SESSION INAUGURALE

Éclairages sur les solutions mises en place pour lever les barrières et augmenter l'attractivité !

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Establishing Successful Clinical Research In The Era Of Molecular Oncology: Why ? How ? Optimisation ? (WHO)

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Clinical Trials Support Unit

Hôpital Erasme | ULB

ONCODISTINCT NETWORK

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Disclosures

Advisory role: Amgen, AstraZeneca, Bayer, Daiichi, EISAI, Genomic Health, Hengrui, Innate, Ipsen, Leo Pharma, Lilly, Merck, MSD, Novartis, Pfizer, Seattle Genetics, Menarini

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Cancer types and settings in 2023: An evolving field

- Common histologies of organ cancers
- Molecular segmentation of common cancers
- Rare cancer histologies
- Molecular segmentation of rare cancers
- Histology-agnostic, age-agnostic tumors
- Positive circulating tumor DNA (cancer screening, residual disease, tumor recurrence, …)
- New clinical entities: oligometastatic disease, brain metastases,…

Eight Lessons Learned from the development of dozens of molecular-targeted therapies (MTT) (1)

1. The identification of a driver genomic abnormalities of carcinogenesis as well as the discovery of selective agents are key. Genomic drivers and passengers are targets for ADCs
2. Studies of unselected populations should be prohibited
3. Molecular groups of common or rare tumors are “good” niches for new MTT -> The need for a comprehensive genomic testing
4. Resistance is the rule and the discovery of the resistance mechanisms (=rare tumor entities) is a high priority for the next generation of specific drugs (studies).

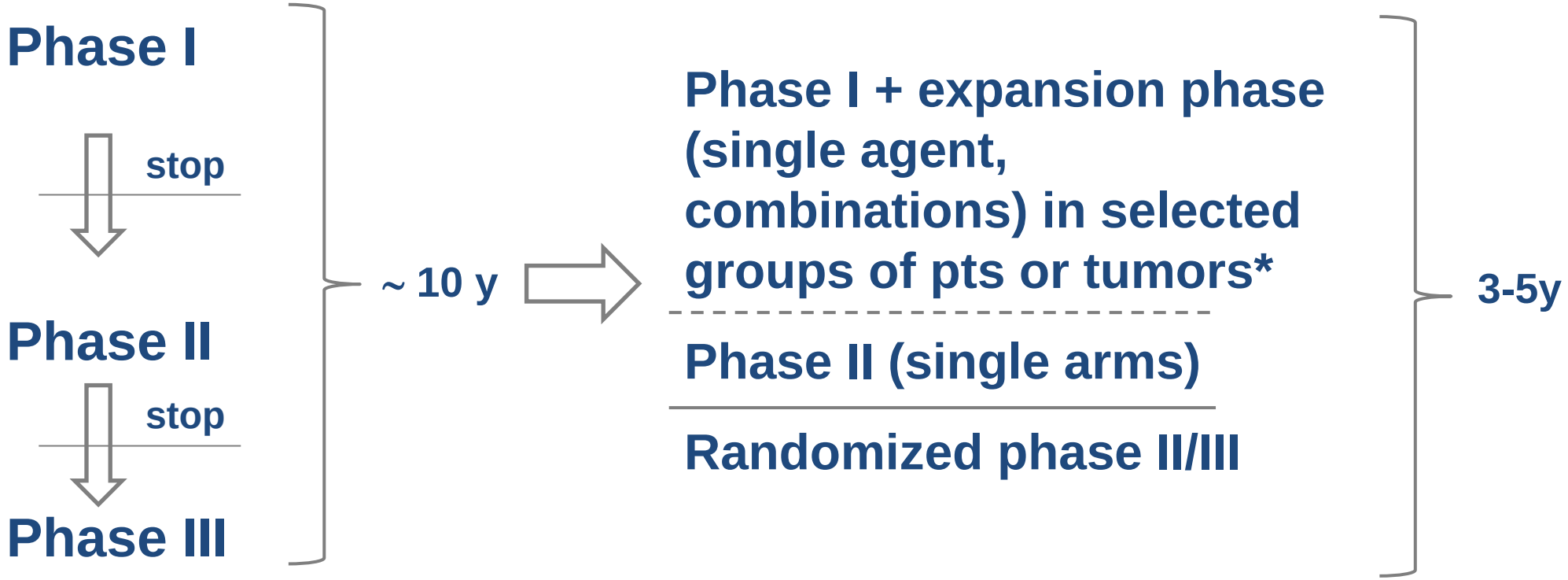
Eight Lessons Learned from the development of dozens of molecular-targeted therapies (MTT) (2)

5. One gene may predict resistance (KRAS mutation in CRC), but no single gene, protein, pathway can predict full efficacy to targeted therapies
6. Chemotherapy remain important for the synergy with targeted agents (and immunotherapy) in selective settings
7. Better outcome of MTT seen in the metastatic setting and much less in the (neo) adjuvant one (seems to be different with immunotherapy)
8. Expected and unexpected side effects arose from MTT and are overall manageable

Immune therapy approaches: Huge clinical benefits but also challenges

- Checkpoints inhibitors
- Adoptive cells therapy approaches (TILs, TCR, CAR-T)
- Intratumoral: Oncolytic viruses (e.g., T-VEC)
- Bispecific antibodies
- Tumor vaccines

Early clinical trials methodology of molecular therapies (including immunotherapy) is evolving



*By clinical, pathological or molecular criteria

Current Early clinical trials methodology of molecular therapies (including immunotherapy)

Advantages

- Speed in drugs development
- Quick discovery of effective agents/combinations (niches!)
- Better PK/PD interpretation
- (↑ samples from blood, biopsies, …)
- Comparison between tumors/settings possible (as ≠ cohorts are in parallel)
- Better definition of some outcomes (side effects, pattern of responses,..)

Limitations

- Loss of control/input by investigators !!
- Major risk (pts, time, cost, …) if negative trial
- Heavy logistic and organisation (pharma, CRO, CTCU, …)
- Risk to miss eligible patients in centers by complexity

Evolution of clinical research landscape (1) Metastatic setting

Past

- RCTs
- Hundreds or thousands of unselected pts

- PFS is the main endpoint (less OS)
- Small benefits expected/accepted

Current new trials

- RCTs whenever possible
- Basket/ Umbrella trials/…
- Much more selected groups of pts* (challenging)
- Less number of pts treated but huge number screened!
- Survival and/or PFS as endpoints / Prespecified groups data analysis
- Large benefits requested!

*By clinical, pathological or molecular criteria
Real world data should rather be supportive

Evolution of clinical research landscape (2) (Neo)adjuvant setting

Past

- Large RCTs
- Thousands of unselected pts
- Mainly adjuvant trials
- Small benefits
  (Expected/accepted)

Expected in new trials

- RCTs (mainly neoadjuvant trials)
- RCTs (adjuvant in high risk population)
- « Selected » groups of patients* (challenging)
- Number of pts is variable
- Large benefits requested with limited follow-up periods

*By clinical, pathological or molecular criteria

Critical question: Does the current design of Targeted therapies and Immuno-oncology trials meet the need of patients?

- **Yes** (several new anticancer agents entered the clinical practice with improved outcome)

- **No** [redundancy in the development of agents with the same mechanisms of action (e.g., PD-1/PD-L1 and CDK4/6 inhibitors,…); the presence of many competitve trials, few studies of clinical importance looking to a therapeutic strategy or as an example optimal sequence of therapies, …)]

How to meet the need of patients in designing and performing clinical trials ?

- Targeting Unmet medical need for patients in your center (settings!)
- Individualizing clinical research (e.g., based on the type/formulation of the new therapy and the mechanism of action, …)
- More and better collaboration between pharma, CRO and investigators (=stakeholders)
- Creating new models of collaboration : Academic networks in line with the « (r)evolution » on drugs development
- More innovative approach in clinical trials design, organization, performance of molecular drugs or combinations

How to meet the need of patients in your center ? (1)

- Have a clear idea of the patients caracteristics in your center (Efficient institutional data center !)
- Creation of a PRC* in your department to discuss all proposed clinical trials in order to answer 4 important questions :

1. Is the clinical trial scientifically sounded ?
2. Presence or not of competitive trials ?
3. Availability of eligible patients ?
4. Logistically feasible ?

*Protocol Review Committee

How to meet the need of patients in your center ? (2)

- For academic trials, creation of a Clinical Trial Promoting Team in order to discuss :
  - Background and rationale of the trial
  - Design of the study
  - Objective(s)
  - Statistics
  - Participating centers or networks
- Close collaboration of all stakeholders of the institution
- The presence of efficient Clinical Trial Conduct Unit (sponsored trials) and Clinical Trial Support Unit (academic trials)

Clinical Trials Support Unit

Head of CTSU Operations

Associate Head of CTSU Operations

Operations and Administrative Collaborator

Quality Assurance

- Quality Manager
- Quality Assurance Officer

Project Management

- Project Manager
- Clinical Trial Assistant

Regulatory Affairs

- Regulatory Affairs Manager

Sites Monitoring

- Clinical Research Associate Manager
- Clinical Research Associate

Pharmaco vigilance

- Pharmacovigilance Manager

Data Management

- Data Managers

Clinical Data Integration Tools

- Team Leader
- Software Developer Referent
- Software Developers
- Development Quality Supervisor
- Clinical Database Analysts
- Technical Support Specialist

Oncodistinct network as an example of new model of clinical research collaboration (Pragmatic, democratic and not centralized) (1)

Groups working together and not separately

Academic centers	+	Non academic centers but expertise in research (accreditation!)
Early drugs developers	+	Late drugs developers
Monospecialized	+	Multispecialized investigators
Clinicians	+	Lab people of participating centers
Clinicians	+	Patients

29
Active Centers

10
Countries

Full Members

Support Members

1. Institut Jules Bordet (Brussels)
2. Clinique Universitaires Saint-Luc (Brussels)
3. CHU UCL Namur - Site Ste Elisabeth (Namur)
4. Grand Hôpital de Charleroi - Site Notre Dame (Charleroi)
5. CHU Ambroise Paré – Site Kennedy HELORA (Mons)
6. University Hospital Centrel Zagreb (UHC) (Croatia) (*Support*)
7. Bank of Cyprus Oncology (Cyprus)
8. Centre Georges François Leclerc Dijon
9. Centre Henri Becquerel-CHU Rouen
10. Centre Oscar Lambret (Lille)
11. Hôpital Saint Louis (France)
12. Hôpital Universitaire de Strasbourg
13. Institut Curie (Paris)
14. Institut Paoli-Calmettes (Marseille)
15. Institut Régional du Cancer de Montpellier
16. Institut Universitaire du Cancer de Toulouse
17. Centre de Lutte contre le Cancer François Baclesse (Caen)
18. Centre Léon Bérard (Lyon)
19. CHU de Poitiers
20. Hôpital européen Georges-Pompidou CEPEC (Paris)
21. Istituto Europeo di Oncologia (Milano)
22. Istituto Nazionale dei Tumori Milano
23. American University of Beirut (AUB) (Libanon)
24. Centre hospitalier de Luxembourg
25. Luxembourg Institute of Health (*Support*)
26. Oslo University Hospital (Norway)
27. Algarve Medical Centre (Portugal) (*Support*)
28. Institute for Oncology and Radiology of Serbia (*Support*)
29. Vall d'Hebron Hospital

Oncodistinct network as an example of new model of clinical research collaboration (Pragmatic, democratic and not centralized) (2)

Advantages

- Scientific input (investigators, lab, …)
- Higher number of screened patients (by including non academic centers)
- Speed and quality in performance of trials
- Able to perform in Oncodistinct early (2-3 centers) to late phase trials within the same network (several centers)
- Able to perform different kind of trials (classical, strategic, pivotal, unmet need, proof of concept, …)
- Trials in different solid tumors (common and rare tumors including pediatric patients)

ONCODISTINCT Ongoing studies

8
Ongoing Studies

Study name	MIME	PELICAN	AURA	AVERECTAL	BRAINSTORM	REGINA	CHANCES	COPERNIC
ODN Number	002	003	004	005	006	009	011	012
	Multiorgan Metabolic Imaging Response Assessment of Abemaciclib	A prospective, multicenter, open-label, randomized phase II Study of Immunotherapy in Combination With Neo-adjuvant EC-paclitaxel regimen in HER2-negative Inflammatory Breast Cancer	Avelumab as Neoadjuvant Therapy in Subjects With Urothelial Muscle Invasive Bladder Cancers	Short-course Radiation Followed by mFOLFOX-6 Plus Avelumab for Locally-advanced Rectal Adenocarcinoma	A Brain Metastases Research Platform to Tackle the Challenge of CNS Metastases in Solid Tumours	A phase II trial of neoadjuvant Regorafenib in combination with Nivolumab and short-course radiotherapy in intermediate-risk, stage II-III rectal cancer	A phase 1 FIH study of the anti CD73, IPH5301 in combination with chemotherapy with or without trastuzuman in patients with advanced solid tumors	A study of on-treatment ctDNA changes in chemo-refractory colorectal cancer patients
Phase of study	II	II	II	II	II	II	I	Pilot study
Patients update								
First patient included	01/2019	08/2018	07/2018	07/2018	07/2020	04/2021	01/2022	
Number of included patients	87 **Recruitment closed**	52/72 **Recruitment closed**	Cisplatin eligible cohort closed = 79 Cisplatin ineligible = 58 **Recruitment closed**	44 **Recruitment closed**	144/600 Part A= 90 Part B= 54 **Recruitment open**	31/60 **Recruitment open**	Dose escalation (DE) =10 **Recruitment open**	**SIVs in progress**
Sites update								
Number of countries	2 (Belgium and France)	1 (France)	2 (Belgium and France)	2 (Lebanon and Jordan)	2 (Belgium and France)	2 (Belgium and France)	DE = 1 (France) and expansion (France and Belgium)	2 (Belgium and France)
Number of activated sites	11 (6 in Belgium and 5 in France)	13 (France)	10 (6 in Belgium and 4 in France)	3 (2 sites in Lebanon and 1 in Jordan)	16 (Belgium and France)	10 (Belgium) + 4 (France)	2 (France)	17 (9 in Belgium and 8 in France)

Molecular evolution of oncology: The need for a new clinical research studies organization in oncology : The Spiderweb model

Awada A., Kotecki N. and the Oncodistinct network team

Background of the Spiderweb Model

- Clinical trials have evolved from **drug-oriented trials to target-oriented trials**
- Common cancers are now divided in smaller tumor molecular sub-groups=rare cancers
- **Molecular oncology** has proven to be efficacious (eg/ NSCLC, Melanoma, NRTK fusion tumor types,…)
- Efforts at national and international levels are currently ongoing to implement NGS **in clinical and research practice**
- **In one center, it will be impossible (logistically and financially) to open hundreds of molecularly-based clinical trials to cover the maximum of these gene abnormalities and consequently the patients !!**

There is an important medical need to:

- **Facilitate access to innovative moleculary-based clinical trials to all cancer patients in their centers and as early as possible whenever the patient is living**

→ So it is urgent and vital to adopt and to improve drug development methodology and organization

The basis of the Spiderweb model within Oncodistinct network

1. **Create new model of organizing clinical trials of molecular-based therapies**

   - ***« BRINGING A NON AVAILABLE CLINICAL TRIAL TO THE MOLECULARY SELECTED PATIENT IN HIS CENTRE AND AT ANY MOMENT! »***
   - ***Master Agreement (MA) between Oncodistinct (ODN) sites which would allow a patient from an ODN center to be treated on-site in a clinical trial opened at another ODN site (as first step) and once successful, extending the model to all centers (outside the network)***

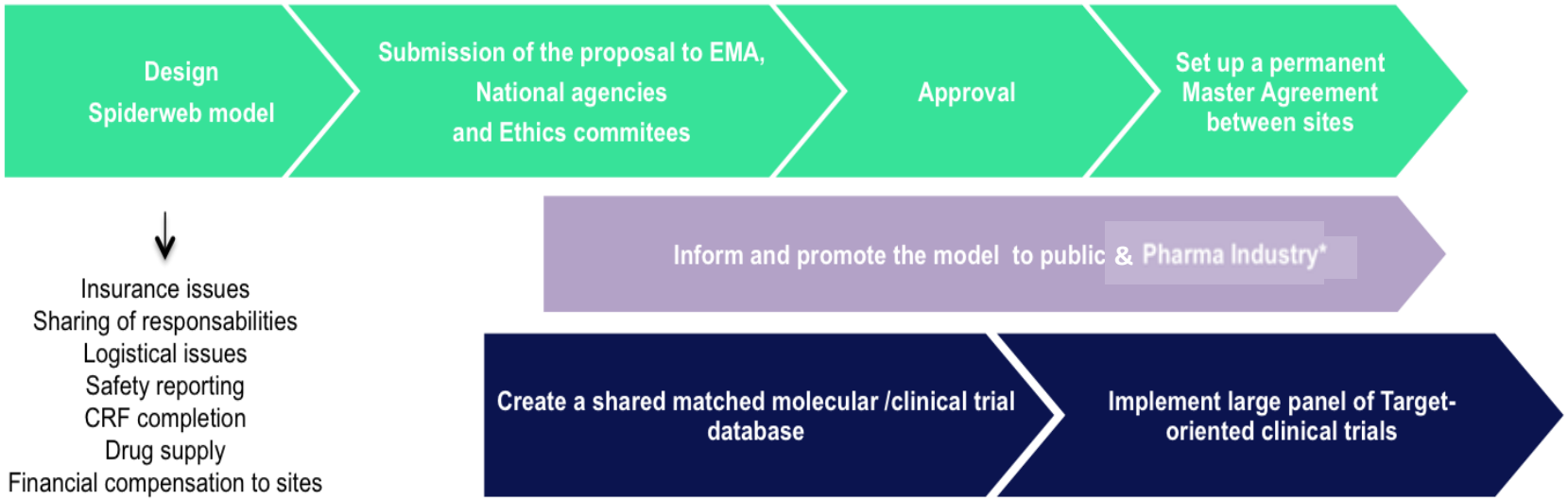
2. **Shared matched molecular alterations/clinical trial database**
   (covering a large panel of targetable genomic aberrations and target-oriented trials)

Aims :

- ***Support development of IIS target oriented trials***
- ***Encourage Partnership with Pharma industry***
- ***Foster access to innovative clinical trials for the patients within the network***

"Spiderweb" model of the Oncodistinct Network - Workflow

Work package 1: Spiderweb Model Master Agreement
Work package 2: Communication plan and lobbying
Work package 3: Shared matched molecular clinical trial database



* *Publications, Meet the industry meetings, Social media, Lobbying*

Responsabilities for all parties

Spiderweb Management Team

- Point of contact for CS/PS and eventually Sponsors
- MA preparation and submission
- Provide support for the site contract if needed and study submissions
- Supervision on the SW procedures
- Management of the SW database

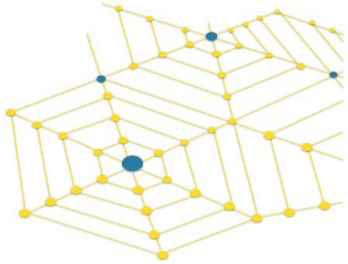
Coordinating Site team (CS)

- Responsibility for all patients treated in the trial (coordinator)
- Activities that apply to the protocol: regulatory submissions, protocol amendments, contract negociation and insurance
- Responsability for patients on their own site (PI) >> See PS section

Participating Site team (PS)

- Responsability for patients on site (PI)
- ICF signature, clinical examination, AE assesment (PI/ sub inv)
- Laboratory analyses, biopsies, imaging, …
- Transmission of information to the CS
- Study planning/ patient (Study-co/ nurse)
- CRF completion

At the Participating Site Level: Process for Study Activation



M

A

Contact the SW management team

Study specific Annex to be signed from both parties

identify Patient based on NGS tests at one site

Identify a clinical trial

Become a Participating Site

Inform patient in the Participating Site

Patient screening and treatment in the participating site

Remote SIV

Drug supply

General Conclusions (1)

- Innovations in science and technology shape the present and the future of clinical research and clinical cancer care
- Integration of molecular biology and molecular-targeted therapies in clinical research and clinical care is a reality in practice

General Conclusion (2)

- Agnostic tumors approaches are a new and evolving entity in practice

- New therapeutic approaches without access to cancer patients aren’t innovation – they are just an invention! Hence new designs of studies and new models of trials organisation are needed.

Thank you