NH TherAguix

Nanomedicine for radiotherapy

SOIRÉE BIOTECH AGORA en collaboration avec PRE-IPO

Présentation NH TherAguix

Mardi 27 Juin 2017 - Paris

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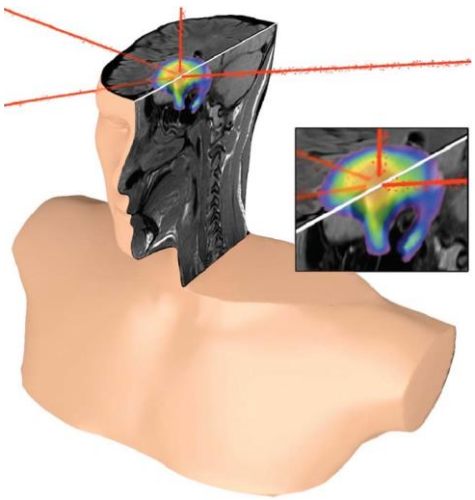
The problem

More sensitive for solid tumours, less destructive for surrounding tissues

60% of cancer patients (4 M/year US-EU) diagnosed with cancer have a radiotherapy



UNMET NEEDS:

30% *Radioresistant or badly positioned tumors*

→ ***AGuIX® could bring a Longer Life***

TREATMENT OPTIMIZATION :

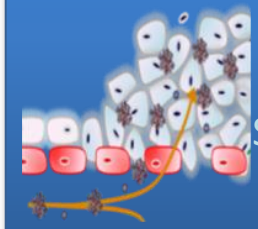
70% *of other patient : Secondary effects*

→ ***AGuIX® could bring a Better Quality of Life***

Report Institut Curie

The AGuIX® solution - Theranostic

See What You Target & Target What You See



Targeting

Specific tumour accumulation

High precision

Unique administration

Intravenous injection

Imaging

Precise treatment contour

Patient selection

Personalized treatment

Treatment

Activable drug

Cytotoxic under radiations

Local Radiation Booster

A new approach grafted on an existing method in the care follow-up

The AGuIX® Technology

2 Safe compounds, no drug delivery

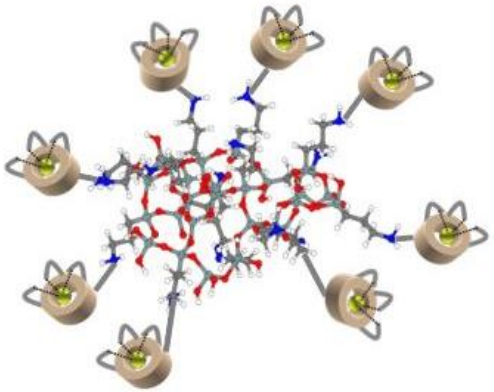
High gadolinium content ≈15 w%

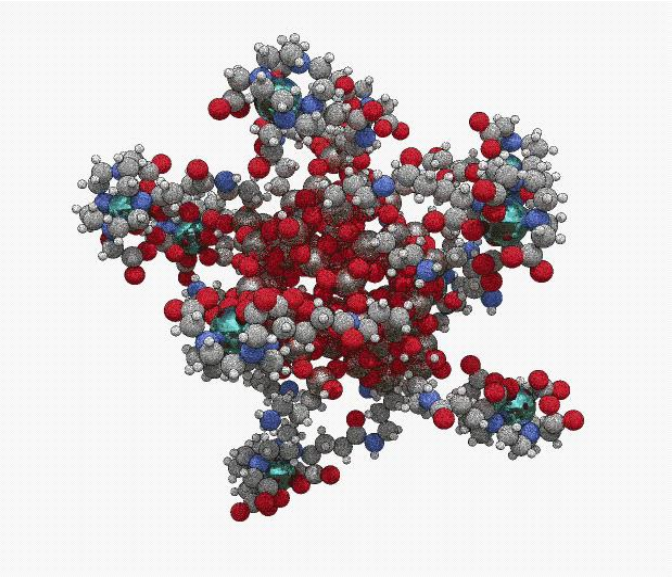
Gadolinium

MRI
Paramagnetic Properties

&

Radiotherapy
High Atomic Number (64)





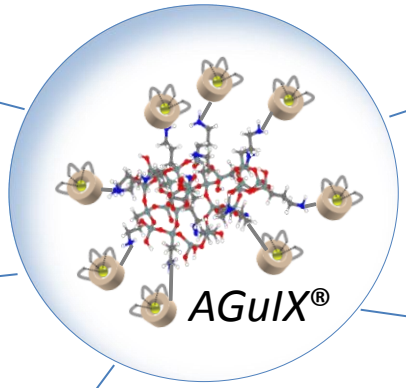
Size 2-5 nm

Preclinical Proof of Concept

10 years of academic research

In vivo radiotherapy efficiency in 6 tumours models
brain, head&neck, pancreas, lung, melanoma

In vivo MRI contrast uptake in tumour models



Regulatory toxicity (rats/monkeys)
Scale-up and industrialization of the production

In vitro demonstration of radiosensitizing effects

- 10+ collaborations
(Harvard, MIT, Yale, IGR, Stanford)
- 50+ publications
- 4 patents (5 +)
- 9-12 PhD students
- POC in 6 in vivo tumour models

O Tillement designed the AGuIX®
G Le Duc discovered the radiosensitizing effect

***Le Duc G**, Miladi I, Alric C, Mowat P**,** Bräuer-Krisch E, Bouchet A, Khalil E, Billotey C, Janier M, Lux F, Epicier T, Perriat P, Roux S**, Tillement O.** ACS Nano. 2011 Dec 27;5(12):9566-74*

Intellectual Property

Portfolio

✔ 4 patents family (exclusive sublicense)

✔ 1 patents family (full property)

✔ 1 coproperty patents (recently filed) : Harvard-ILM , AGuIX Bi/Gd

✔ 2 co property patents IGR/ILM (nano-radio Im, and Combix)

✔ FTO has been confirmed

PCT number	subject	Date of filing	Country	Status
WO2005/088314	Coeur Coquille	02/03/2004	FR, EP, US, JP, CA	delivered
WO2009/053644	Radiosensibilisation	16/10/2007	FR, CN JP, CA	delivered published
WO2011/135101	SRP	30/04/2010	FR EP, US	delivered published
WO2013/153197	Lung	13/04/2012	FR, EP, US, CA, JP	published
EP17305709	New method for synthesis	13/04/2017	WO including CN	filed

Competition

first in class versus best in class

NANOBIOTIX	NH TherAguix
Hafnium, 50 nm, Med Dev (drug US)	**Gadolinium, 5 nm, Drug**
• Intra-**Tumoral** administration • Elimination by the **liver** if IV • Interventional radiology	• **Intravenous** administration • MRI and Radiotherapy using the **same** injection • Elimination by the kidney (2h) • Inhalation and intratumorous also
IPO en 2012 (45 M€) - Phase 1 int. 280 M€ Market Cap	• Easy **implementation** • On top of **current medical** practices • **Theranostic** • Addressable to **all solid cancers**

Team organization

Géraldine Le DUC
CEO
Founder

Olivier TILLEMENT
CSO
Founder

Strategic Board

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Chairman
Business Advisor

François LUX
Chemistry
Production, IP, R&D

Sandrine DUFORT
Bio & Pharm
Clinical trials, R&D

Irene GOW
Chief Medical
Officer

Laurent Bracco
Investor Advisor

Brad HOY
Chief Financing
Officer

KOLs- Early Followers
Pr. E. Deutsch - Institut Gustave Roussy
Pr. K. Price - Queens University
Dr. R. Berbeco - Harvard
Dr. G. Appelboom - Stanford

Advisory committee	
B. Bigot	General Director CEA
Pr. J.F. Le Bas	Neuroradiologist
L. Poncin de Latournerie	CEO Ezus
C. Ulrich	CEO AVNIR
C. Louis	CEO Nano-H
F. Mouthon	CEO Theranexus

Summary

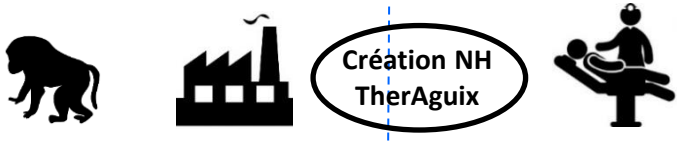
2005 2010 2015 2016 2017

Preclinical PoC - Academic institutions

- 10+ collaborations
- 50+ publications,
- 4 patents (2+)
- 9-12 PhD students

→ PoC 6 *in vivo* tumours models

~ 10 Millions € invested
academic



Scale-up

Regulatory toxicity

→ 1000 vials for clinical trials (Carbogen)

1,5 Millions € invested
academic

Clinical trials

- First In Man Nanorad

3 Trophies

- Tremplin-Senate
- France Biotech
- R2B Onco

Capital 100 k€
Sales 120 k€
BPI 200 k€

Clinical trials

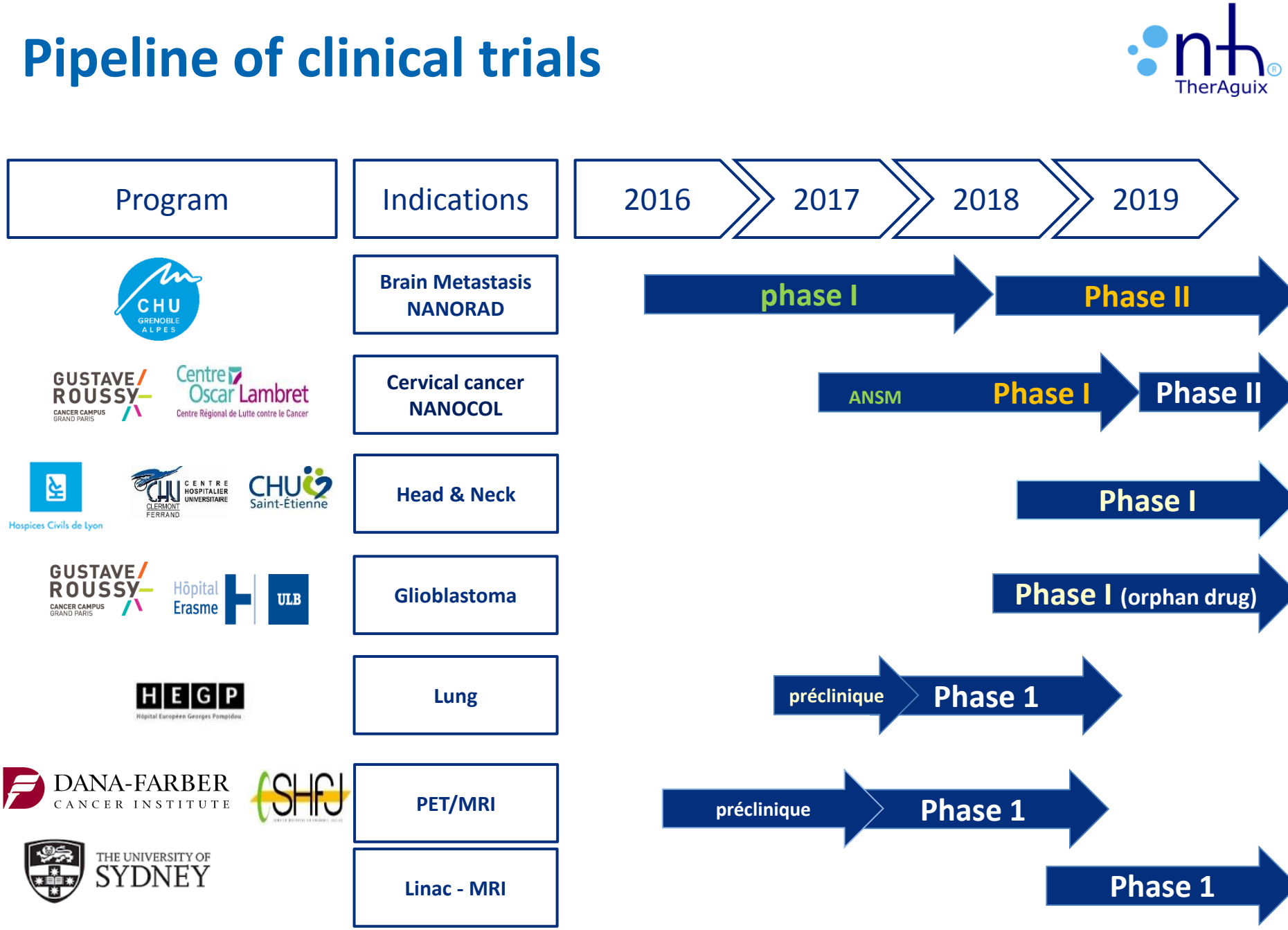
- *Nanorad* (10 pat/15)
- *Nanocol* trial submitted
- *Phase 2* designed

Production of Batch 2
On going, for Phase 2

Fund raising 600 k€
Bank Loan BPI 200 k€

In progress
Fund Raising > 675 k€

Pipeline of clinical trials



NANORAD – Phase 1 Trial
Brain Metastasis

First in Man NANORAD – Phase I

Sponsor CHU Grenoble Alpes

PI Dr C. Verry , Radiotherapy Department
Head: Pr J. Balosso

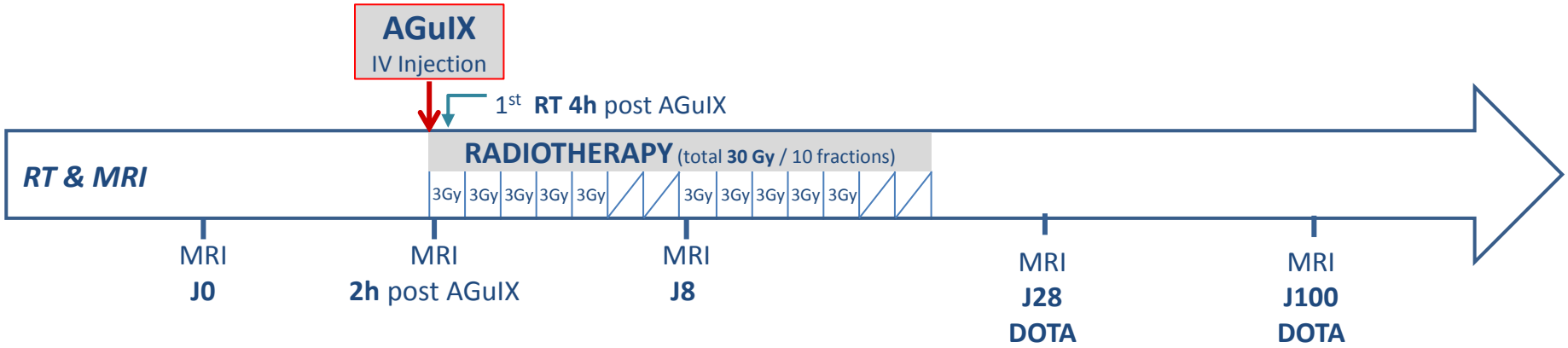
Dose-escalation 5 dose levels (n=3 patients)
15, 30, 50, 75 and 100 mg/kg

Inclusion criteria

Multiple BM ineligible for local treatment by surgery or stereotactic radiation

Primary cancer : Melanoma, Lung , Breast, Colon

25 % of cancer patients, Life expectancy < 4 months



NANORAD – Phase I

Study Objectives

Objective 1 : Determination of the Maximal Tolerated Dose (MTD)
Evaluation of the incidence of **dose limiting toxicity (DLT)**

Objective 2 : Pharmacokinetic characteristics of AGuIX
Blood samples at T0, 15min, 30min, 1h, 2h, 4h, 6h, 10h (or 12h), 24h and D8, *D28*
Urine samples over 24h (3 fractions of 4h and 1 fraction of 12h), *D3, D5,* D8, *D28*

Objective 3: **MRI & AGuIX tumor targeting**
Evaluation of distribution and elimination of AGuIX in brain metastases and surrounding healthy tissue

Objective 4 : **Therapeutic response**
Evaluation of **intracranial progression free survival (MRI)**
Evaluation of **overall survival**

Patient recruitment

	15 mg/kg			30 mg/kg			50 mg/kg		
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Primary cancer	**Lung** multisite	**Melanoma** multisite	**Lung** multisite	**Lung** multisite	**Melanoma**	**Melanoma** multisite	**Melanoma**	**Lung**	**Colon carcinoma** multisite
Sex	M	M	M	M	F	M	M	M	M
Age	70	64	60	79	37	60	46	69	68
Number of brain mets	5	30	8	4	> 50	24	12	13	4

4 lung cancers / 4 melanoma / 1 colon carcinoma
8 men / 1 woman
> 60 years old
Number of brain metastases : 4 → > 50

Melanoma patients → greater number of metastases

SAFETY & PK results

Tolerance of AGuIX® administration

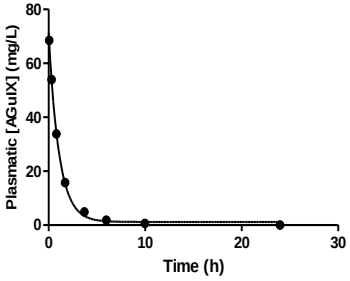
	15 mg/kg			30 mg/kg			50 mg/kg		
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Complication at injection site									
• Pain	No	No	No	No	No	No	No	No	No
• Erythema	No	No	No	No	No	No	No	No	No
Systemic response									
• Urticaria	No	No	No	No	No	No	No	No	No
• Quincke edema	No	No	No	No	No	No	No	No	No
• Itching	No	No	No	No	No	No	No	No	No
• Hypotension	No	No	No	No	No	No	No	No	No
• Hypertension	No	No	No	No	No	No	No	No	No
• Muscle contraction	No	No	No	No	No	No	No	No	No
• Warm feeling	No	No	No	No	No	No	No	No	No
• Cold feeling	No	No	No	No	No	No	No	No	No
• Pain	No	No	No	No	No	No	No	No	No
• Fever	No	No	No	No	No	No	No	No	No
• Shiver	No	No	No	No	No	No	No	No	No
• Feeling of faintness	No	No	No	No	No	No	No	No	No
• Asthenia	No	No	No	No	No	No	No	No	No
• Abnormal movements	No	No	No	No	No	No	No	No	No

Good tolerance of AGuIX injection for the 3 first dose levels – MTD ≥ 50 mg/kg

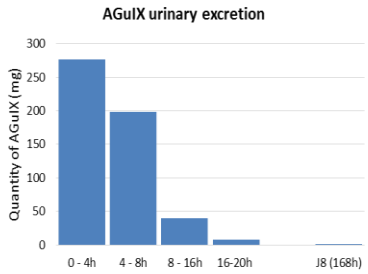
Passage to the fourth dose level (75 mg/kg)

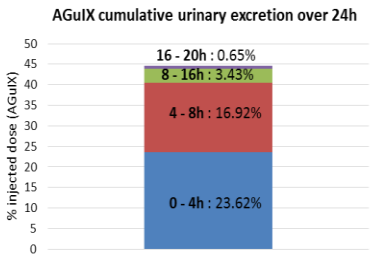
Pharmacokinetic and Elimination

Plasmatic data



Urinary data





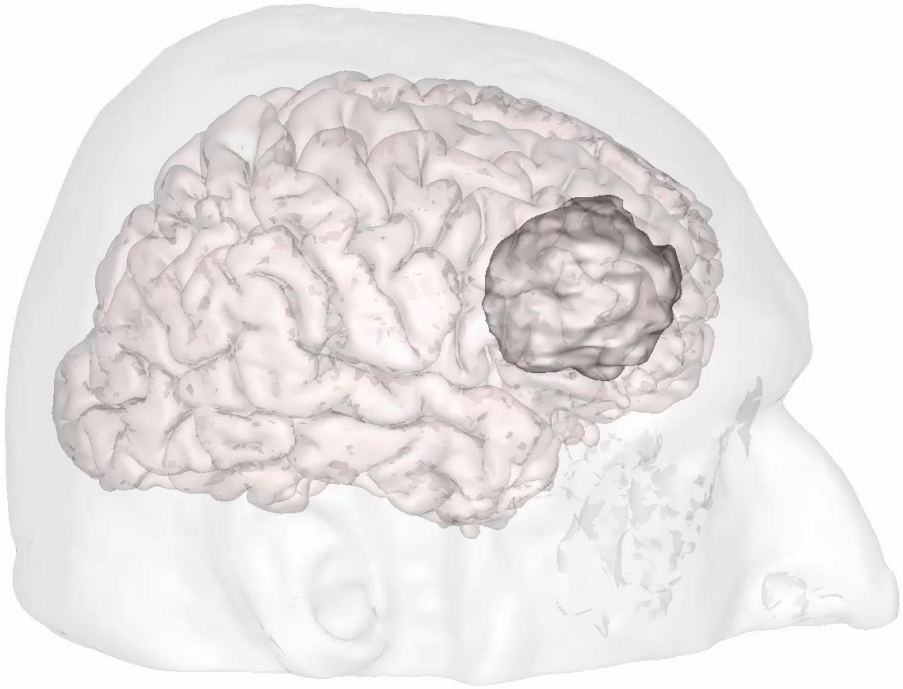
	15 mg/kg			30 mg/kg			50 mg/kg		
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
T1/2 (h) plasma	**2h**	**45min**	**1h20**	**50 min**	**1h18**	**57 min**	**56 min**	**1h06**	**48 min**
Urinary excretion (over 24 h)	**45%**	**45%**	**55%**	**48%**	**/**	**49%**	**70%**	**50%**	**50%**

Short half life: $T_{1/2}$ ***: 45min - 2 h***

Urinary excretion: ***≈ 50% of the injected dose over the first day***

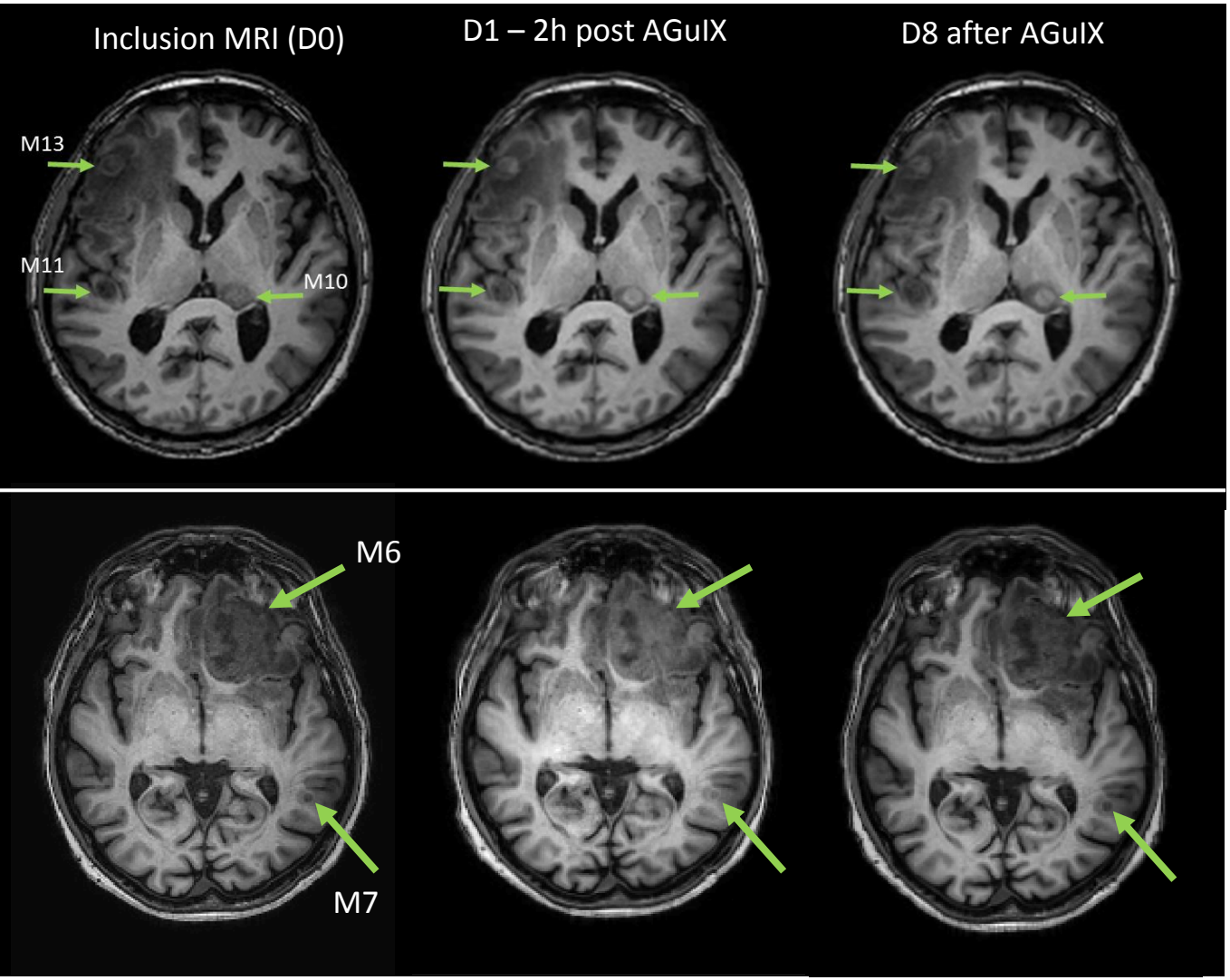
Tumour AGuIX® targeting & MRI

The MRI contrast uptake
Pat#3 , 15 mg/kg, lung cancer

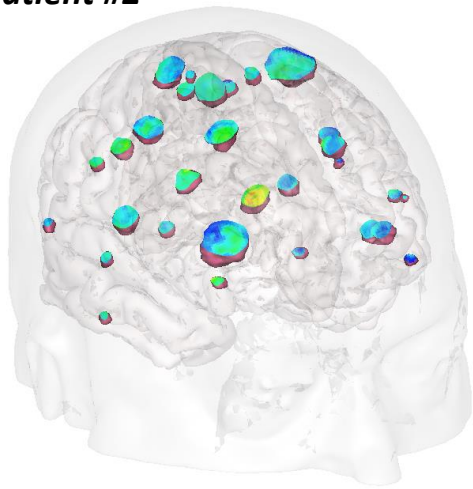


- Relaxivity@ 3T : 8.9 $mM^{-1}.s^{-1}$ / AGuIX 3.4 $mM^{-1}.s^{-1}$ /Dotarem
- MRI performed 2 hours after injection ECG monitoring

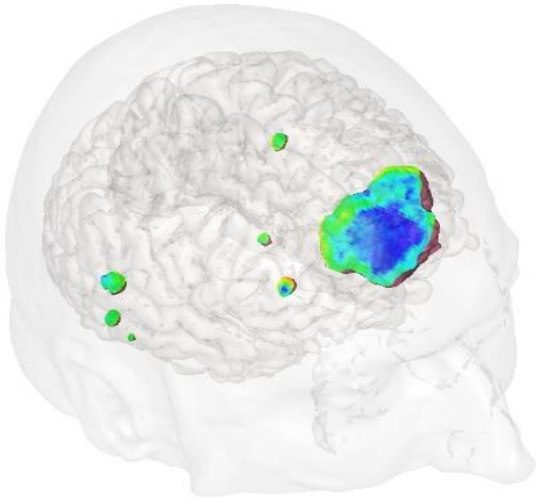
MRI T_1 enhancement of metastases



Patient #2



Patient #3



AGuIX targeting and tumour uptake

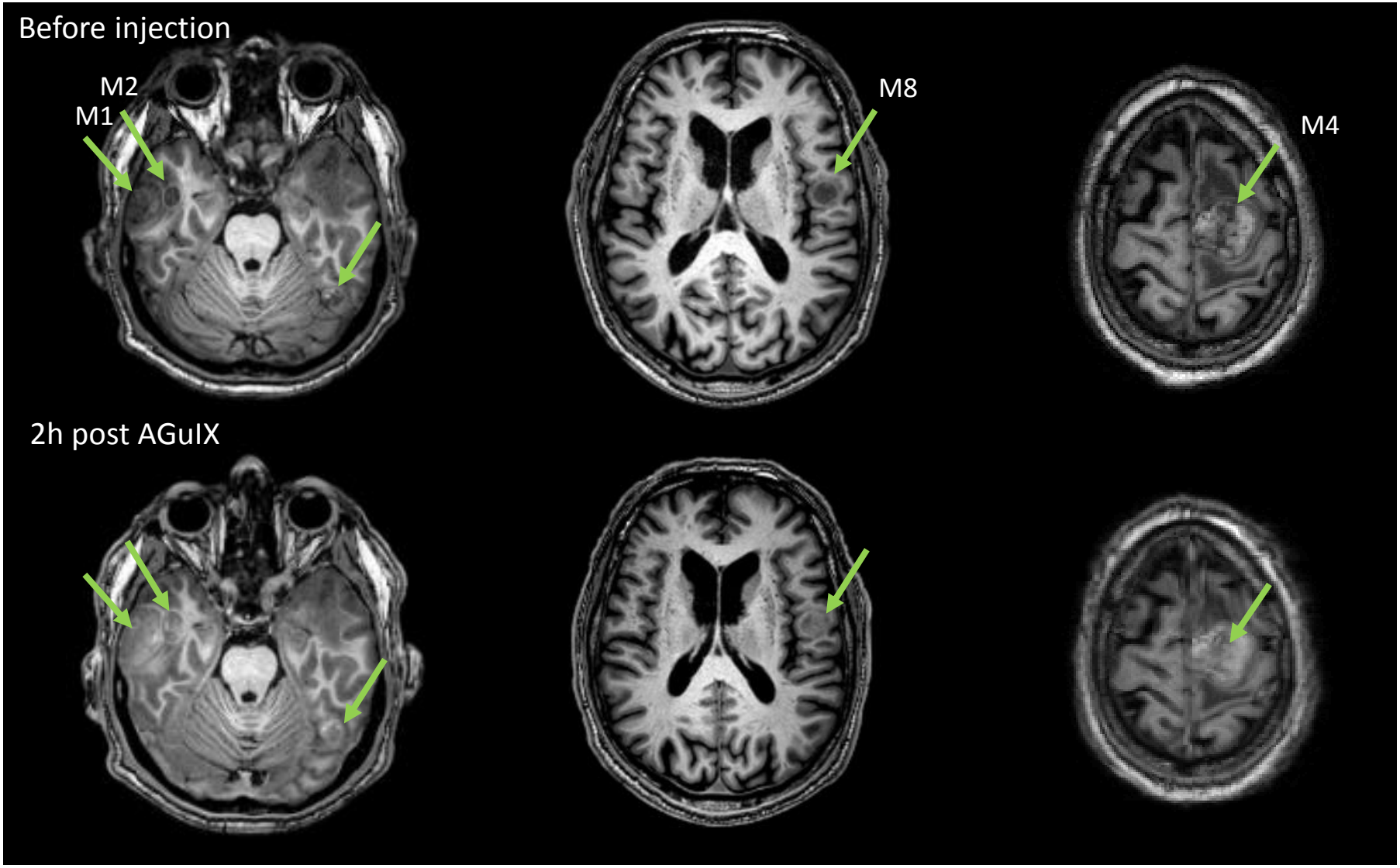
MRI T_1 enhancement of metastases *2h after IV injection and still after 1 week*

Third dose level - AGuIX 50 mg/kg

Patient #7
Melanoma

Patient #8
Lung cancer

Patient #9
Colon cancer



The MRI contrast uptake

	15 mg/kg			30 mg/kg			50 mg/kg		
	Patient1	Patient2	Patient3	Patient4	Patient5	Patient6	Patient7	Patient8	Patient9
Primary cancer	Lung cancer	Melanoma	Lung cancer	Lung cancer	Melanoma	Melanoma	Melanoma	Lung	Colon carcinoma
Enhancement D1	**19.50 %**			**17.50 %**			**44 %**		
Enhancement D8	**/**			**/**			**12 %**		
Ratio AGuIX.Dotarem	**11 %**			**15 %**			**37 %**		

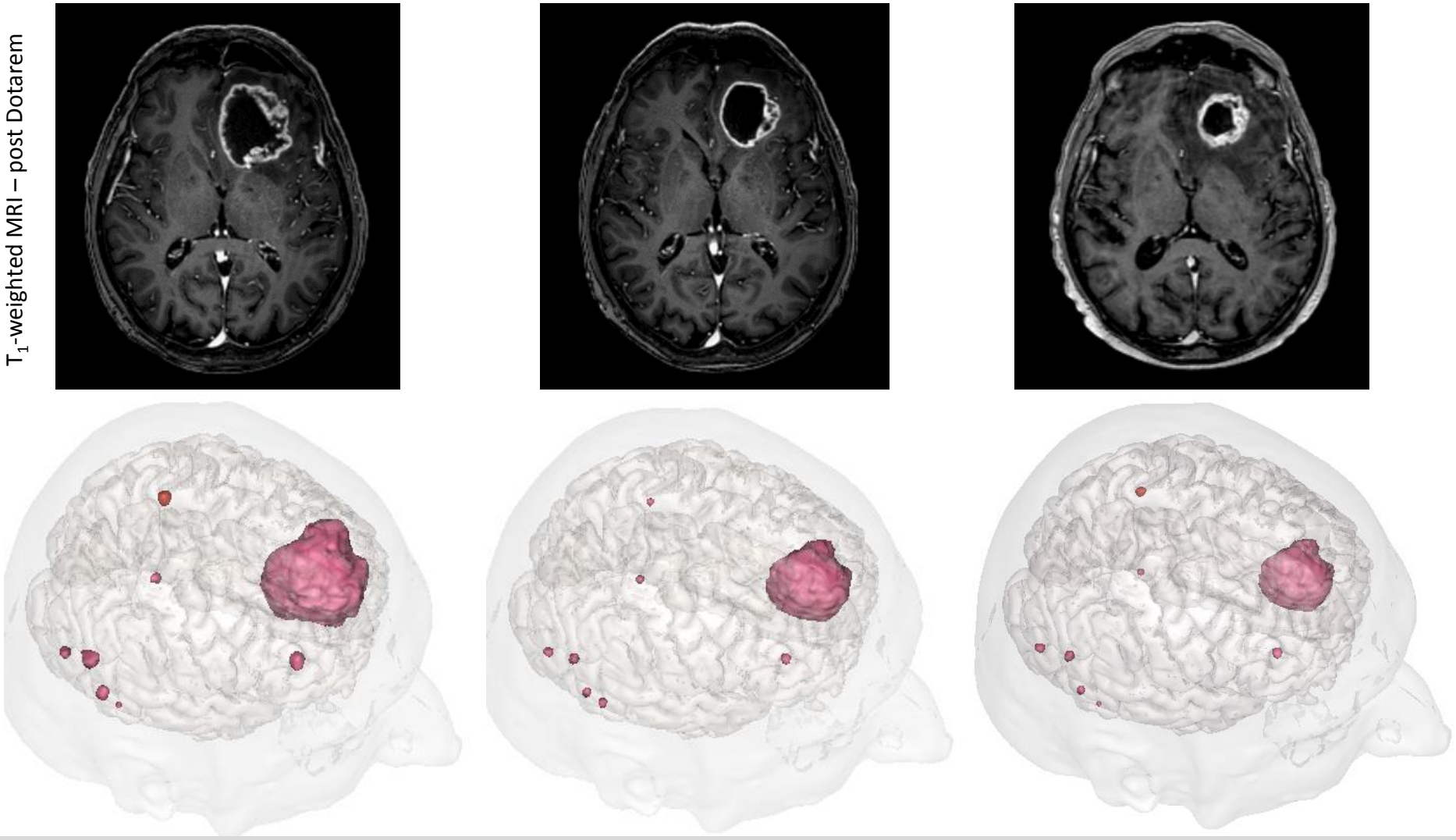
T1 enhancement : *1/3 efficiency compared to DOTAREM (2h after injection of half dose)*
AGuIX tumour uptake : *targeting increases with doses, visible for 3 tumour types*
AGuIX persistance in tumours : *still present and visible 1 week after administration*

Tumour response

Patient #3 – Lung – AGuIX® 15mg/kg

T_1-weighted MRI – post Dotarem

Inclusion MRI (D0)	*1 month post treatment*	*3 months post treatment*



Reduction of the total tumor volume after treatment by a factor 3

Total Brain metastases volume: 45.5 cm^3 at D0 → 21 cm^3 at 1 month → 15.5 cm^3 at 3 months

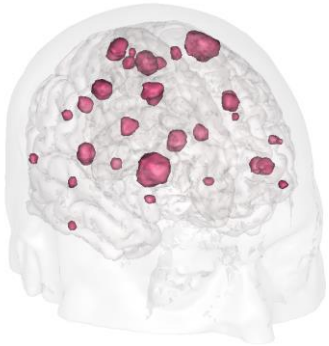
Therapeutic response

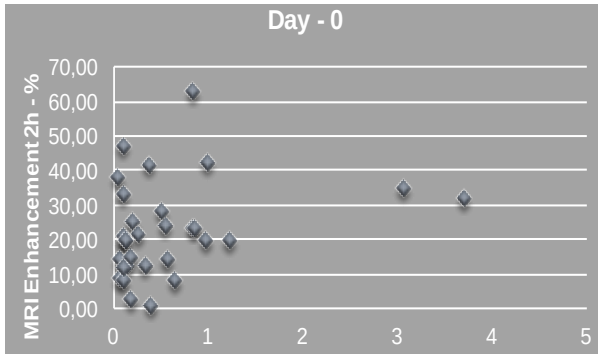
	15 mg/kg			30 mg/kg			50 mg/kg		
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Primary cancer	**NSCLC**	**Melanoma**	**NSCLC**	**NSCLC**	**Melanoma**	**Melanoma**	**Melanoma**	**NSCLC**	**Colon carcinoma**
Number of brain mets	5	30	8	4	> 50	24	12	13	4
Total sum of metastases longest diameters (mm)									
D1 **1 month** **3 months**	33 mm 17 mm ↘ /	243 mm 295 mm ≈ 118 mm ↘	78 mm 72 mm ↘ 69 mm ↘	31 mm / /	331 mm 689 mm ↗ /	210 mm 219 mm ≈ /	215 mm 191 m ↘ /	127 mm 128 mm ≈ *ongoing*	77 mm 66 mm ↘ *ongoing*
Overall Survival from D1 from diagnosis	**2.5 m** **5 m**	**5.5 m** **8 m**	**4 m** **8 m**	**No treatment**	**1 m** **8 m**	***ongoing***	***ongoing***	***ongoing***	***ongoing***
Cause of death	**Sepsis AGuIX free**	**Disease progression**	**Disease progression**	**Heart attack AGuIX free**	**Disease progression**	***ongoing***	***ongoing***	***ongoing***	***ongoing***
Clinical benefits evidence	**Yes**	**Yes**	**Yes**	No treatment	**No**	***Yes***	***Yes***	***Yes***	***Yes***

Contrast Enhancement
Versus
Tumour response

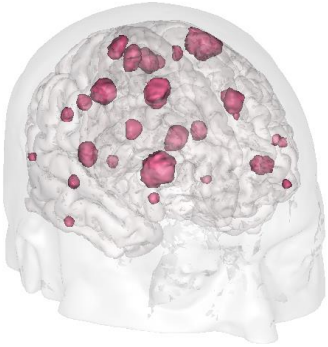
AGuIX® uptake, prediction of tumour response

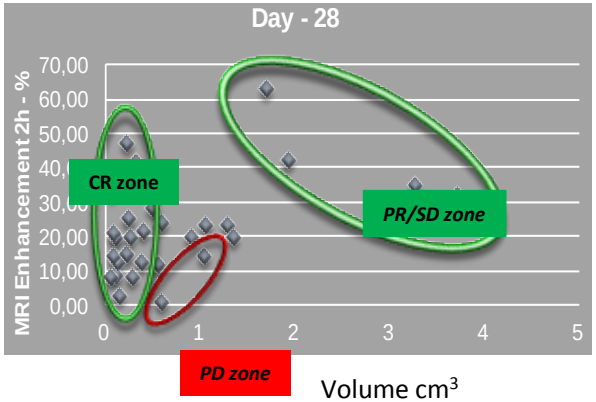
Inclusion MRI (D0)



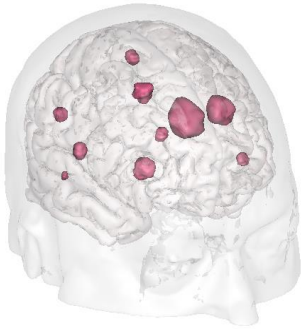


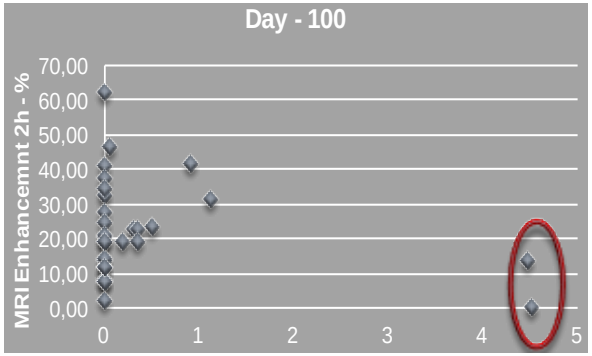
1 month post treatment



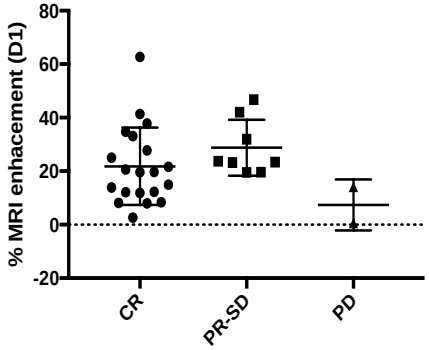


3 months post treatment





Tumour response and AGuIX MRI enhancement D1



Tumour responses

Decrease of tumour volume: V_{D100}/V_{D28}: 58%

20 CR Complete Responses

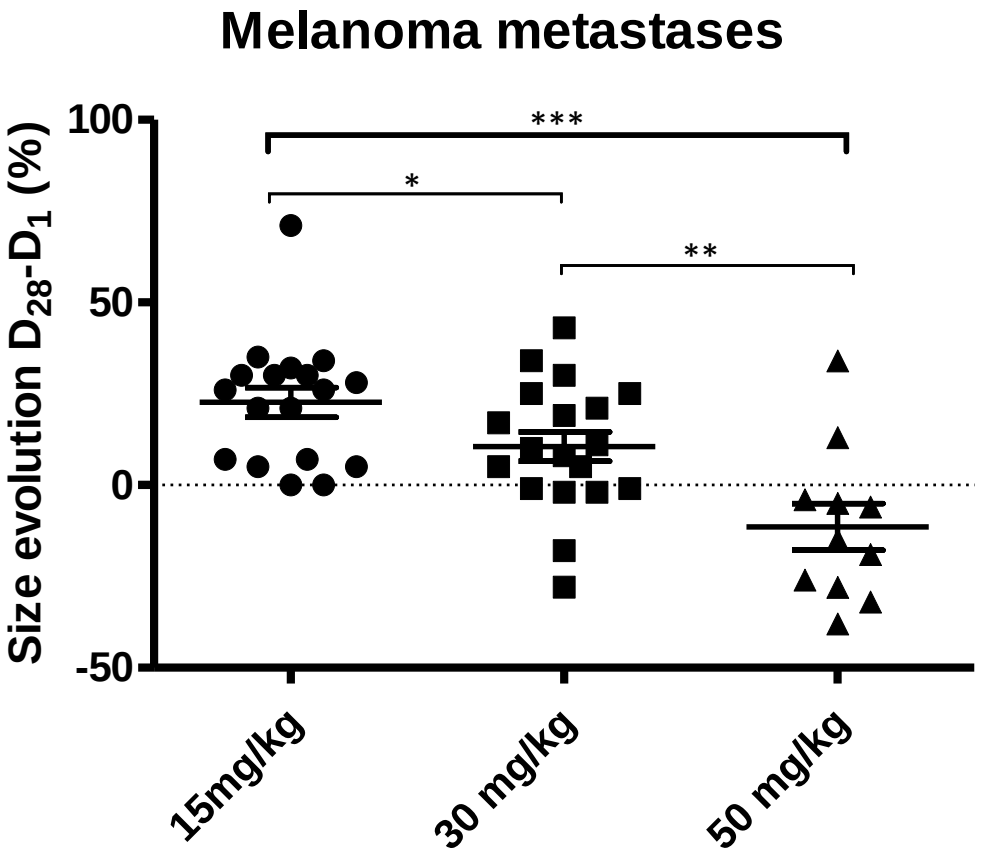
8 PR/SD Partial Response or Stable disease

2 PD Progressive disease

AGuIX® uptake: dose effect

Effect of injected dose on the size evolution of each metastasis
comparison patient #2, #6, #7 with multiple melanoma metastases

Size evolution D28-D1 (%)
Mean ± SEM



Correlation between AGuIX tumour uptake and tumour response
Higher doses of AGuIX give better tumour response

NANORAD Phase I on brain metastases
Intermediate results after 9 patients

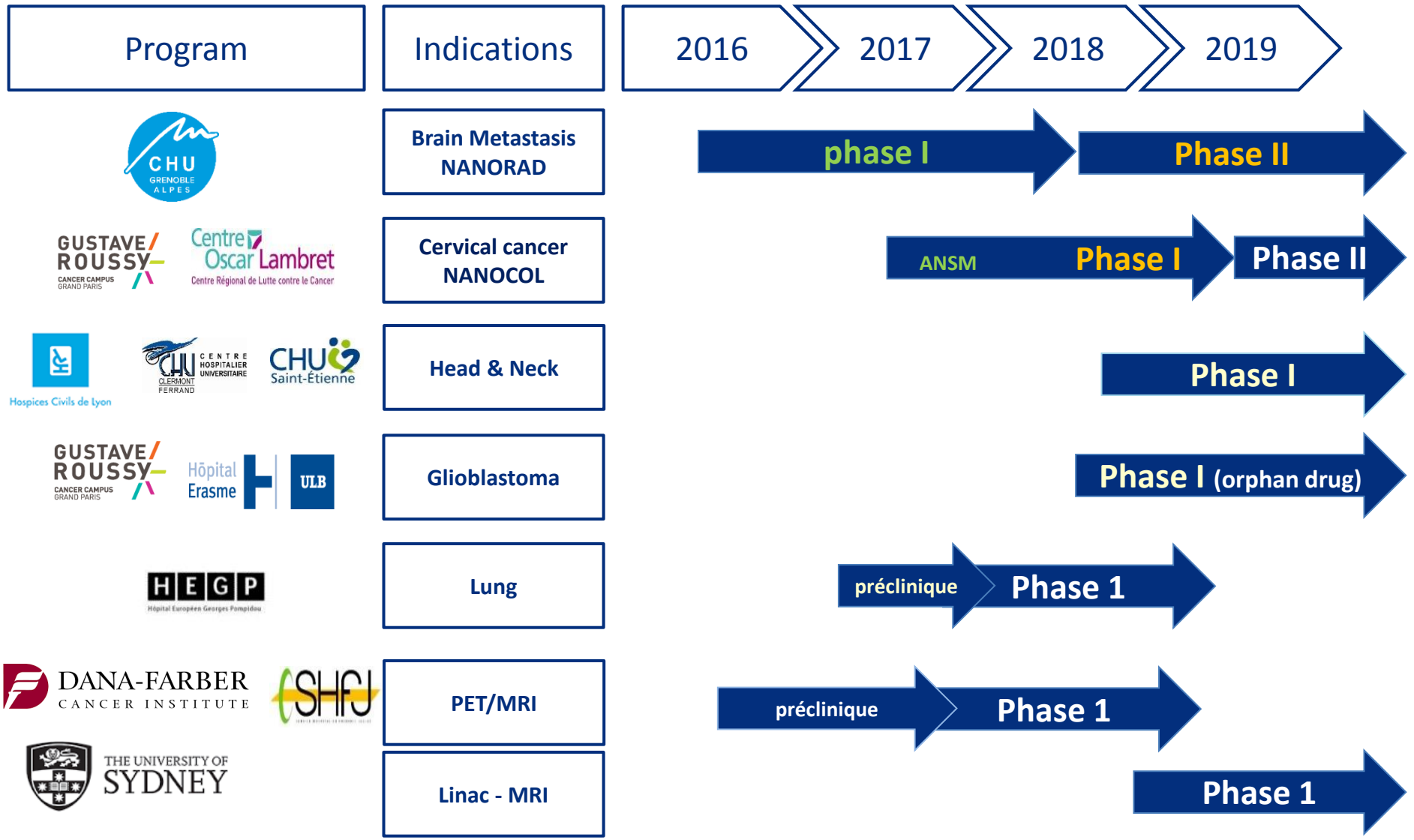
15 mg/kg	30 mg/kg	50 mg/kg	75 mg/kg	100 mg/kg
n=3	n=3	n= 3		

✔ **First proof of safety**
No adverse effects due to the injection of the drug (even minor)
Fast blood half life and renal elimination

✔ **First proof of contrast uptake**
Contrast uptake for 9/9 patients (15 - 30 - 50 mg/kg)
(melanoma, NSCLC, Colon carcinoma)
Remanence of the contrast enhancement 8 days after injection in tumour tissues

✔ **Therapeutic response**
Response to the treatment (WBRT + AGuIX)
Clinical benefit
Correlation between AGuIX contrast uptake and tumour response
Dose effect

Pipeline of clinical trials

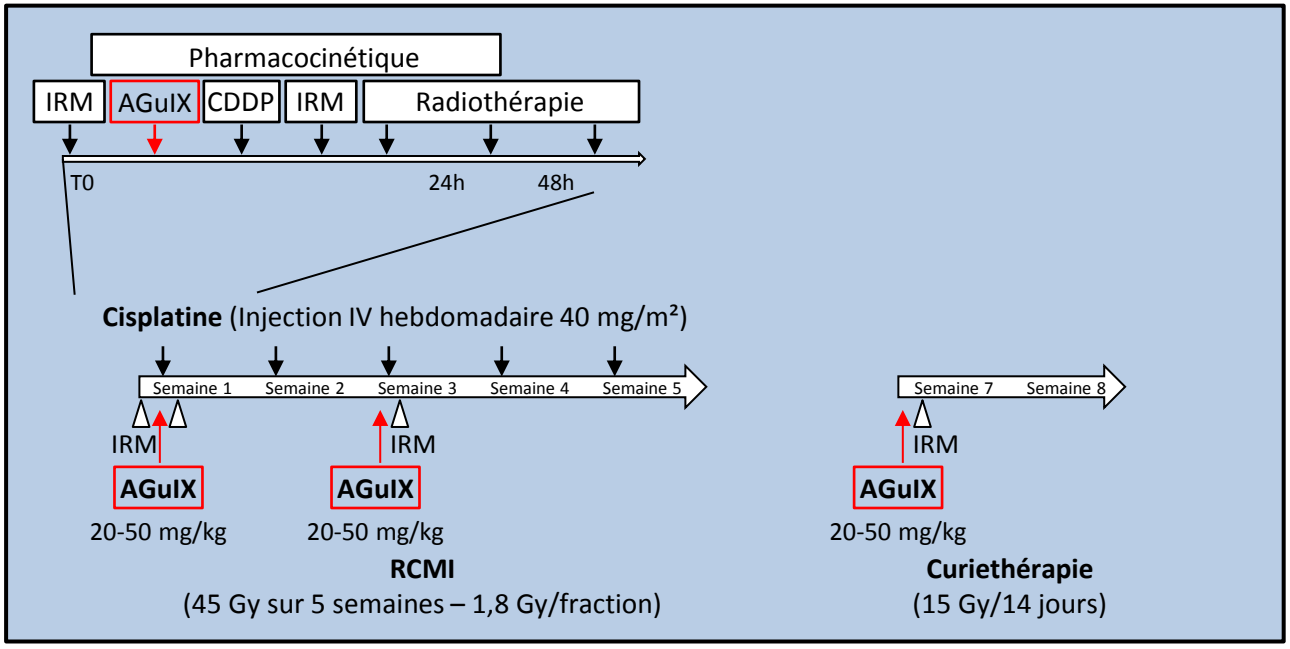


NANOCOL Phase 1

Advanced cervical cancer

PHRC

• Better prognosis	30-45 % @ 5 years versus 2,5 months for Nanorad
• Safety Results from Nanorad	30 mg/kg versus 15 mg/kg
• Other indication	primary cancer versus metastasis
• Dose effect	3 injections versus 1 injection



Fund raising

PRE-IPO

The goal for NHT is:
to move to Phase 2 with Batch 2 and run others Phase 1 in parallel
to recruit a chemist (ILM) and a biologist (IGR)

Q2 2017 – Target 1 M€ - 30 Juillet

Fund raising in progress with PRE-IPO, Allinvest group

Q1 2018

Series A round – 10 M€

2019 – IPO and BIG PHARMA - Fin de la Phase 2

Fund raising

PRE-IPO

1 **LE PRODUIT**

Un produit qui **améliore l'efficacité des radiothérapies** dans le traitement des cancers

2 **L'INNOVATION**

Une solution **non invasive et personnalisée** qui améliore l'**imagerie** et le **traitement** du cancer, **sans changer la pratique médicale**

3 **LE MARCHÉ**

AGuIX® a un potentiel de vente de **3 Mds€** en US+EU sur un **marché en croissance pour 1 indication (métastases cérébrales)**

4 **L'ÉQUIPE**

Une équipe d'experts aux **compétences complémentaires et bien entourée**

5 **LA PERSPECTIVE**

Traiter ou adapter le traitement de l'ensemble des cancers solides en radiothérapie grâce à **la taille nanométrique** des particules

PRE-IPO

Biotech AGORA

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