Clinical research challenges : the role of Oncodistinct network

Anthony Gonçalves
Department of Medical Oncology, Head
Institut Paoli-Calmettes
Marseille, France

Nuria Kotecki,
Jules Bordet,
Bruxelles, Belgium

INSTITUT PAOLI-CALMETTES
unicancer Marseille

CRCM
Centre de Recherche en Cancérologie de Marseille

Aix*Marseille université
Initiative d'excellence

Disclosures (2015-2019)

- Personal fees from pharmaceutical companies: none
- Financial shares in pharmaceutical companies : none
- Non-financial support (grants, travel expenses)
  - *Astra Zeneca*
  - *Novartis*
  - *Pfizer*
  - *Roche*

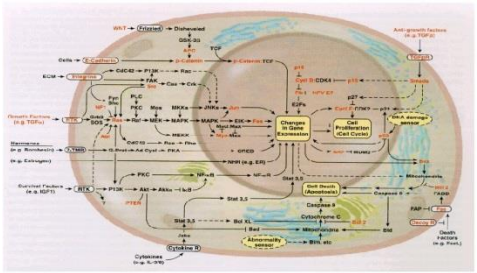
INSTITUT PAOLI-CALMETTES unicancer Marseille
CRCM Centre de Recherche en Cancérologie de Marseille
Aix*Marseille université initiative d'excellence
ONCODISTINCT NETWORK

Outline

- Clinical research in modern oncology : opportunities and challenges
- Oncodistinct network : general objectives and main features
- Oncodistinct network : first ongoing trials
- Perspectives

Clinical research in oncology *…Opportunities (1)*

A wealth of novel therapeutic strategies …



Molecular targeted therapies (MTT)

Oncogenic drivers “de-addiction”
Inhibition of critical signaling pathways
Specific cytotoxicity

- Targets = *RAS, RAF, MAPK, PI3k/Akt/mTOR, cell cycle inhibitors, DNA repair, Angiogenesis, Epigenetic, Apoptosis, Invasion/metastasis, Metabolism/energy*

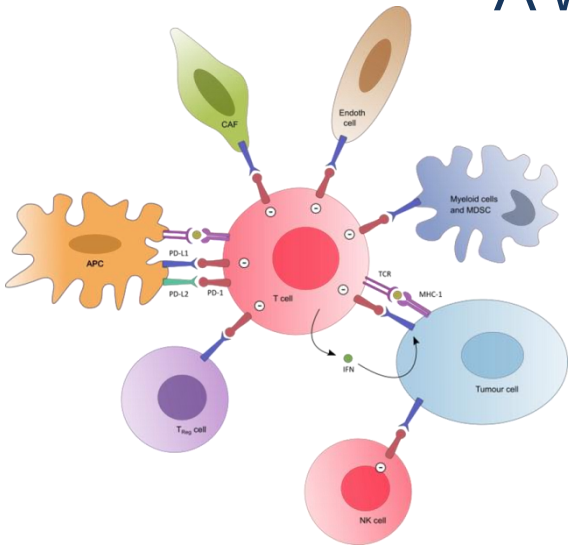
- Agents = *TKIs, Mab, ADC …*

INSTITUT PAOLI-CALMETTES unicancer Marseille
CRCM Centre de Recherche en Cancérologie de Marseille
Aix*Marseille université initiative d'excellence
ONCODISTINCT NETWORK

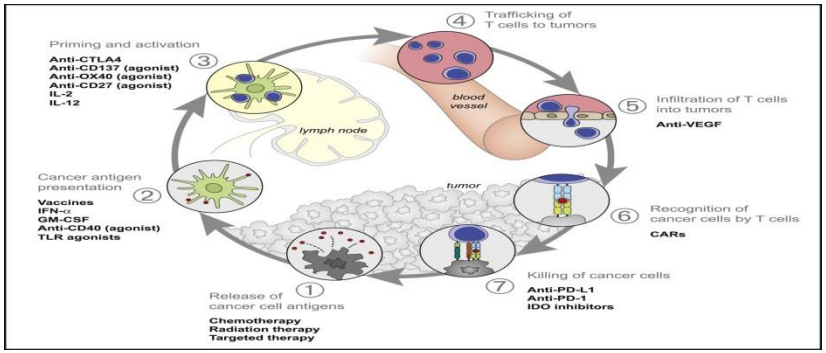
Clinical research in oncology *…Opportunities (2)*

A wealth of novel therapeutic strategies

Immuno-oncology agents (IOA)



- **T cells**



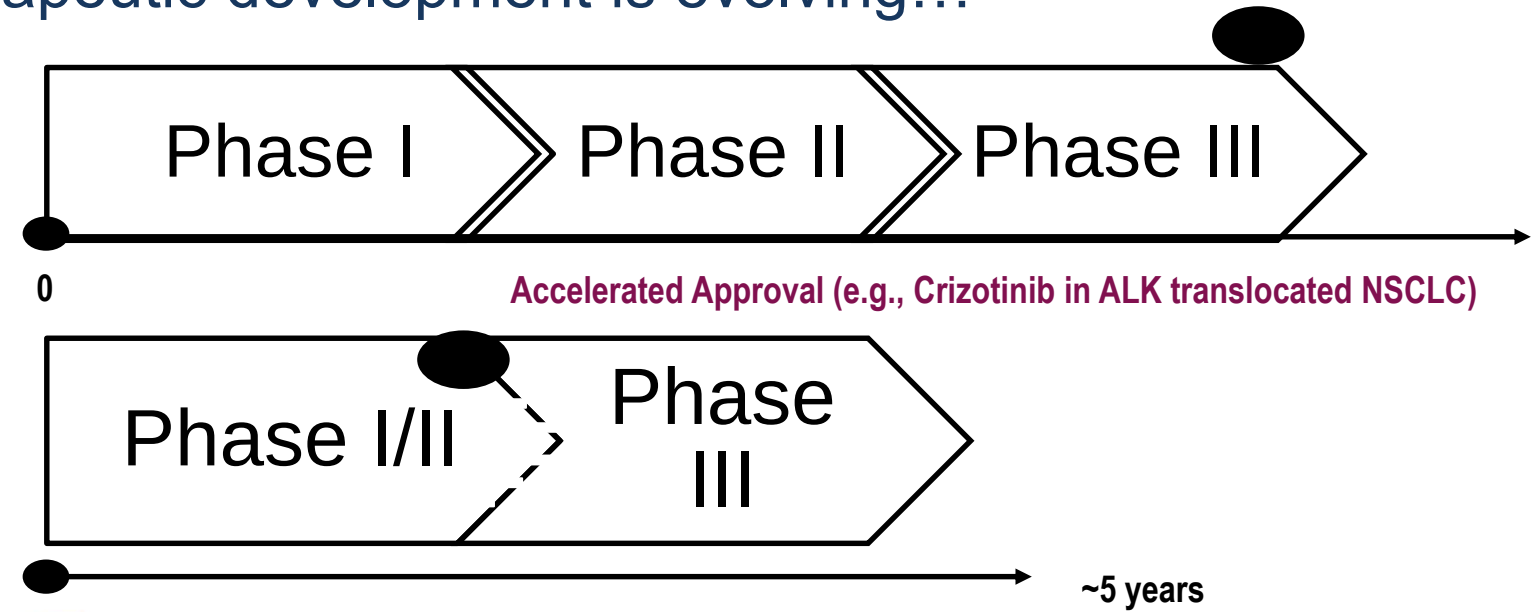
- **Other Immune effectors** = NK cells, APC, MDSC, Endoth cells, CAF, Macrophages, Treg…

- **Adoptive cell transfer immunotherapy**
  CAR T and others

INSTITUT PAOLI-CALMETTES unicancer Marseille
CRCM Centre de Recherche en Cancérologie de Marseille
Aix*Marseille université initiative d'excellence
ONCODISTINCT NETWORK

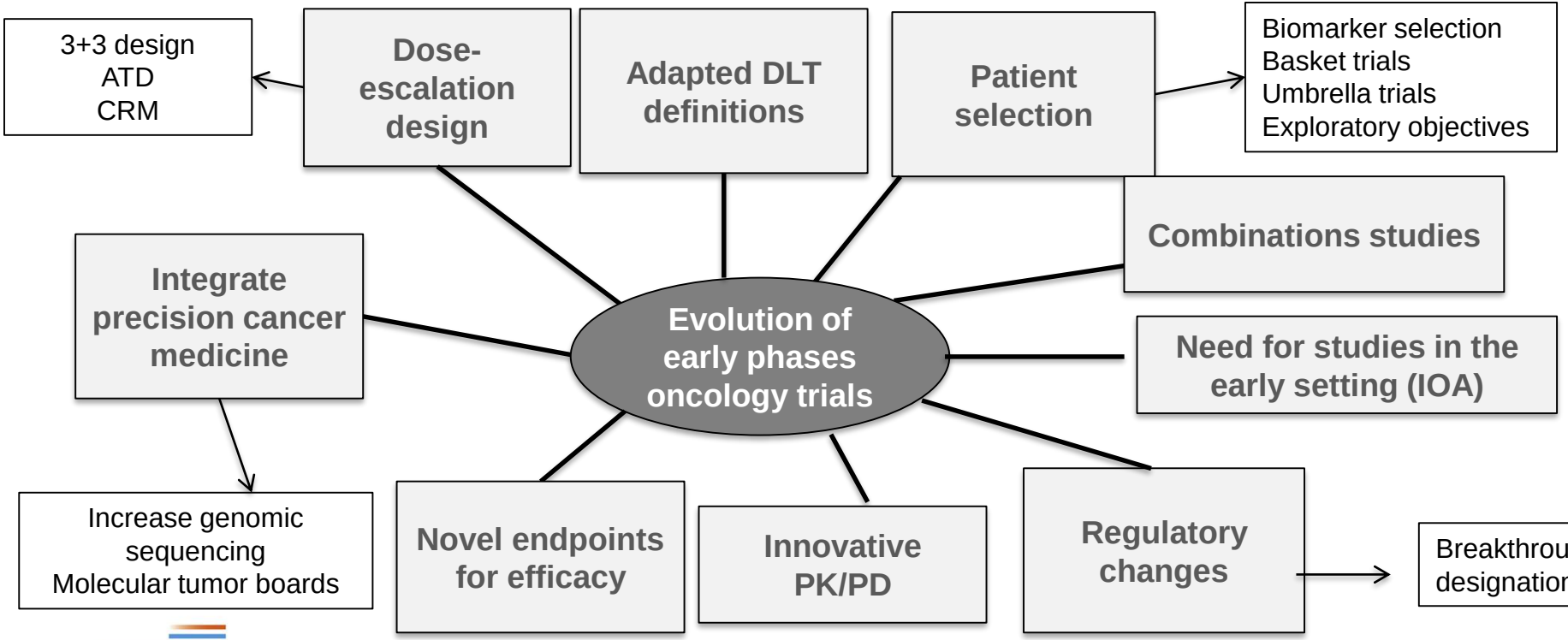
Clinical research in oncology *…Challenges (1)*

Therapeutic development is evolving…



Adapted from Postel Vinay et al. Annals of Oncol. 2016

Clinical research in oncology *…Challenges (2)*



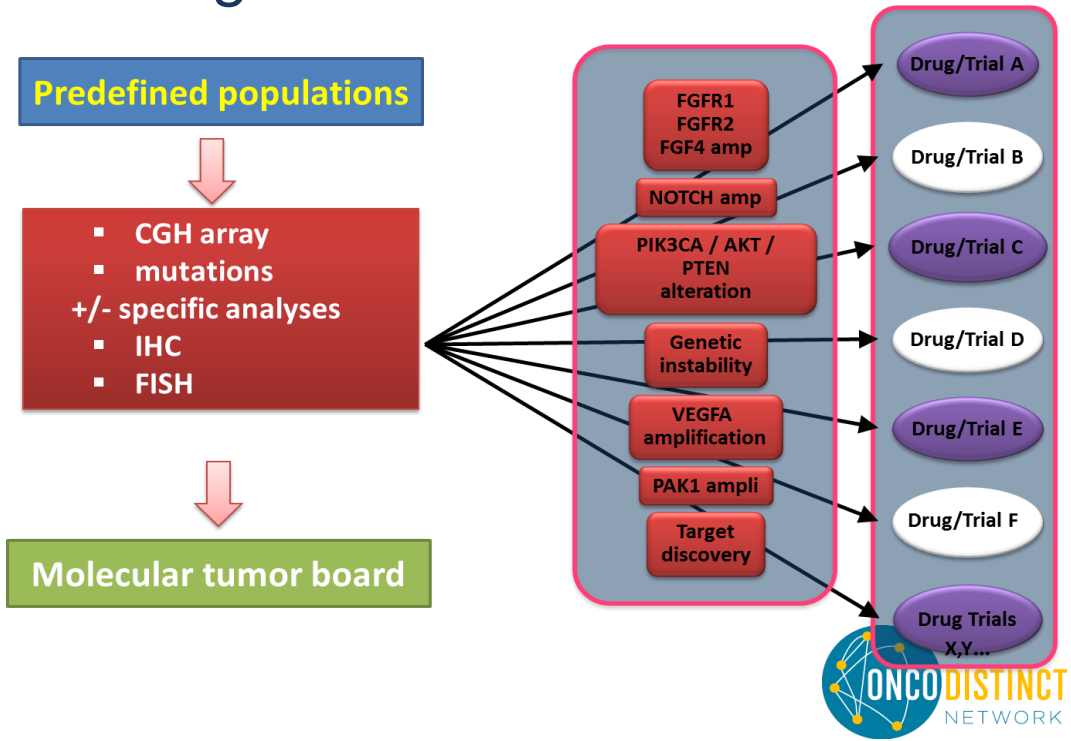
Methodological issues

Clinical research in oncology *…Challenges (3)*

Therapeutic development is evolving…

Precision medicine trials

- Molecular screening (tumor, blood)
- Validated biomarkers
- Access to drugs, combo
- Heterogeneity (spatial, temporal)
- Mechanisms of resistance
- Adaptive design
- Statistical challenges



INSTITUT PAOLI-CALMETTES unicancer Marseille
CRCM Centre de Recherche en Cancérologie de Marseille
Aix*Marseille université initiative d'excellence
ONCODISTINCT NETWORK

Clinical research in oncology *…Challenges (4)*

Therapeutic development with IO agents…

1. **Optimal dose and schedule selection ?**
   > Minimal immunologically active dose (dose is not linearly associated with efficacy and toxicity)
   > Optimal dose for prolonged exposure
2. **Optimal sequence/duration/rechallenge ?**
   > Maximize benefit for patients and minimize economic burden
3. **Identify resistant/sensitive disease to immunological approaches ?**
   > Biomarkers (immunoscore, Immunomics, …)
4. **New patterns/definitions of tumor assessment and disease progression ?**
5. **Combinations issues – importance of testing in early setting ?**
6. **Competitives trials and redundancy ++++ ?**

Clinical research in oncology *…Challenges (5)*

Strategic issues

Drug development may be more commercially-driven than patient-centered

Rare “orphan” diseases
Rare genomic entities
“Underserved” clinical entities : CNS mets, CUP…

appropriate/pertinent control arms ?

Biomarker-driven studies
Collecting tumor samples
= to identify/validate biomarkers ?

Dose, duration, sequence, side effects, QOL, de-escalation strategies ?

Combinations between drugs from concurrent pharmas ?

Need for more academic-driven therapeutic development

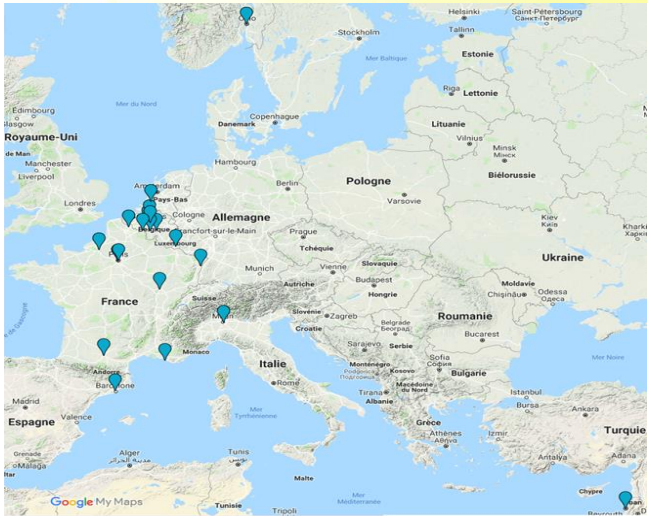
INSTITUT PAOLI-CALMETTES unicancer Marseille
CRCM Centre de Recherche en Cancérologie de Marseille
Aix*Marseille université initiative d'excellence

ONCODISTINCT NETWORK

Oncodistinct network

"Accelerating Oncology drug Development and Innovative strategies in Clinical Trials"

1. A. Awada (IJB, Brussels)
2. G. Argiles (Vall d'Hebron)
3. A. Gonçalves (IPC)
4. L. Decoster (UZB, Brussels)
5. J-P. Delord (ICR, Toulouse)
6. L. Teixera (Saint Louis, Paris)
7. N. Penel (COL, Lille)
8. E. Raymond (Saint Joseph, Paris)
9. F. Clatot (H.Bequerel, Rouen)
10. P. Barthélemy (CHU, Strasbourg)
11. N. Isambert (JF Leclercq, Dijon)
12. C. Le Tourneau (I.Curie, Paris)
13. A. Shamseddine (AUB, Beirut)
14. T. Kyrre Guren (UH, Oslo)
15. M. Lolkema (Erasme, Rotterdam)
16. P. Vuylsteke (St Elisabeth, Namur)
17. G. Berchem (CH, Luxembourg)
18. J-P. Machiels (UCL, Brussels)
19. S. Holbrechts (AP, Mons)
20. H. Prenen (UZA, Anvers)
21. J-L. Canon (GHC, Charleroi)
22. G. Curigliano (IEO, Milan)
23. P. Papanastasopoulos (Bank of Cyprus Oncology, Nicosia)
24. D. Tosi (Institut régional du cancer, Montpellier)
25. P. Cassier (Centre Léon Bérard, Lyon)
26. E. Coquan (Centre François Baclesse, Caen)
27. A. Stathis (OI, Bellinzona)
28. N. Massimo (I. Dei Tumori, Milan)
29. T. Silovski (UHC, Zagreb)
30. N. Isambert (CHU Poitiers)
31. S. Rottey (UZ Gent, Gent)
32. R. Bartsch (Medical University of Vienna)



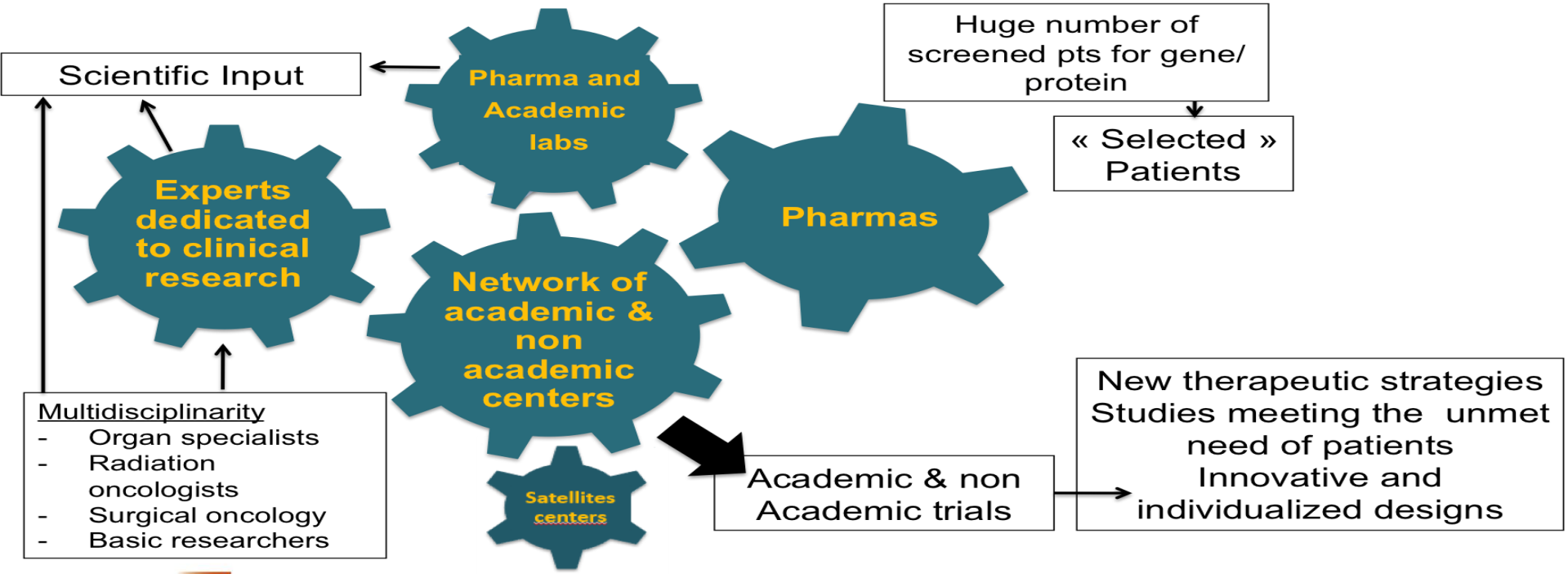
Soon more than 30 sites …

INSTITUT PAOLI-CALMETTES unicancer Marseille
CRCM Centre de Recherche en Cancérologie de Marseille
Aix*Marseille université initiative d'excellence

ONCODISTINCT NETWORK

Oncodistinct network

ACADEMIC MODEL OF CLINICAL RESEARCH COLLABORATION BASED ON THE PROGRESS ON MOLECULAR BIOLOGY AND METHODOLOGICAL ISSUES



www.oncodistinct.net

INSTITUT PAOLI-CALMETTES unicancer Marseille
CRCM Centre de Recherche en Cancérologie de Marseille
Aix*Marseille université initiative d'excellence

Speed and quality academic and non academic trials

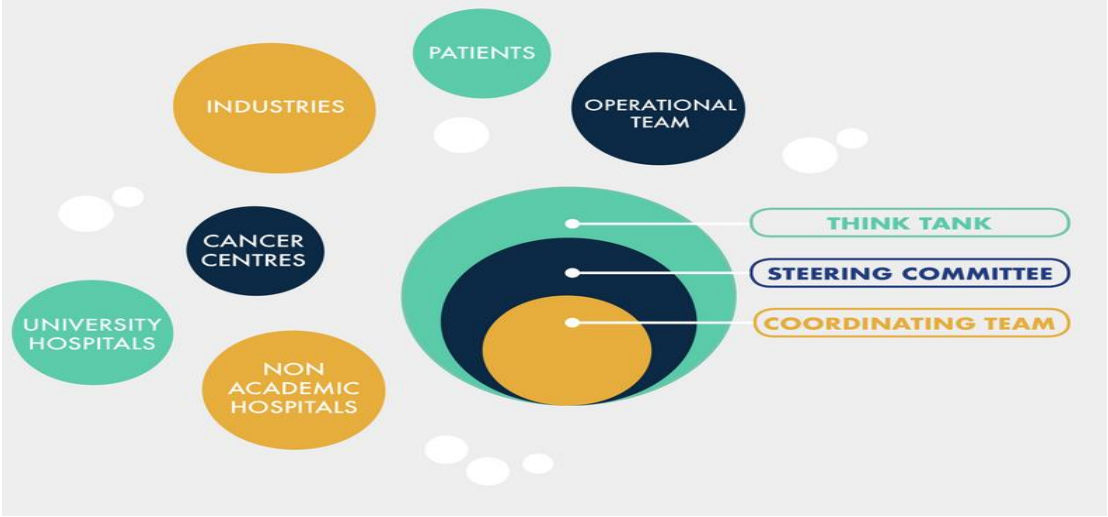
ONCODISTINCT NETWORK

Oncodistinct network : which clinical trials ?

- New drug development from phase I to later phases trials
- Innovative trial designs
- Unmet medical need projects
  (e.g. rare tumors, oligometastasis, brain metastasis, inflammatory breast cancer,…)
- Early setting projects (e.g: development of immunotherapy)
- Biomarkers studies with high potential for clinical practice
- “Proof of concept” studies

INSTITUT PAOLI-CALMETTES unicancer Marseille
CRCM Centre de Recherche en Cancérologie de Marseille
Aix*Marseille université initiative d'excellence
ONCODISTINCT NETWORK

Oncodistinct network : organization



Think tank

The driving force of the Oncodistinct Network is firmly its **Investigators' Think Tank**. It is the forum for scientific discussions, ideas and strategies which brings innovative clinical research projects. The think tank is composed by a large panel of experts in cancer care (investigators, scientists...) involved in drug development.

Operational Team

The role of the Operational Team is to manage the day-to-day management of activities.

Steering Committee

The Steering Committee has the responsibility of strategic decisions and is composed of one representative per Oncodistinct center.

Coordinating Team

The Coordinating Team is composed of physicians elected by the Steering Committee and implements the decisions of the Steering Committee.

INSTITUT PAOLI-CALMETTES unicancer Marseille
CRCM Centre de Recherche en Cancérologie de Marseille
Aix*Marseille université Initiative d'excellence

ONCODISTINCT NETWORK

Oncodistinct network : organization

Working subgroups

Early Settings

Non metastatic, treatment-naive

- peri-operative setting
- baseline and post-XT tumor collection for biomarkers
- Minimally immune-exhausted patient population

Unmet needs

Rare or underserved diseases :

- CNS mets
- IBC
- CUP
- Sarcoma
- Rare histo-clnical, molecular entities
- …

Early Drug Development

Novel drugs :

- Innovative associations
- Molecularly selected patient
- Innovative design/endpoints
- Specific translational programs

INSTITUT PAOLI-CALMETTES unicancer Marseille CRCM Centre de Recherche en Cancérologie de Marseille Aix*Marseille université initiative d'excellence

ONCODISTINCT NETWORK

Oncodistinct Translational Research group

- **Missions**
  - Expertise and participation to the TR activities in Oncodistinct studies

- **Composition**
  - Research groups related to Oncodistinct sites
  - Steering core of 2-3 persons
    - Review of the Oncodistinct study proposals and evaluation of the needed expertise
    - Select appropriate oncodistinct TRG members

INSTITUT PAOLI-CALMETTES unicancer Marseille
CRCM Centre de Recherche en Cancérologie de Marseille
Aix*Marseille université initiative d'excellence
ONCODISTINCT NETWORK

Oncodistinct Patient Advisory Panel

Advisory group of patients “trained” in clinical research and available to :

1. Review and provide opinions on research protocols under development
2. Proofread patient information documents and consent forms

Involving Junior Oncologists

- Taking part in the education and training of young oncologists, physicians and scientists, sharing the knowledge of the panel of experts involved in the network

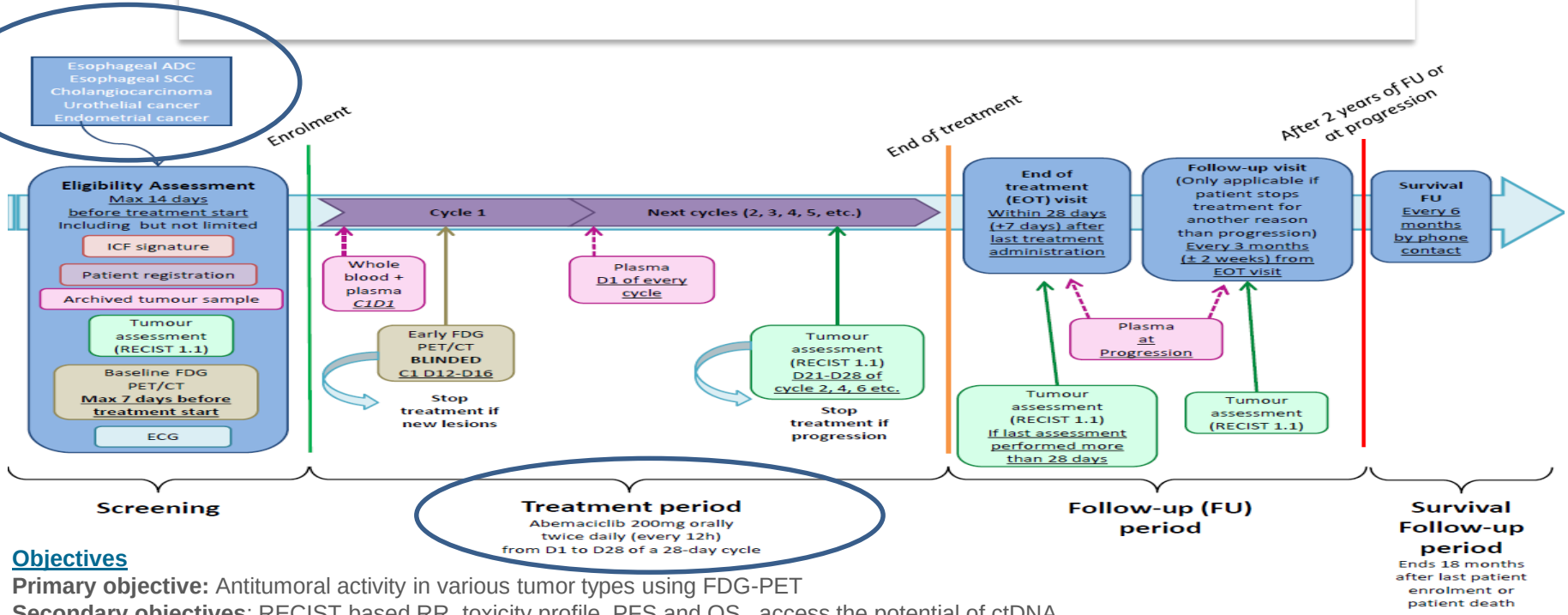
- Provide opportunities for young investigators by taking leading roles and participating into the WG

Ongoing Oncodistinct studies

ODN N°	Setting	Sponsor	Study drug	Pharma	n =	Countries	FPI	Pts
002 **MIME** *L.Polastro* *A.Hendlisz*	Platinium-R CholangioK Endometrial C Bladder C ADK/SCC eso	IJB	**Abemaciclib**	Lilly	Min 75 Max 175	• Belgium • France (11/2019)	**01/2019**	**51**
003 **PELICAN** *A.Gonçalves*	T4d BC	IPC	**Pembrolizumab**	MSD	81	• France	**07/2018**	**15**
004 **AURA** *N.Martinez* *A.Awada*	MBIC eligible for NAC cT2-T4 N0/x M0	IJB	**Avelumab**	Merck	178	• Belgium • France	**06/2018**	**35**
005 *A.Shamseddine*	LA potentially resecable rectal ADK	AUB (CRO)	**Avelumab**	Merck	36	• Lebanon/ Jordan	**06/2018**	**13**

Innovative design
Unmet medical need

MiME trial – Oncodistinct 002
Multiorgan Metabolic imaging response assessment of Abemaciclib



Objectives

Primary objective: Antitumoral activity in various tumor types using FDG-PET

Secondary objectives: RECIST based RR, toxicity profile, PFS and OS, ,access the potential of ctDNA

Statistics

Optimal 2-stage Simon design used independently in each stratum.

H0: Rate of treatment success is less or equal to 20% versus the one-sided alternative that this rate is >20%.

•**First stage**: **If** ≤2 metabolic responses (class I/II)/13: stop **Second stage**: 16 additional evaluable patients (29).

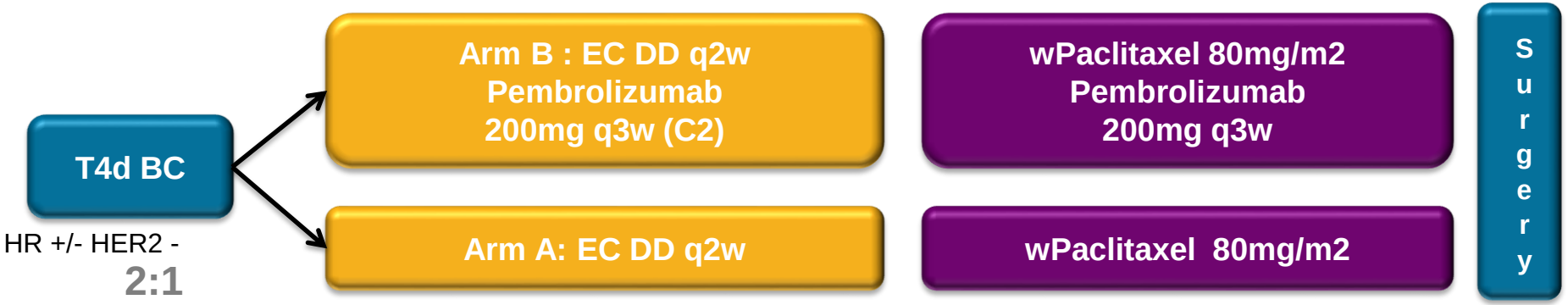
H0 rejected if ≥9 responses/29 pts (α10% power 85% if true metabolic response rate is 40%)

Early setting
Unmet medical need

PELICAN trial - Oncodistinct 003

Study of Immunotherapy in Combination With
Chemotherapy in HER2-negative Inflammatory Breast Cancer

Non comparative randomized phase II study



Primary Endpoints: pCR + Safety run-in 6pts HR +/-

Statistics:

H0: pCR <= 20% with 5% error risk and 90% power assuming a true pCR rate of 40%.
Simon 2 stage design = 54 pts (Arm B (19+35) / 27 pts Arm A

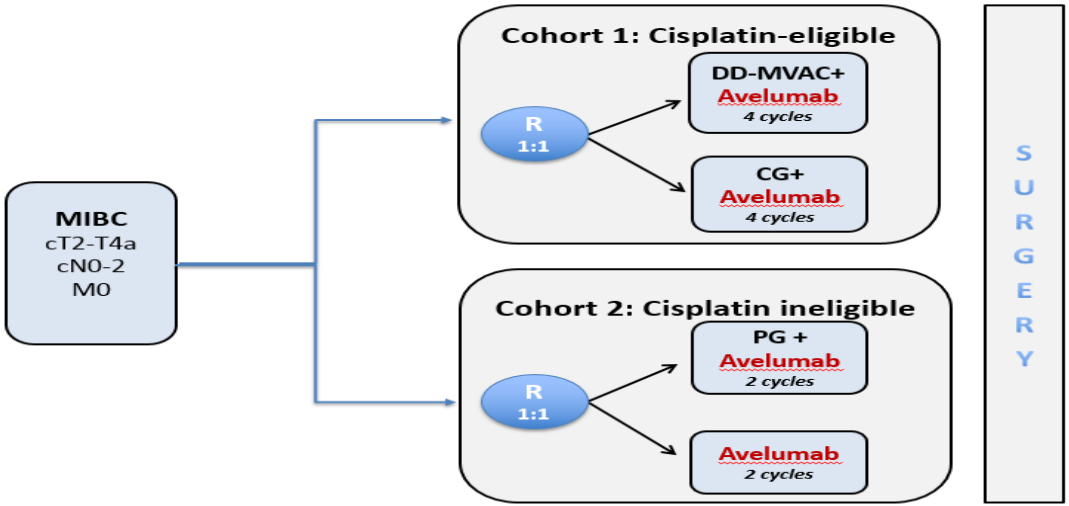
INSTITUT PAOLI-CALMETTES unicancer Marseille
CRCM Centre de Recherche en Cancérologie de Marseille
Aix*Marseille université initiative d'excellence

ONCODISTINCT NETWORK

Early setting

AURA trial - Oncodistinct 004

Avelumab as Neoadjuvant Therapy in Subjects With Urothelial Muscle Invasive Bladder Cancers



Primary endpoint:
PCR rate (ypT0ypN0)

Statistics:

CDDP eligible
- H0= PCR rate ≤ 25%
- *one-sided test α5%, power 90% if true RR ≥ 50%*

>> Two stage Flemming design / arm
- if ≤ 0/28 PCR or 16/49 = STOP for futility
- if > 13/28 = STOP for early rejection of H0
- Otherwise accrual will go on up to 49 pts

If ≥ 17/49 PCR avelumab is considered worthy of further study.

CDDP ineligible: assuming PCR ≥ 5%
Simon 2 stage / arm
- If < 1/12 = STOP for futility
- if > 13/28 = STOP for early rejection of H0
- Otherwise accrual will go on up to 26 pts

INSTITUT PAOLI-CALMETTES unicancer Marseille
CRCM Centre de Recherche en Cancérologie de Marseille
Aix*Marseille université initiative d'excellence
ONCODISTINCT NETWORK

Innovative design
Early setting

Oncodistinct 005

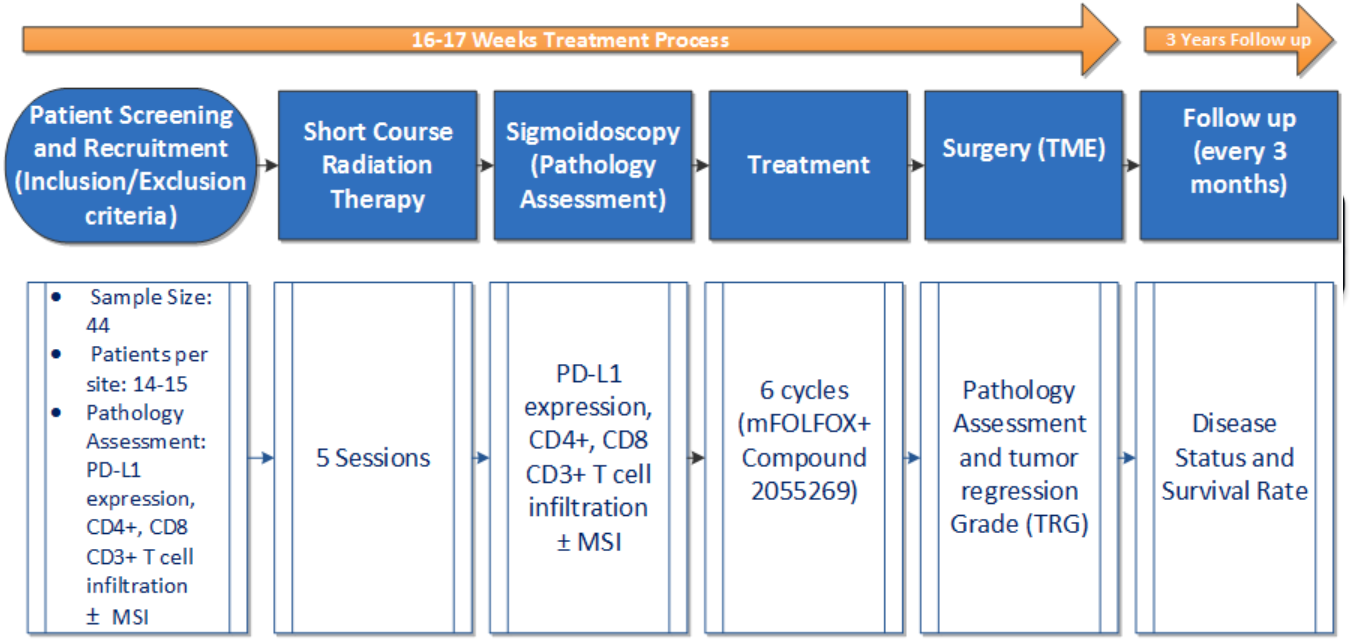
Short-course RT followed by mFOLFOX6 + Avelumab agent for LA rectal ADK

Single-arm phase II study

LA potentially resectable rectal adenocarcinoma

cT2 N1-3, cT3 N0-3, evidence of extramural vascular or mesorectal fascia involvement

N = 31
Interim analyses



Primary objective: pCR rate

Secondary objectives: 3-year DFS, Safety and tolerability, QoL, explore changes in PD-L1 expression and T-cell infiltration

INSTITUT PAOLI-CALMETTES unicancer Marseille
CRCM Centre de Recherche en Cancérologie de Marseille
Aix*Marseille université initiative d'excellence
ONCODISTINCT NETWORK

Perspectives

- Improving internal organization (clinical trials support units, SOP and follow-up on trials, young investigator fellowship, novel legal structure ?)
- Increase multidisciplinary partnership and develop translational research group
- Further develop collaboration with Pharma and CROs (« meet the industry » meetings)
- Novel tools and novel issues
  - ctDNA , immuno-monitoring
  - Big data and AI
  - Toxicity and PROMs