The EORTC

STAR

initiative

Synergy of Targeted Agents and Radiotherapy

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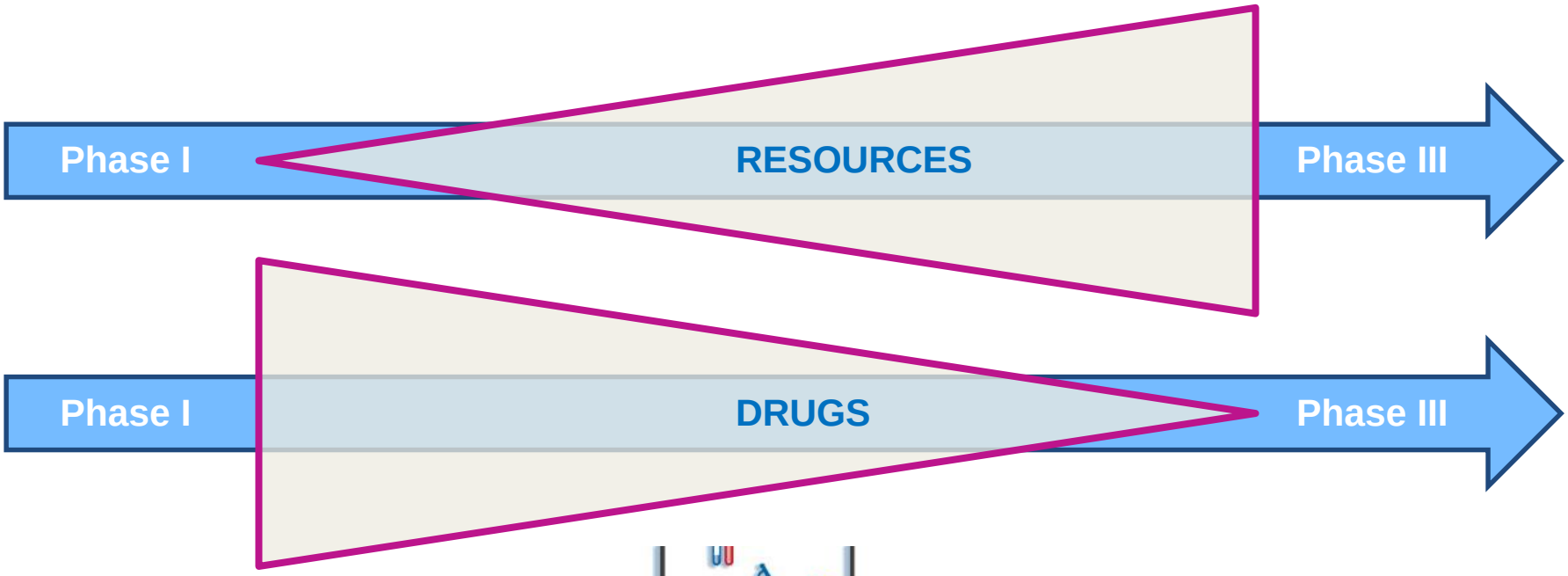
ICTR 18/02/2016

EORTC

The future of cancer therapy

STAR : A ROG working party based on what we have learned from targeted agents development

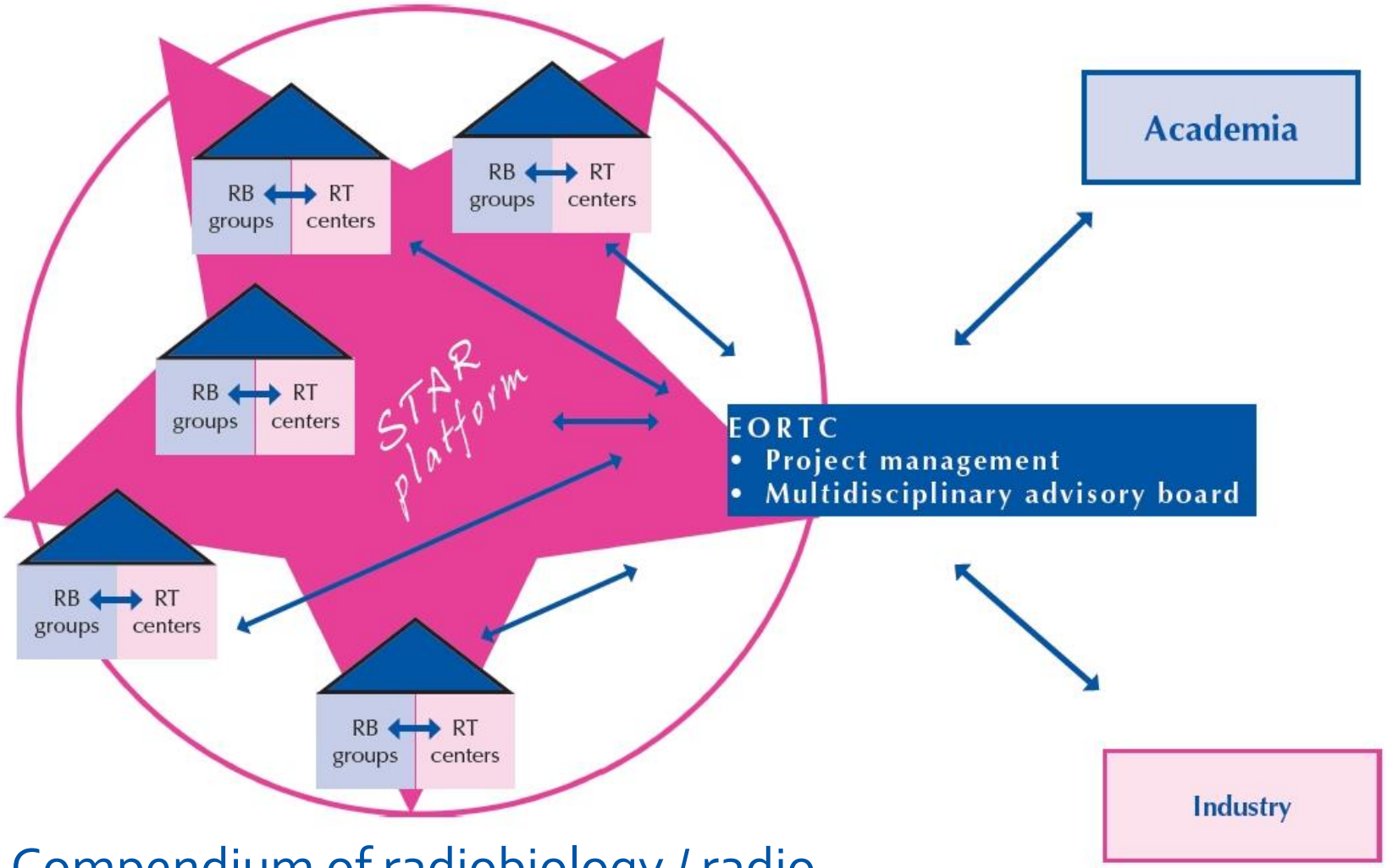


Drug and RT combinations….
Only 2 success stories
Cetuximab and Temodar

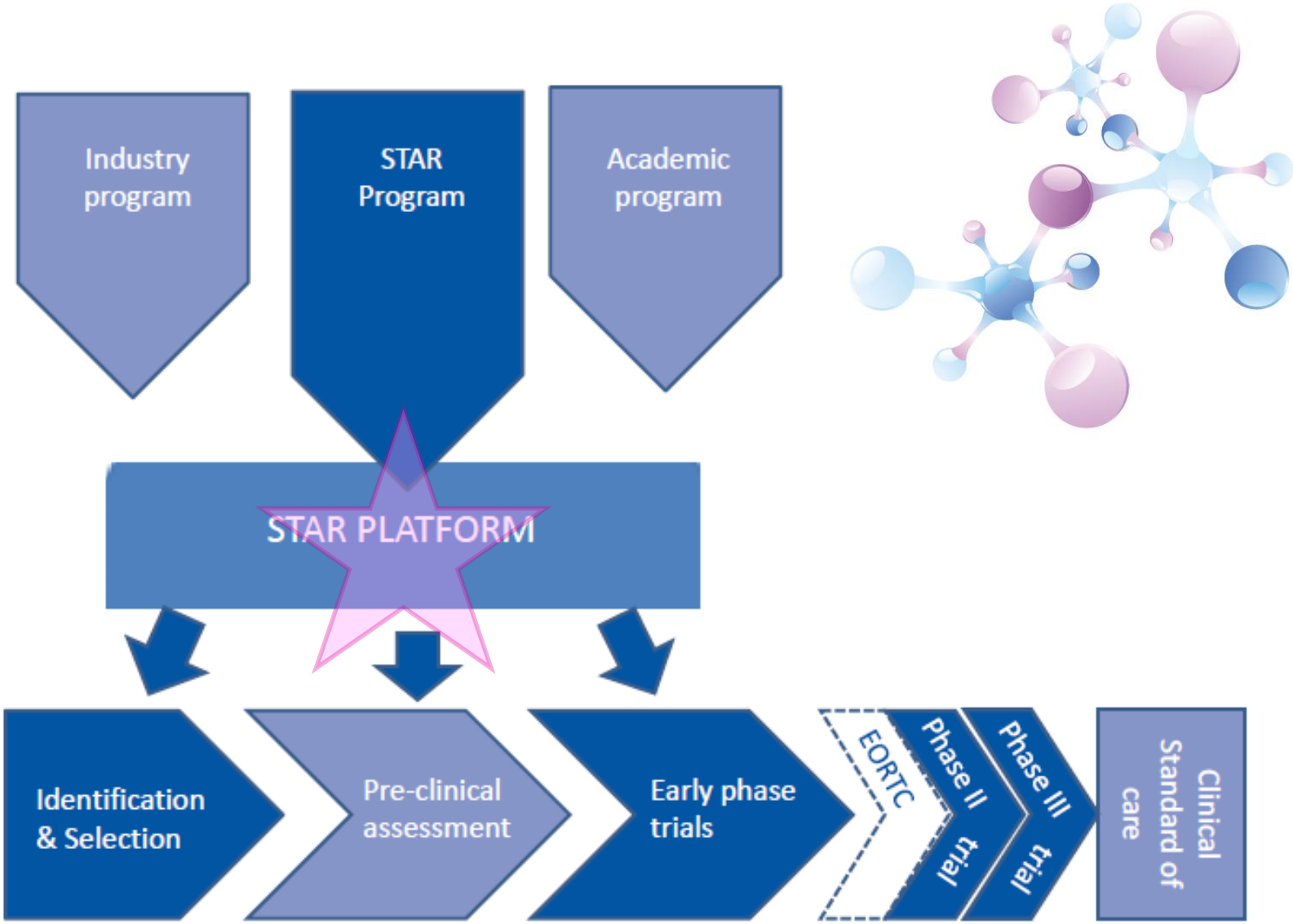
Causes for RT/drug combination misses

* lack of appropriate expertise or tools (biomarkers)
* RT quality issues
* wrong choice of tumor (RT setting) or target, wrong model
* weak rational of combination benefit
* few (financial) opportunities to run RT trials with pharma, late access to drug in their development

=> **limited proof of concept due to investment in trials that are less likely to succeed**



Compendium of radiobiology / radio-oncology expertise and models


Industry program
STAR Program
Academic program
STAR PLATFORM
Identification & Selection
Pre-clinical assessment
Early phase trials
EORTC
Phase II trial
Phase III trial
Clinical Standard of care

STAR working party initial objectives :

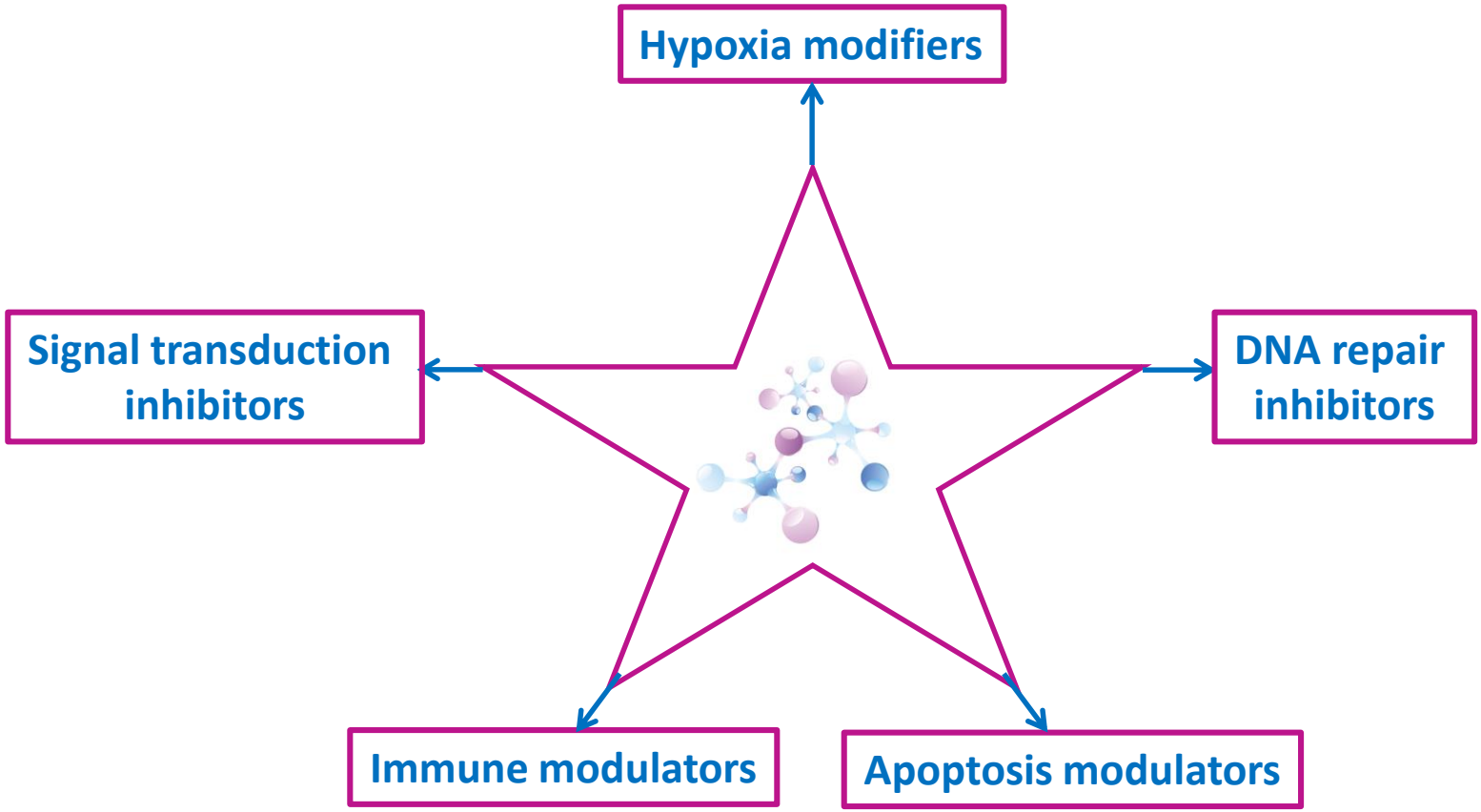
- **Development of RT-drug combinations:**
  enlarging therapeutic window

- evaluate potential RT + novel agent combinations

- support early implementation of RT combinations with new targeted agents and/or new chemotherapies

- Facilitate, optimize and promote early phase trials with combined modalities

STAR achievements: Identification of drugs of interest



STAR achievements: Contact with industries

- **Approached pharmas:**
  - Merck, AbbVie, Celgene, Sanofi, Noxxon (BTG), Rinat/Pfizer, Apogenix, Astra Zeneca, Inovio (ROG-GCG), Roche, Nanobiotix, Oncodesign, CellProtect
- **Approach strategies:**
  - EORTC official contacts, personal direct contact, institution contacts
- **Results:**
  - Scarce funding opportunities
  - RT-drug combination not seen/recognized as a priority

STAR achievements:
Contact with investigating centers

- **Questionnaire online**
- **Aiming at a STAR Web Platform**

http://www.eortc.be/services/forms/STAR/STARsurvey.asp

- **Little response rate and feedback**
  - Lack of interest?
  - Lack of communication?
  - Lack of projects to propose
  - Lack of projects to join
  - Direct contracts pharma/single institution

EORTC STAR:

Synergy of Targeted Agents and Radiotherapy
The new drug and Radiotherapy EORTC programme

General Survey FORM

Instruction: this form has to be completed by the site no later than *dd/mm/yyyy* in order to evaluate adequately the centers which will join this programme.

Country
Institution name
Institution number
Name of the EORTC contact Radiobiologist
Email address
Name of the EORTC contact radiation oncologist
Email address
Names of other persons involved in you team
Names and affiliations of other leaders from you institution

STAR achievements: Studies and follow-up

STAR*001:

Hypoxia activated drug as radiosensitizer for NSCLC and HNSCC

STAR Evaluation: High priority

STAR Proposal: Assessment of RT combination toxicity and efficacy *in vitro* and *in vivo* to guide most effective early clinical trial

STAR involvement: Multicentre proposal including UMC St Radboud, NKI, IGR

Status: Pending on the success of phase III monotherapy trial. Management decision from the company to cut finances for any development of this drug.

STAR*001:

Hypoxia activated drug as radiosensitizer for NSCLC and HNSCC

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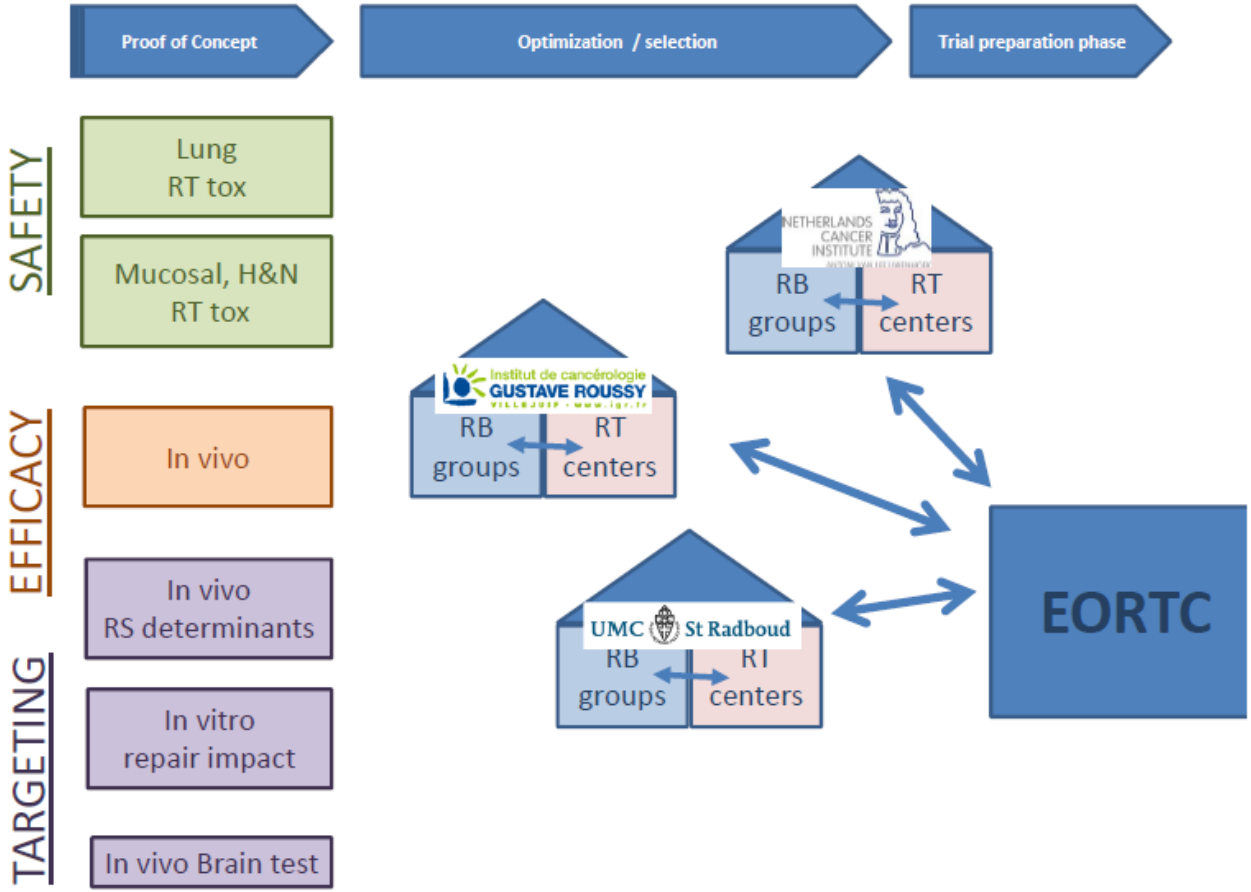
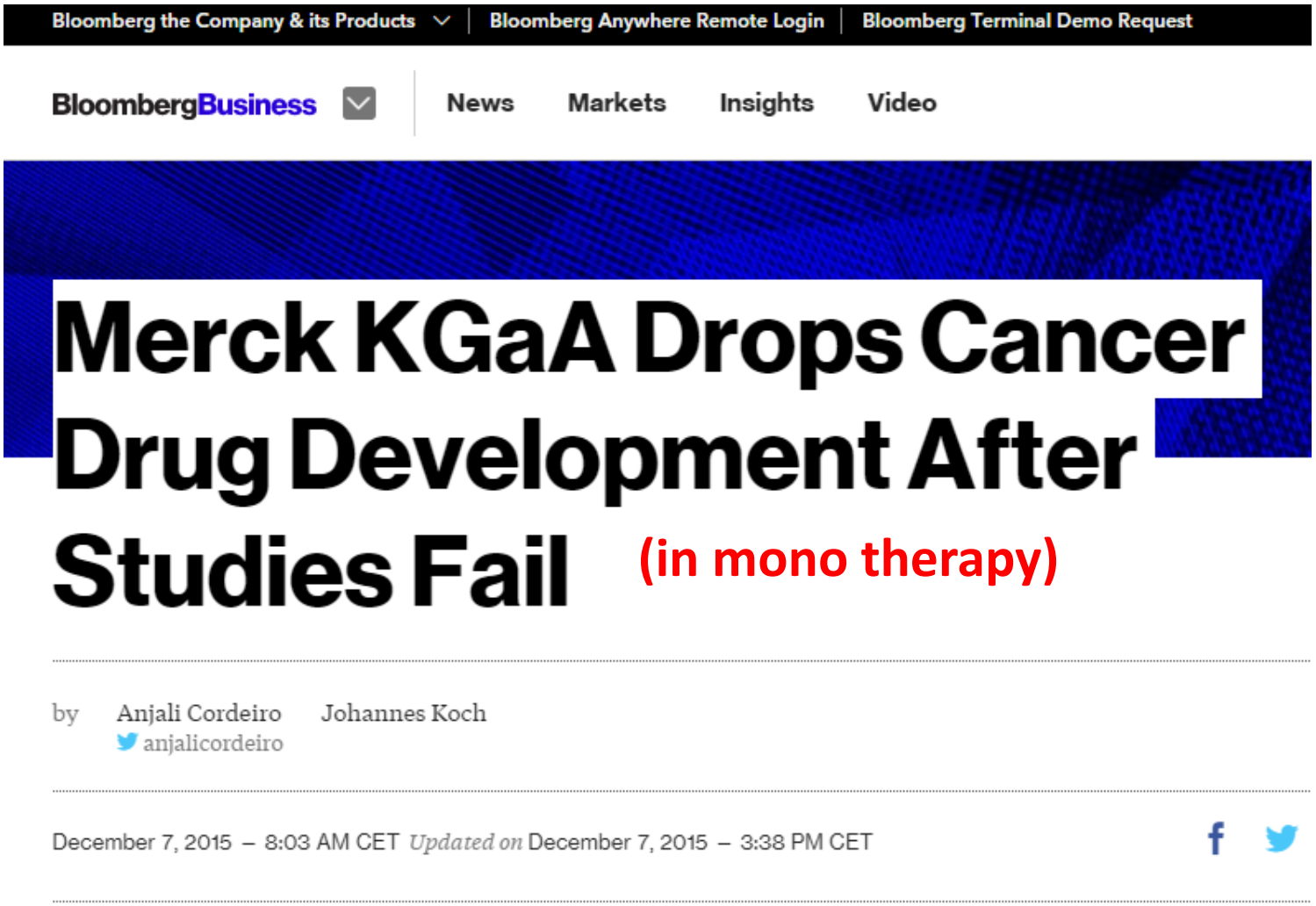


Status: 2 Negative phase III trials in combination with chemo in Pancreas and Sarcomas. Finances for this drug were cut down besides rational for better chances with RT

Promissing radio sensitizers subordinated to drug alone development may fail to be tested in radiotherapy..



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Merck KGaA Drops Cancer Drug Development After Studies Fail (in mono therapy)

by Anjali Cordeiro anjalicordeiro Johannes Koch

December 7, 2015 – 8:03 AM CET *Updated on* December 7, 2015 – 3:38 PM CET

STAR studies:

STAR*002:

Rational/Background: **Immune modulator** combined with RT to increase tumor response in multiple tumor sites

Sponsorship: Drug provision from large pharma. Limited funding available for preclinical proof of concept RT combination study
Company Proposal: Start drug only phase I dose escalation trials in several tumor sites. Assessment of pharmacokinetics, pharmacodynamics and bio distribution.

STAR involvement: NKI, other academic centers (Rotterdam); involve STAR sites for combination studies
Agreement: sponsor involved, candidate drug for combination with RT, evaluate radiation dependent expression of the target
Status: CDA in place; elaborating on study design and conditions

STAR studies:

STAR*003a:

Rational/Background: **apoptosis modulator (death receptor ligand)** combined with RT in tumor sites expressing drug target

Sponsorship: Medium-sized pharma with drug provision and funding for preclinical studies, funding for clinical studies t.b.d.

STAR proposal: Preclinical assessment *in vitro* and *in vivo*

STAR involvement: NKI

Agreement: preclinical study proposal approved by sponsor

Status: MTA in place

STAR studies:

STAR*003b:

Rational/Background: **apoptosis modulator (synthetic alkyl-phospholipid)** combined with RT in multiple tumor sites

Sponsorship: Medium-sized pharma with drug provision and funding for preclinical studies, funding for clinical studies t.b.d.

STAR proposal: Preclinical assessment *in vitro* and *in vivo*

STAR involvement: NKI

Agreement: preclinical study proposal approved by sponsor

Status: MTA in place; compound in use

STAR studies:

STAR*004a:

Rational/Background: **PARP inhibitor** in combination with RT +/- cisplatin in NSCLC, HNSCC, breast cancer

Sponsorship: Large pharma with drug provision and mixed academic/company funding

Proposal: Extension and continuation of current phase I trials to Phase II/III studies

STAR involvement: NKI (in discussion with Beatson institute; Institut Curie)

STAR internal agreement: Could serve as a model for STAR endorsement/label of ongoing studies

Status: 3 phase I studies (Lung/HNSCC/Breast) open & recruiting: STAR label proposed

STAR studies:

STAR*004b:

Rational/Background: **DNA-PK inhibitor** in combination with RT in oligometastatic HNSCC

Sponsorship: Large pharma with drug provision and mixed academic/company funding

Proposal: Extension and continuation of current phase I-II trials

STAR involvement: NKI

Agreement: IIS sponsored by company

Status: 1 phase I study (HNSCC) open & recruiting: STAR label proposed

STAR studies:

STAR*007:

Rational/Background: **TGFβR modulator** combined with RT in NSCLC and pancreas

Sponsorship: small sized pharma, support for preclinical studies and drug provision opportunities

STAR evaluation: strong RT combination potential, but very limited RT combination data (efficacy and toxicity)

STAR Proposal: confirmation of RT combination efficacy *in vitro,* evaluation of efficacy *in vivo* and initial (limited) assessment of influence on RT toxicity

STAR involvement: Centre GF Leclerc, NKI, IGR

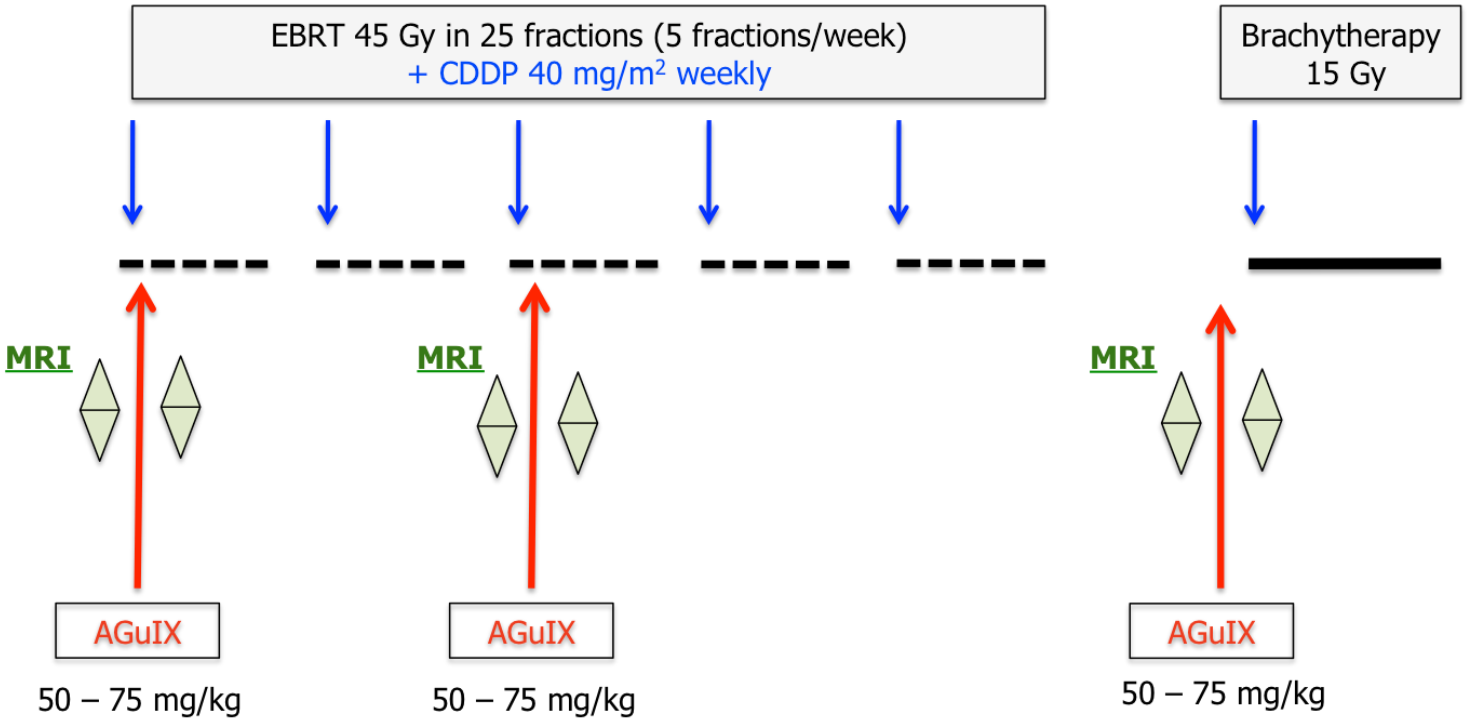
Agreement: multi-phase preclinical assessment *in vitro* and *in vivo* executed by STAR to evaluate real potential and guide early clinical trial setting selection

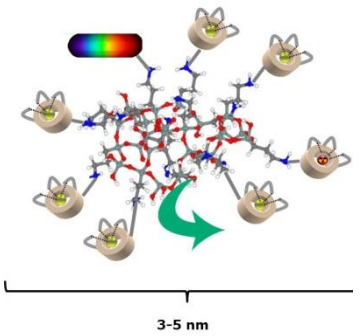
Status: preliminary proposal accepted by the company - study design, budgeting and contractual negotiations ongoing

STAR team studies:

A multicenter Phase I study evaluating the safety of AGuIX gadolinium-based nanoparticles (AGuIX-NP) in locally advanced cervical carcinoma, a treatment of radiosensitization and of theranostic optimization (NANOCOL study)

PI: Cyrus Chargari





The future of cancer therapy

STAR studies: RT and immune therapies

A robust rationale

IR ↗ Tumoral associated antigens availability. Increased PD-L1 expression after RT: good candidate for anti-PD-L1 Ab

Immune synapse is as a promising therapeutic target under intensive clinical research

More agents/targets to come (ox40, MDSCs, Macrophages, TGFβ)

IR → Immunogenic hub to induce an in situ vaccination imunomodulatory agents can enhance systemic immune response.

Great clinical expectations

Impact on local and systemic disease

Challenges :

Tumors with existing T cell response :

⬇

Enhance existing T cell response
IR + checkpoints blockers

No T cell response

⬇

Generate Systemic cell response
IR + Vaccines +/- checkpoints blockers

EORTC Immunotherapy Masterplan

- **Locally advanced head and neck squamous cell cancer**
- **SCC of the esophagus**
- **Rectal cancer**
- Locally advanced lung cancer (NSCLC and SCLC)
- Locally advanced cervical cancer
- Bladder cancer
- Incompletely resected glioblastomas
- Adenocarcinoma of the GE-junction
- Locally advanced prostate cancer

W. Budach ECCO 2015

STAR team studies: RT and immune therapies

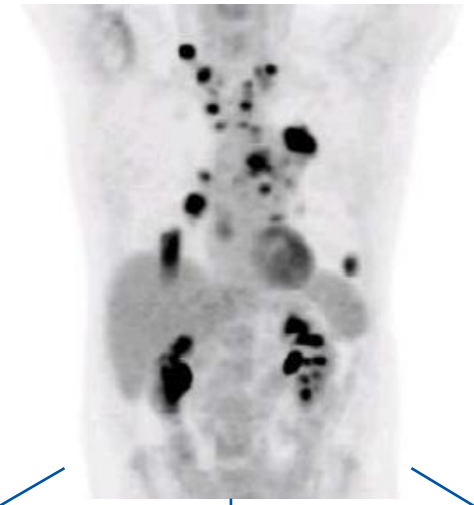
- **PD-L1 blockade + SBRT trial**

→PDL1 ‘responsive’ tumors :

NSCLC

→Ablative SBRT of 1-3 sites

→At least 1 un-irradiated lesion

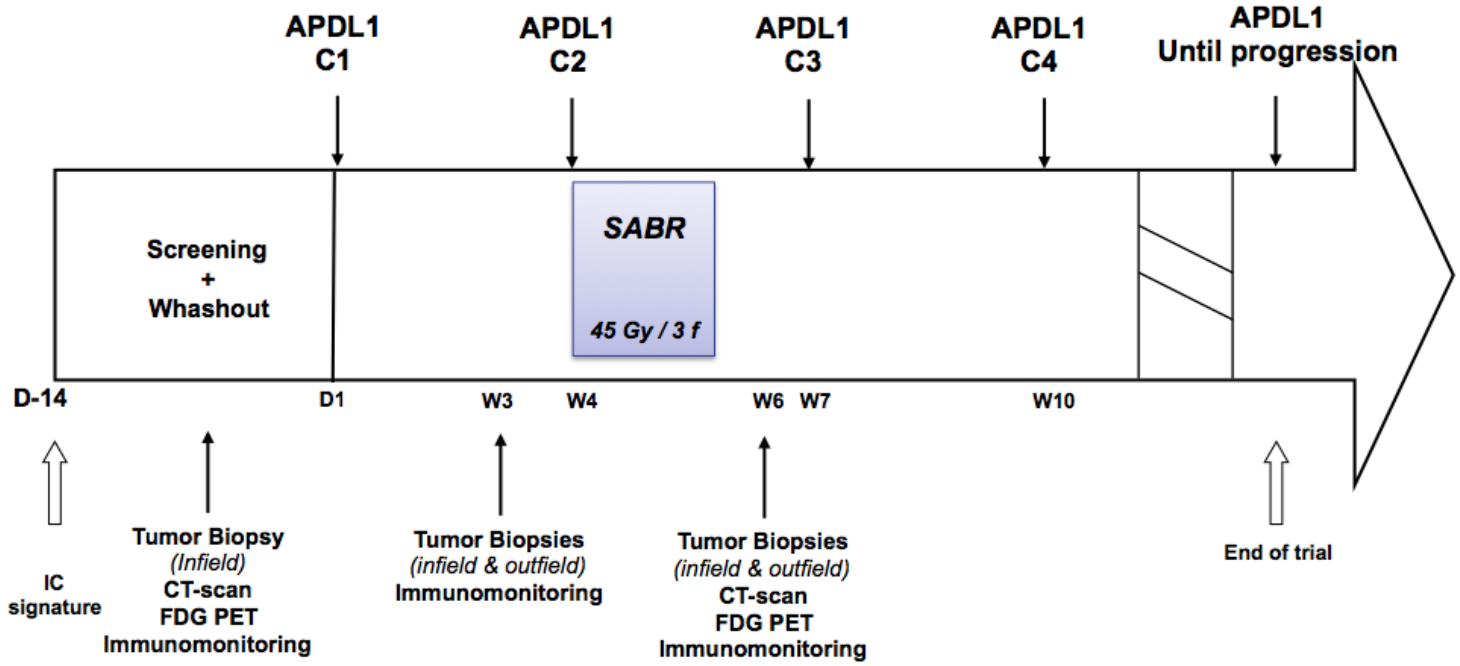


« in field response »

« abscopal reponse »

Time to progression

STAR team studies: RT and immune therapies

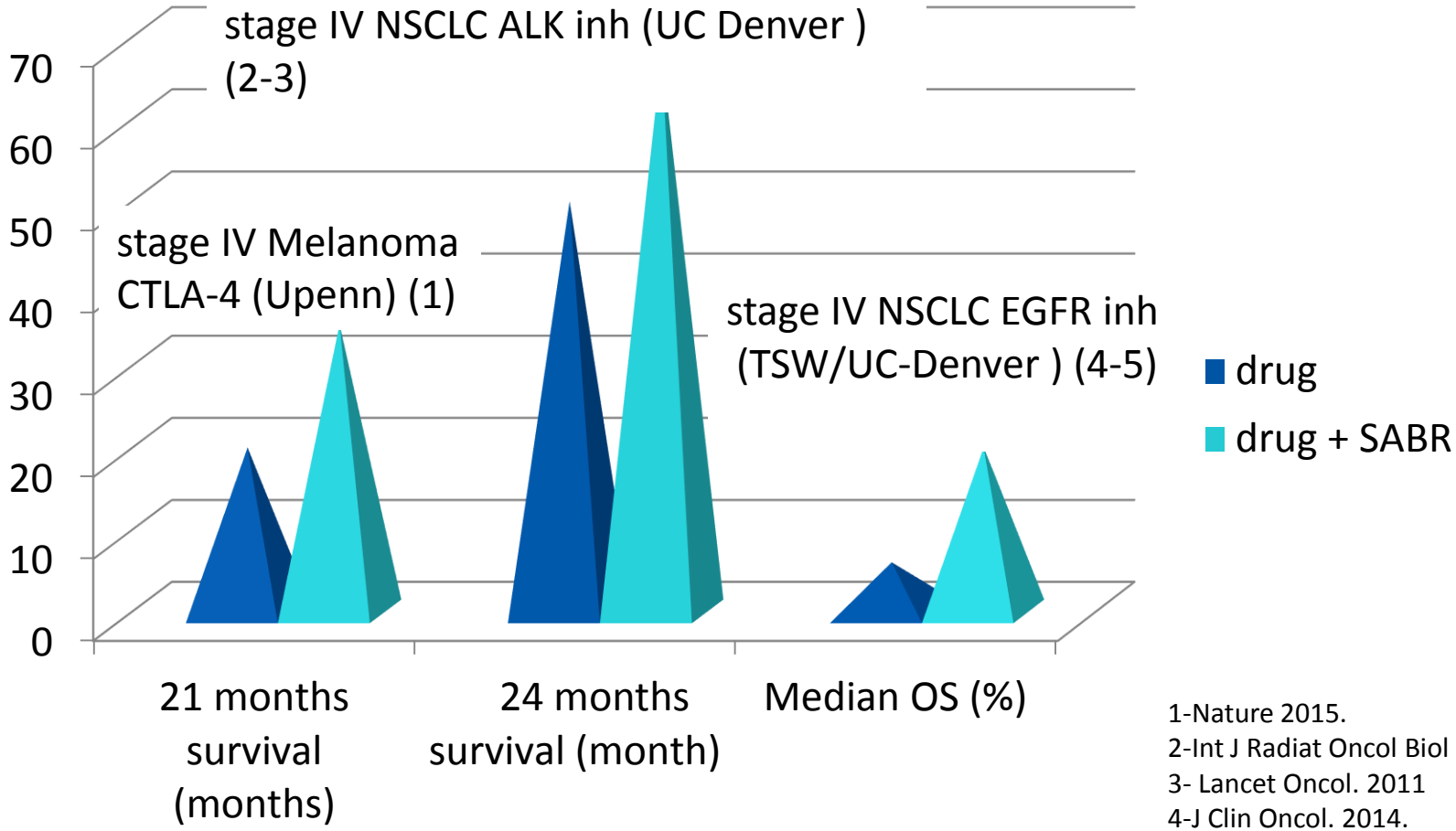


APDL1: MPDL3280A
SABR: Stereotactic Ablative Radiotherapy
f: fractions

PI: Antonin Levy

The future of cancer therapy

New drugs + SABR in stage IV desease
positive trend from back to back comparisons?



> 20 trials combining SABR + targeted or immune therapies

1-Nature 2015.
2-Int J Radiat Oncol Biol Phys. 2014).
3- Lancet Oncol. 2011
4-J Clin Oncol. 2014.
5-N Engl J Med. 2005

Conclusions

- Scares funding
- RT-drug combination opportunities are not seen by the industry
- benefit of EORTC-ROG consortium in early trial setting not clear. Current structures favour individual investigator connections.

EORTC · ROG
European Organisation for Research and Treatment of Cancer
Radiation Oncology Group

STAR studies:

STAR*… :

Your future proposals

star@eortc.be