-03	1.82E-02	2.38E-02	0.00E000	1.19E-04
Red Marrow	0.00E000	4.48E-03	9.52E-03	1.40E-02	1.68E-03	1.68E-03
Osteogenic Cells	0.00E000	8.24E-03	8.97E-03	1.72E-02	5.16E-04	1.72E-04
Skin	0.00E000	2.57E-03	5.02E-03	7.59E-03	0.00E000	7.59E-05
Spleen	0.00E000	1.88E-02	1.54E-02	3.42E-02	2.05E-03	1.71E-04
Thymus	0.00E000	2.57E-03	8.47E-03	1.10E-02	0.00E000	5.52E-05
Thyroid	0.00E000	7.75E-03	8.43E-03	1.62E-02	4.25E-04	7.09E-04
Urinary Bladder Wall	0.00E000	6.38E-02	3.77E-02	1.01E-01	6.08E-03	5.07E-03
Uterus	0.00E000	2.57E-03	1.50E-02	1.76E-02	0.00E000	8.79E-05
Total Body	0.00E000	5.95E-03	9.30E-03	1.53E-02	0.00E000	0.00E000
Effective Dose Equivalent (mSv/MBq)					2.98E-02	
Effective Dose (mSv/MBq)						2.66E-02

Internal Dosmietry can predict all tissue doses (Efficacy and Toxcity)

Schaefer et al.

Theragnostic Evolution



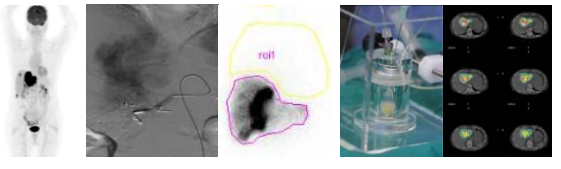
Outcome based on Statistics

Outcome based on cellular mutation to predict response

Outcome and toxicity based on dosimetric calculation

Radioembolisation (SIRT)

a theranostic procedure



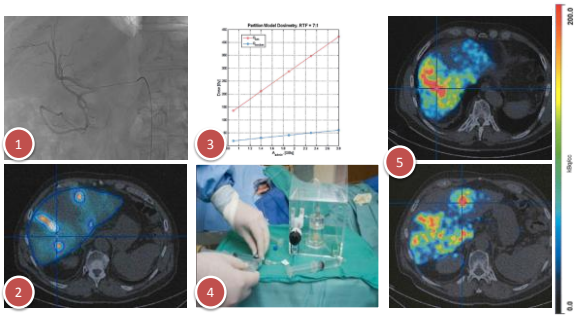
d0 d+10

Administration
Imaging
Patient Selection

Angiography
Coiling
MAA Scintigrahpy

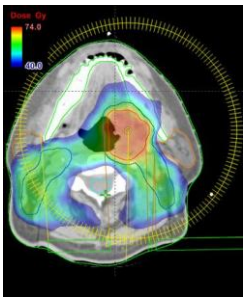
Angiography
Radioembolisation
BS Scintigraphy

Trials in Theragnostique



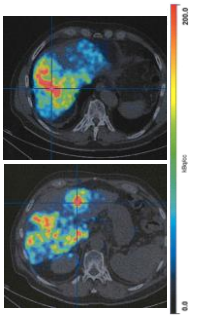
Measure | Calculate | Verify (Gy)

Trials in Theragnostique : Can we use the EBRT paradigm ?



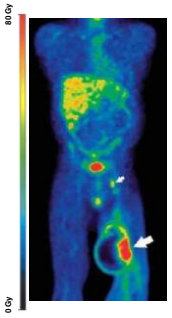
Radiotherapy Paradigm

VS.



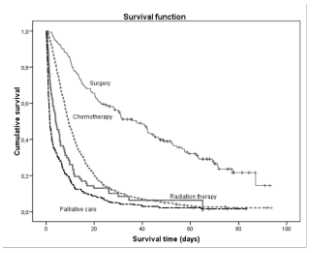
Internal Absolute Values (Gy)

Trials in Theragnostique : will it replace phase III studies ?



Predictive Dosimetry

VS.



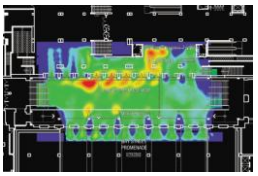
« retrospective » survial analysis

and how can we get there?

Better Image Analysis and New Tracers

Better Image Analysis Radiomics

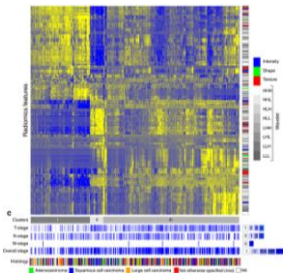
Images Are More than Pictures, They Are Data



Radiomics

Some Bascis

RADIOMICS



GENOMICS
characterization and quantification of genes, which direct the production of proteins with the assistance of enzymes and messenger molecules

TRANSCRIPTOMICS
expression level of mRNAs, reflects the genes that are being actively expressed at any given time

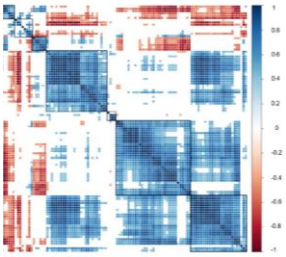
PROTEOMICS
the large-scale study of proteins the entire set of proteins, produced or modified by an organism or system

METABOLOMICS
study of chemical processes involving metabolites.

..MICS (engl. Neologism) : study of large, comprehensive biological data sets

Aerts et al. Nature Comm. 2014

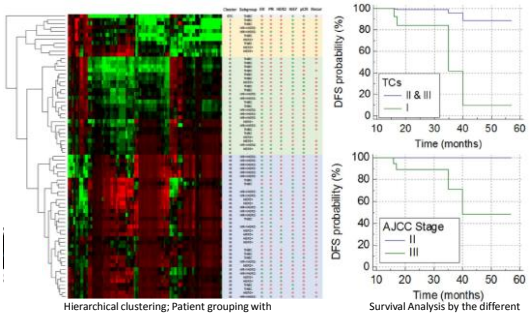
Radiomics
how can it be used



Correlation Matrix : correlation analysis between features to remove strongly related factors

Ho-Young Lee et al. Sci. Rep. 2017

Radiomics
How can it be used



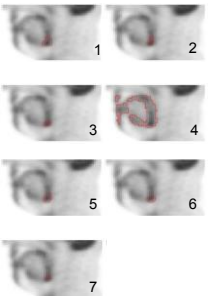
Hierarchical clustering; Patient grouping with similar radiomic features

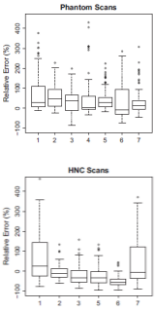
Survival Analysis by the different groups

Ho-Young Lee et al. Sci. Rep. 2017

Translation to PET
Problem of Segmentation

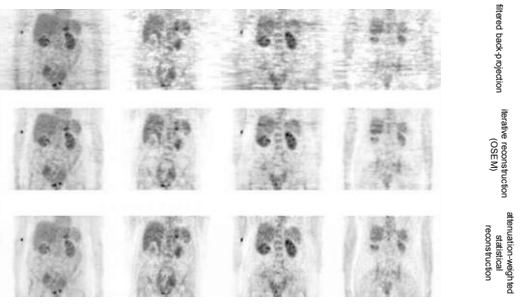
Approach	Segmentation approach/software
1	In-house developed software based on an active contour segmentation approach
2	In-house developed software utilizing a graph-based optimization approach[21]
3	Commercial software package Mirada Medical RTx
4	Combination of commercial software packages VCAR and PMOD
5	Commercial software package MIM
6	Commercial software package PMOD
7	In-house developed software based on 3D level-set segmentation approach





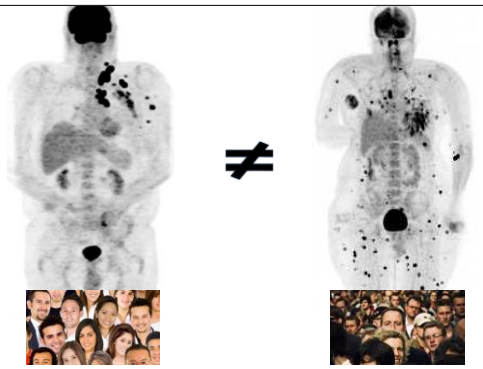
Beichel, Gilles et al. et al. Med Phys 2017

Translation to PET
Problem of Reconstruction

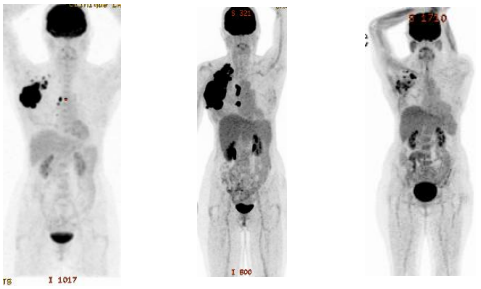


PET has many sources of « errors » : reconstruction, scanning time, machine, biologics, etc.

How can we use Radiomics in PET
power of PET lies in the system approach



How can we use Radiomics in PET

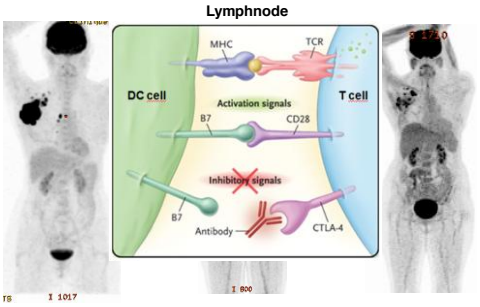


Pre - Ipilimumab

Cycle 2

Cycle 4

How can we use Radiomics in PET

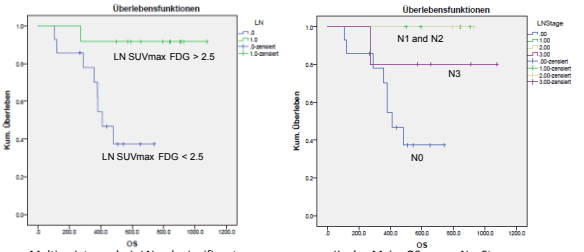


Pre - Ipilimumab | Cycle 2 | Cycle 4

What is the Power of PET ?

PET pre Ipilimumab (SUVmax > 2.5)

FDG avid lymphnodes (SUVm > 2.5) independently predicts survival prior to Ipilimumab
In multivariate Analysis



Multivariate analysis LN only significant
Covariate (p = 0.031)

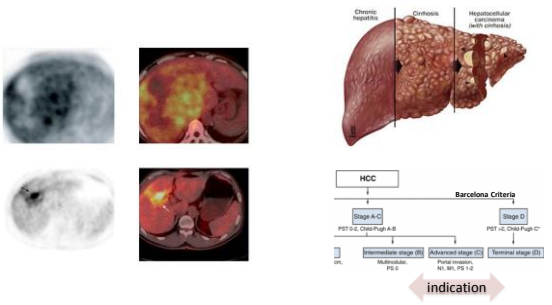
Kaplan Meier OS versus N – Stage
p < 0.05

LN morph (axis/clustering) not relevant (p = 0.14)

Dummer, Maiwald, Schaefer; Melanoma Res. 2016

FDG - PET as System Approach

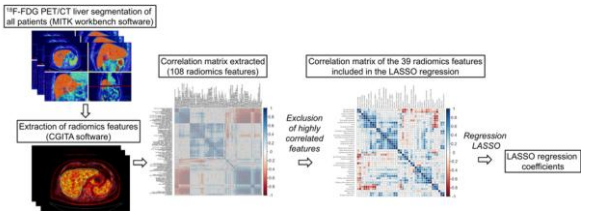
FDG - PET pre SIRT : A whole Liver Radiomics



We have to make use of the SYSTEM MEDICINE power of PET

Liver System Approach

the use of FDG in a whole liver approach



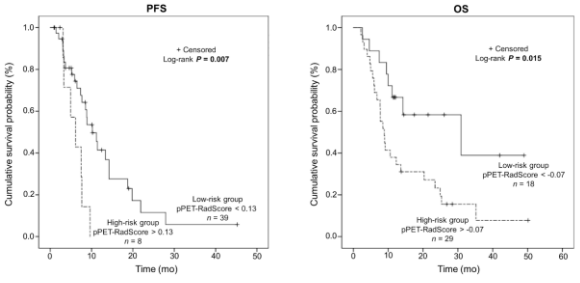
Significant Factors :

Strength (clear, perceivable characteristics ,identifiable as texture)
Variance (variation of intensity around the mean)

Blanc – Durand P, van der Gucht A, Denys, Schaefer; Oncotarget 2018

Translation to PET

Signature of Survival : A whole Liver Radiomics (Univariate)



Blanc – Durand P, van der Gucht A, Denys, Schaefer; Oncotarget 2018

Translation to PET

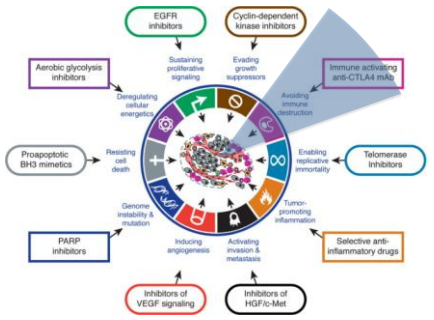
Signature of Survival : A whole Liver Radiomics (multivariate)

PFS			OS		
Characteristics	**HR (95% CI)**	***P***	**Characteristics**	**HR (95% CI)**	***P***
PFS pPET-RadScore	30.3 (2.89-317)	0.004	OS pPET-RadScore	15.4 (2.97-79.7)	0.001
BCLC staging system			BCLC staging system		
Stages A vs. B	0.62 (0.08-4.96)	0.66	Stages A vs. B	1.26 (0.29-5.58)	0.76
Stages A vs. C	0.56 (0.25-1.27)	0.16	Stages A vs. C	0.65 (0.30-1.38)	0.26
Serum AFP level	0.77 (0.53-1.12)	0.17	Serum AFP level	0.75 (0.45-1.24)	0.26
Stratified for BCLC staging system					
PFS pPET-RadScore	35.5 (3.04-414)	0.004	OS pPET-RadScore	21.9 (3.6-133)	0.001
Serum AFP level	0.79 (0.55-1.14)	0.21	Serum AFP level	0.75 (0.45-1.26)	0.28

Blanc – Durand P, van der Gucht A, Denys, Schaefer; Oncotarget 2018

New Tracers

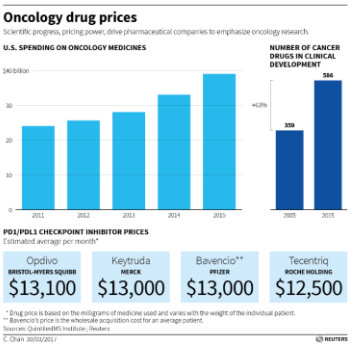
Modern Oncology : With Targeted Oncology Treatment
Specific Tracers get more important !



Hallmarks of Cancer (adapted), Hanahan et Weinberg, Cell 2011

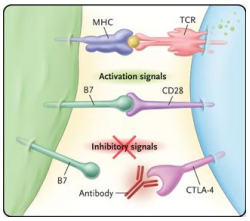
Why is this playing a role ?

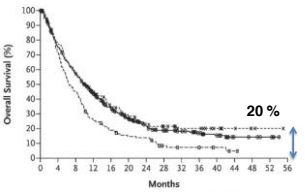
In modern Oncology



Example

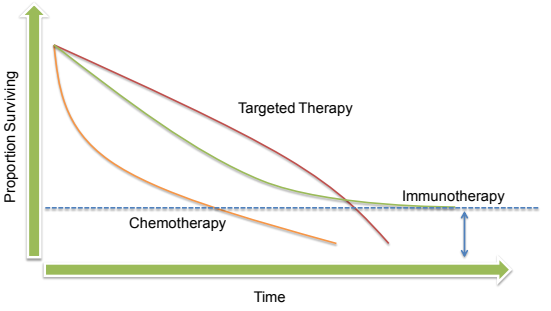
Ipilimumab - Melanoma





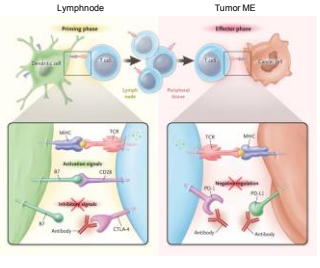
Antibody anti - CTLA4 : Prolongation of OS in Melanoma Patients in 2nd line after Chemotherapy. 1Million Euro Question : Who are the 20 %

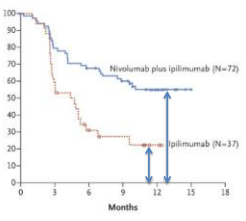
The Immunotherapy Paradigma



How to Enhnace Immunotherapy

smart combinations



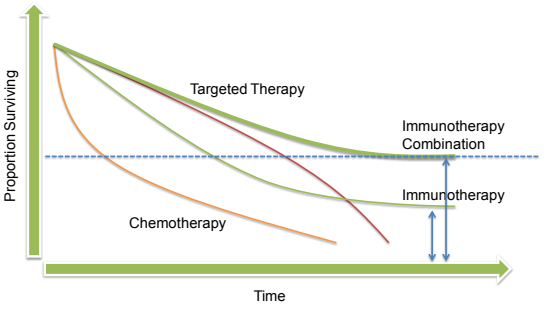


Combination of anti PD1 and antiCTLA4 block

Postow et al, NEJM 2015

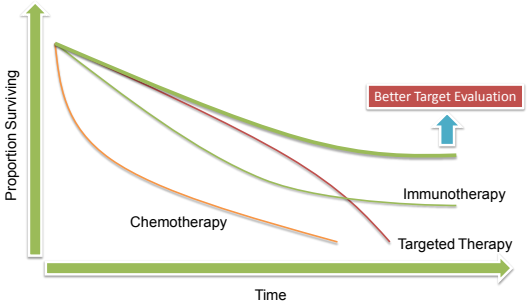
How to Enhnace Immunotherapy

smart combinations



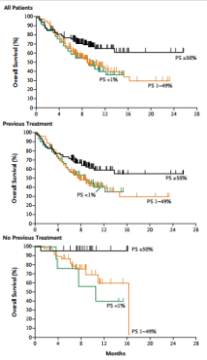
How to Enhnace Immunotherapy

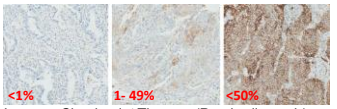
smart combinations



How to Enhance Immunotherapy

The Role of Target Evalutation



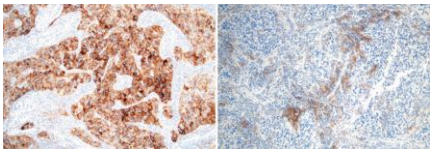


Immune Checkpoint Therapy (Pembrolizumab) is highly active in patients with NSCLC

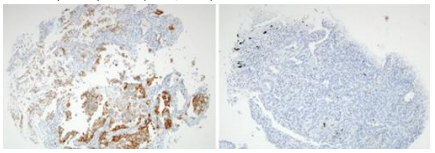
KEYNOTE – 001, Garon et al. NEJM 2015

How to Enhance Immunotherapy

Heterogeneity in Expression Levels



PD – L1 Expression patient #1 (Core 1, Core 2)

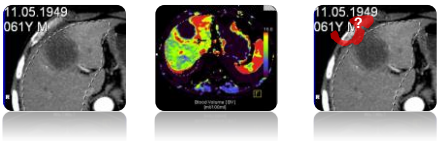


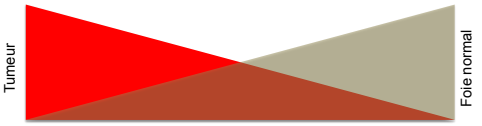
PD – L1 Expression patient #2 (Core 1, Core 2)

David Casadevall et al, Clin Lung Cancer 2017

Target Evaluation

What is the Target ?

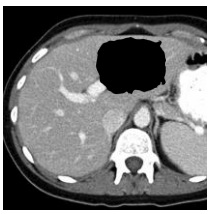




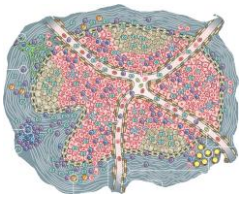
Target Evaluation

Fundamental Problem of Imaging

What is Cancer and Where is it ?



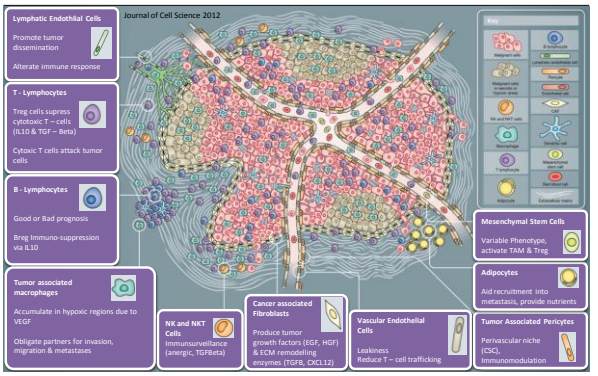
This how we understand Cancer



This is how we have to understand cancer

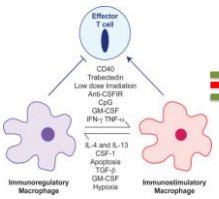
Better Target Identification & Modulation

Immunsuppressive Tumor Microenvironment



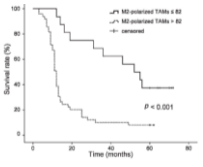
Tumor Microenvironment

Macrophages (M1pol vs M2pol)



Factor	p-value	HR	95% CI
Gender	0.303	0.574	0.200-1.649
Age	0.393	1.317	0.700-2.480
Differentiation	0.670	1.175	0.558-2.476
Lymph node metastasis	0.011*	2.778	1.260-6.123
P-TNM staging	0.039*	3.021	1.055-8.649
TAM count	0.015*	3.602	1.279-10.142
M1-polarized TAMs count	0.860	0.881	0.214-3.628
M2-polarized TAMs count	0.031*	4.280	1.146-15.984
Intratumoral LMVD	0.327	1.189	0.841-1.679
Peritumoral LMVD	0.038*	1.073	1.004-1.147

*Statistically significant. Advanced NSCLC Data



Zhang et al, CLINICS 2011

Tumor associated macrophages

Accumulate in hypoxic regions due to VEGF

Obligate partners for invasion, migration & metastases

PREDICTION OF SITE SPECIFIC REPONSE IN MELANOMA PATIENTS PRIOR TO CHECKPOINT INHIBITOR TREATMENT

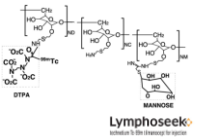
Tumor associated macrophages (TAM) in the tumor microenvironment play an essential role in cancer progression

During melanoma progression the anti-tumoral M1 polarized phenotype shifts towards the immune-supressive M2 phenotype

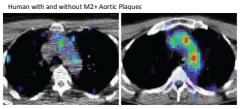
CD206 in macrophages renders them to produce IL10 and TGFb identifying this TAM population as anti-inflammatory subtype

Tc99m - Tilmanocept is a FDA/EMA approved drug (Lymphoseek™) for lymphnode scintigraphy/SPECT and targets CD206 with nano-molar affinities

Due to its high specificity even smallest targets as atherosclerotic plaques in mice and humans can be visualized



Human with and without M2+ Aortic Plaques



Zanni MV et al. J Infect Dis. 2017

Tumor associated macrophages

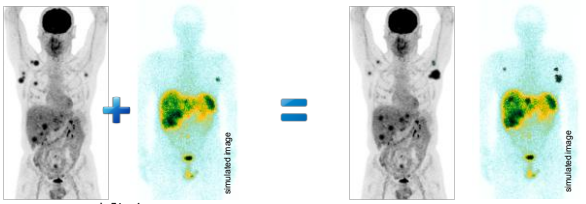
Accumulate in hypoxic regions due to VEGF

Obligate partners for invasion, migration & metastases

Applied for Grant : Confidential

PREDICTION OF SITE SPECIFIC REPONSE IN MELANOMA PATIENTS PRIOR TO CHECKPOINT INHIBITOR TREATMENT

Niklaus Schaefer & Krisztian Homicsko



d – 7 to – 1
Pre - Nivolumab

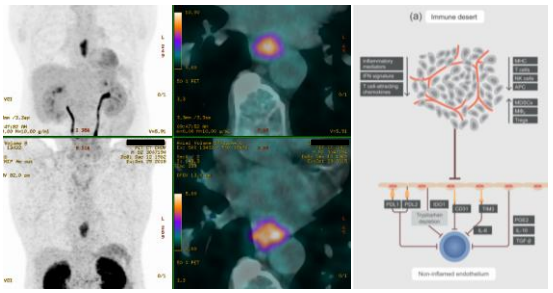
d + 21 to + 27
Nivolumab (post cy2)

Hi-Res TOF PET/CT | Quantitative SPECT | Hi-Res TOF PET/CT | Quantitative SPECT

Applied for Grant : Confidential

Tumor Microenvironment

Activated Immunosuppressive Endothelium : Angiogenesis



Immune desert also driven by altered tumor neoangiogenesis

Vascular Endothelial Cells

Leakiness

Reduce T – cell trafficking

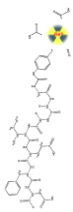
Companion Diagnostics

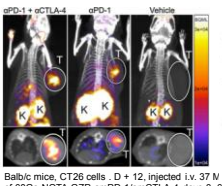
Ga68 anti - Granzyme B PET (visualizing t cell exhaustion grant under evaluation)

T - Lymphocytes

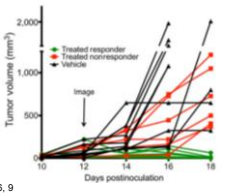
Treg cells supress cytotoxic T – cells (IL10 & TGF – Beta)

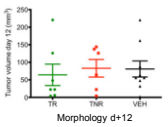
Cytoxic T cells attack tumor cells



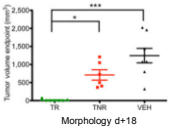


Balb/c mice, CT26 cells . D + 12, injected i.v. 37 M of 68Ga-NOTA-GZP amPD-1/amCTLA-4 days 3, 6, 9





Morphology d+12

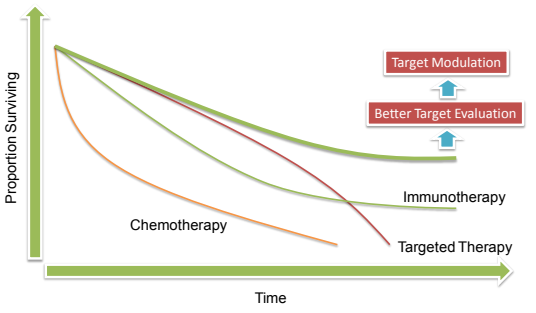


Morphology d+18

Mamood U et al. Canc Res 2017

How to Enhnace Immunotherapy

Systemic Modulation

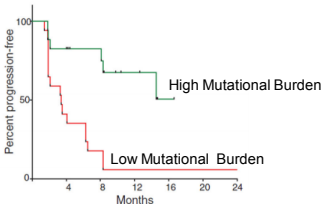


Target Modulation

Induction of Mutations

Nucleous

Direct and Indirect DNA Damage

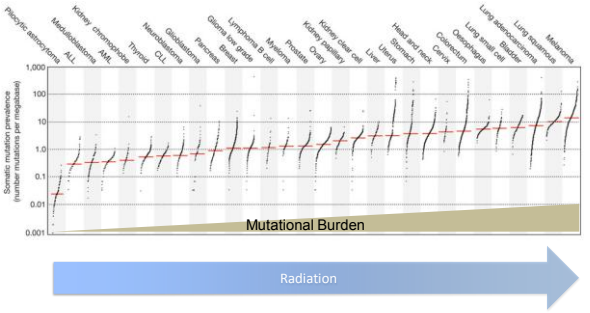


Survie globale au traitement PD - 1 dans le CPNPC selon la charge mutationnelle

Rivzi et al. Science 2015

Synergistic Radiotherapy

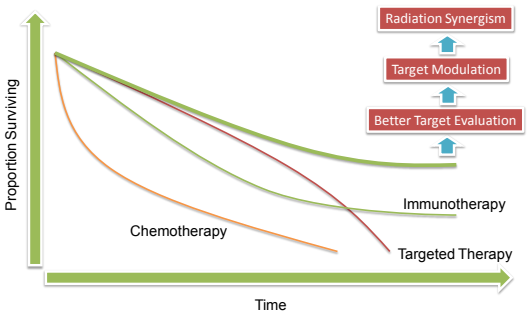
mutational status and Immunotherapy



Alexandrov et al., Nature 2014

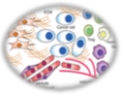
How to Enhnace Immunotherapy

Systemic Modulation



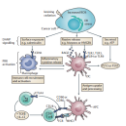
Synergistic Radiotherapy

Local Synergism in the Microenvironment



Microenvironment

Changes in Immune Homeostasis



MHC – I, and Fas/CD95, NKG2D Upregulation	• recognition and killing of irradiated tumor cells through T cells and NK cells (Van den Broek et al. Clin Cancer Res. 2013)
CXCL16 release	• Enhance T-cell their recruitment to the tumor site (Darmaria et al. J Immunol. 2008)
IFN-γ production	• creating a microenvironment beneficial for T-cell infiltration (Lord et al. J Immunol. 2008)
Reprogramming immune suppressive TME cells	• Transfomring M2like phenotype in M1 proinflammatory phenotype (2Gy) (Klug et al. Cell 2013)

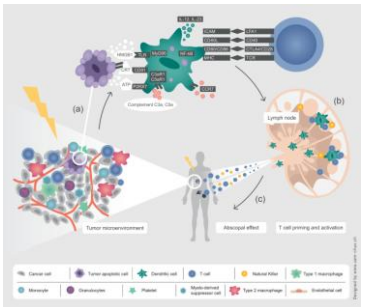
Synergizes with Immunetreatment

Synergistic Radiotherapy

Distant Synergism

Distant Effects

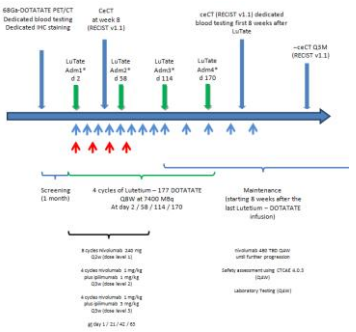
Changes Systemic Immune Status



Herrera & Coukos, CA Ongology 2017

The LuMed Trial

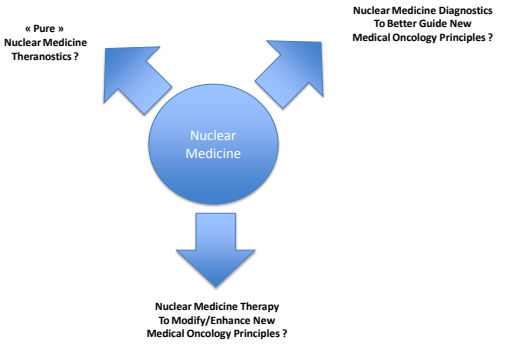
Phase I Trial Ipi/Nivo + Lutetium DOTATATE



Schaefer, Peters, Prior and Coukos, Funded by BMS and Tripple AAA

Theranostics : What is it about

(In my humble opinion)



The Promise of Modern Oncology

Nuclear Medicine has the diagnostic and therapeutic methods and could be part of the revolution