Site Readiness to Perform Clinical Trials in Hematology & Oncology

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Radoslaw Jadczak MD, MBA

Director, Therapeutic Strategy, Oncology

Current responsibility

- I use my expertise in drug development strategy, knowledge of clinical research methods and understanding of medical science and the therapeutic landscape to shape design and delivery strategies for oncology studies and programs that meet the needs and expectations of Sponsors. I have provided therapeutic strategy input for many cancer indications and trial designs across Phase FIH to IIIb, including adaptive designs, basket studies and biosimilar interchangeability

Profile overview

- Over 12 years experience in pharmaceutical industry on regional and global positions (Novo Nordisk, GSK)
- Over 10 years experience in Clinical Research (IQVIA):
  - Managing the team developing the IQVIA networks of qualified sites (Prime sites, Phase 1 units etc.)
  - Managing the feasibility and site identification team in CEE
  - In oncology experience across all phases from methods and modelling studies and translational medicine to life-cycle management. I have worked with many solid and hematological tumors and with both small-molecule and biologic products

Education

- Board certification in Internal Medicine
- MBA Executive, Management

Areas of expertise

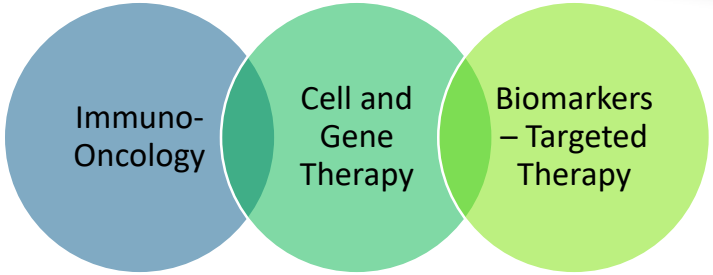
- Oncology
- Early Clinical Development (Phase 1-2)

Relevant experience

Currently involved as a Therapeutic Strategy Director in several oncology / hematology studies.

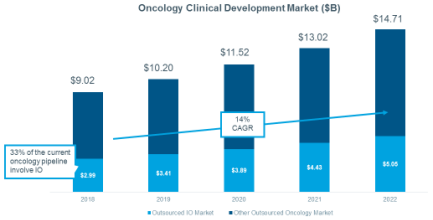
Summary Key Oncology Tends/Opportunities

Market is driving high growth and high complexity in Oncology Clinical Development



Outsourced IO Market expected to be ~$5B[1] to $7B[2] by 2022

Assumes IO outsourced at similar levels to rest of oncology R&D



- Immunotherapy market expected to grow at CAGR of ~13.8%[1]
- Growing R&D investments by major players and growth prospects in the developing countries such as China and India provides significant opportunity in this market
- It is estimated that immunotherapy drugs will occupy half of the cancer treatment by 2022[2]
- Checkpoint inhibitors represented by PD-1 / PD-L1 expected to take the largest part

Projected 2018 outsourced oncology market to grow at 13% CAGR*

1 https://www.prnewswire.com/news-releases/cancer-immunotherapy-the-global-market-is-expected-to-grow-at-a-cagr-of-13-8-from-2018-to-reach-182-83-billion-by-2024--300746602.html

2 https://www.creative-biolabs.com/blog/index.php/cancer-drug-nt-and-market-trends

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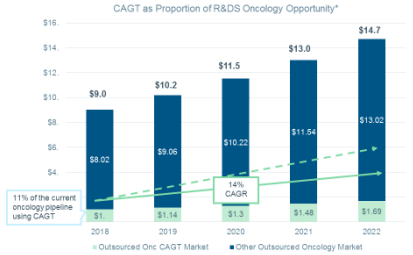
Outsourced Oncology CAGT Market Expectations

Assumes IO/CAGT outsourced at similar levels to rest of oncology R&D



- Rapid proliferation of cell therapy agents in last year could drive higher growth rate than underlying IO growth
- High discovery and development activity at academic centers – enabled by rapid advancement of local cell production technologies
- Large set of Phase 2 trials started in 2018 with majority of industry CAGT trial work occurring at EBPs

CAGR likely to be higher – at least based on last two years
- Seeing shift out of academic centers into industry
- huge growth will come in solid tumor once they ID antigens… (timeline unclear on cracking this)
- Other break though will be increased Ag expression

*Based on pipeline analysis estimating CAGT as 34% of IO pipeline – NEED TO TEST IF ALL CAGT ARE IO; growth rate assumes similar to IO – need to validate – may be higher based on recent CAGT trends
Source: Pharmaprojects 2018, Cancer Research Institute, and Jun Tang

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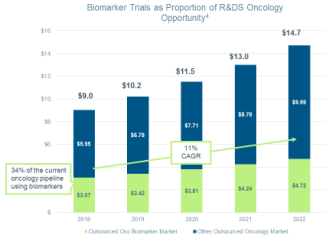
Outsourced Oncology Biomarker Market Expectations

Assumes industry on a 10 year trajectory to 100% biomarker utilization on trials



- **Patient stratification** is expected to **continue to increase**
- Experts claim that **all oncology drugs** will have associated biomarkers within **5-10 years**
- Highly invested area for VC (e.g. Tempus labs raised $110M in 2018) and **Big Pharma** (e.g. Roche is aiming to have biomarker(s) for each of their oncology drug)

Based on pipeline analysis estimating CAGT as 34% of IO pipeline, Pharmaprojects 2018, Cancer Research Institute, and Jun Tang

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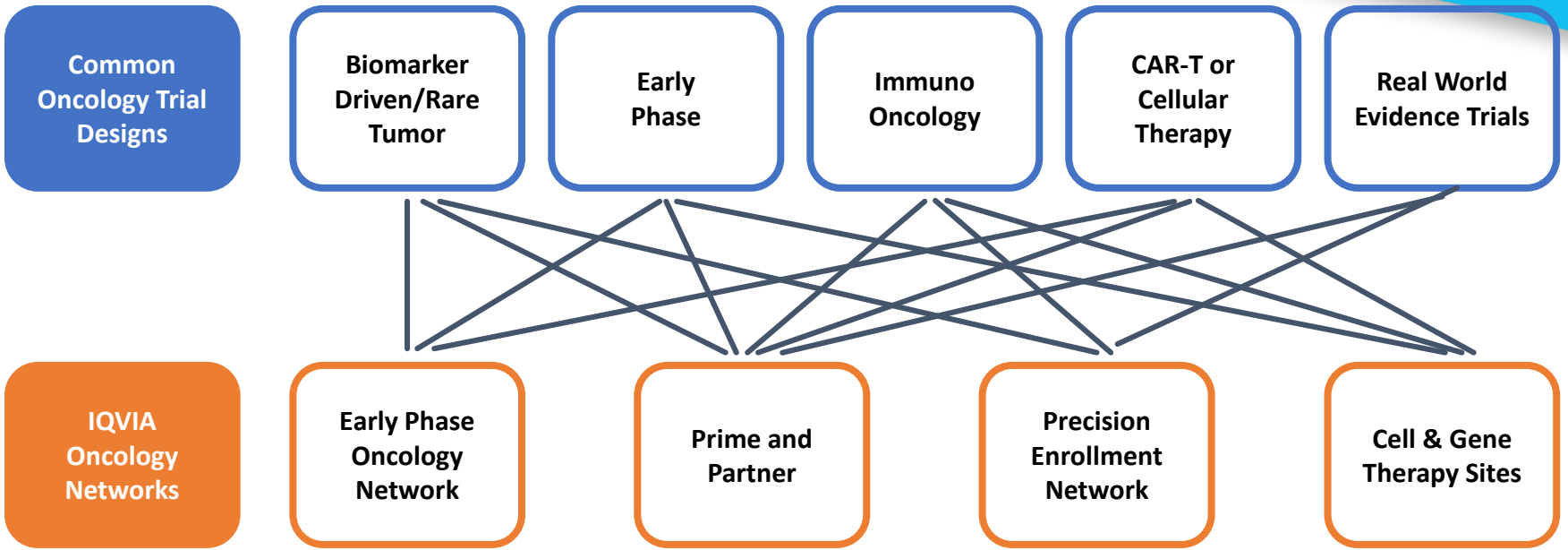
*e.g., novel ("synthetic) sources of data, RNA therapies, emerging technologies/devices

Specialty Oncology Networks

Combine the right sites with strategic relationships to accelerate startup and boost study performance



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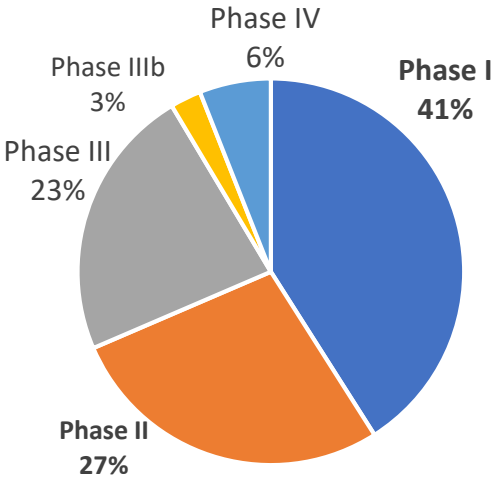
Solid tumor and hematologic malignancies (2013 – 2018)

Highlights

Industry-leading delivery model designed for early phase oncology

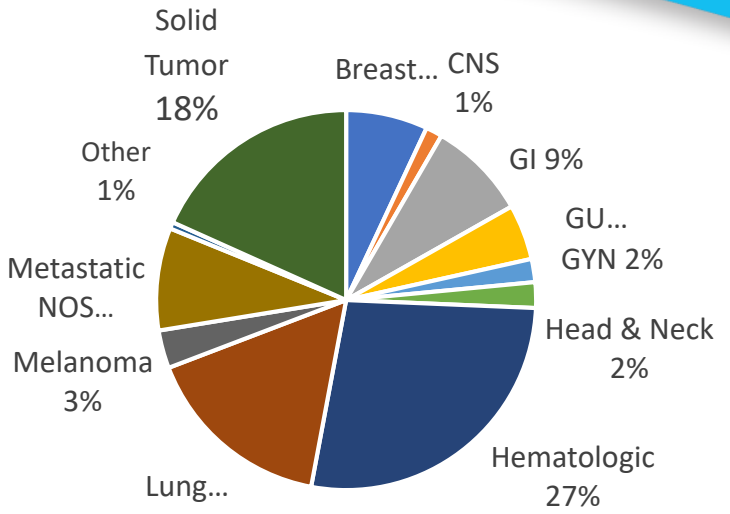
Strong global networks to ensure successful coverage for specific indications or genetic alterations

Strong site and KOL relationships leading to specialized networks



70%

of projects are early phase



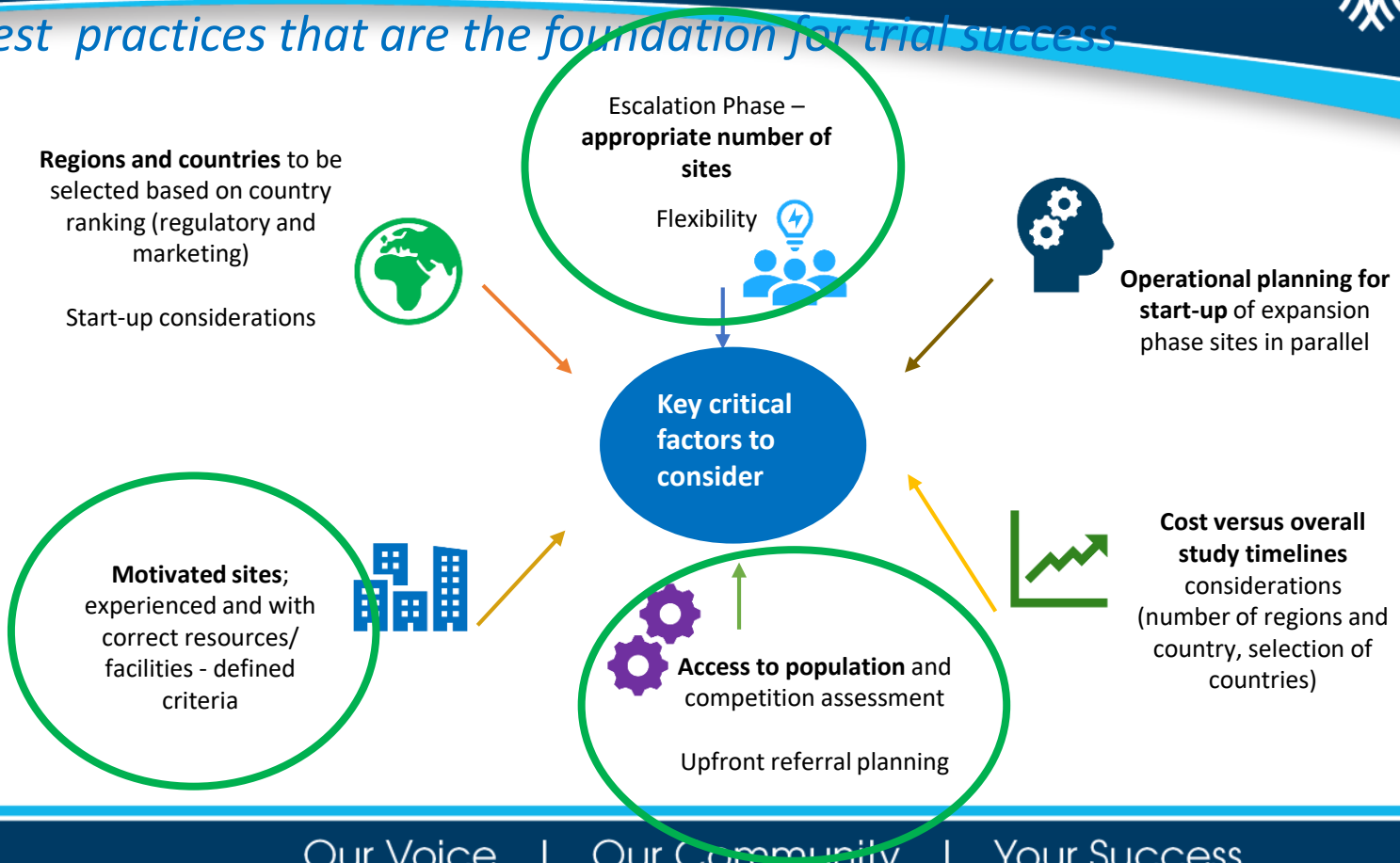
Source: Internal IQVIA data 2013- 2018_RFI_May 2018 dataset_Oncology CSR

Oncology Strategy (sites and market expectations)

Core-Enabled Clin Dev	✓ Cross-Oncology/IO	✓ CAGT	✓ Biomarkers
Develop & Design	**Expertise (KOLs) to design trials that manage complexity**, combination therapies, **rare patients** and evolving regulatory rules and implications		
Site Selection	**Dedicated Sites that are enabled to find the rare oncology patient** and validated to execute uniquely complex oncology trials		
Recruitment	**Deep and varied data/analytics and network of dedicated sites** and test providers **to identify and access trial ready patients, and ability to support unique oncology patient needs**		
Execution	**Focused oncology partnership and execution**, delivering the right strategy and value to execution including unique roles or tools to manage complexity		

Early Phase Study Strategies

Best practices that are the foundation for trial success



The most important assessment points to incorporate in the evaluation plan to support the ultimate selection decision include:

- ***Staff Qualifications***: staff availability, specialty, credentials, experience in clinical research and the studied indication, including their performance as it relates to regulatory compliance.
- ***Facilities and Equipment***: adequate facility space, drug/device storage space and security, types of source documents, and equipment needed for the study.
- ***Site Profile and Timelines***: site types (e.g., hospitals or clinics, academic centers, Veteran Affairs facilities, non-profit, government, and private sites), site's Institutional Review Board (IRB) meeting timeframe, and typical contract negotiation timeline.
- ***Population Profile and Access***: eligible participants' availability and proximity, disease/condition incidence, ongoing trials recruiting similar patients, and recruitment capabilities including resources for conducting outreach.
- ***Past Performance***: clinical trial experience including in trials with similar enrollment timelines, enrollment target, and complexity, and past enrollment rates.
- ***Competition***: concurrent trials in the same indication or targeting the same population profile that are ongoing or scheduled to start during study conduct.

Oncology Trials– The ideal site profile

Differentiators	• Familiarity with the management of unknown or emerging safety reactions • Managing in-patients with advanced disease • Highly experienced in complex protocols and schedule of events • Requirements for rapid data collection and decision making

PI	**Infrastructure and Resources**
• Interest, experience, track record in early phase trials • Access to a large patient pool (indication specific or advanced disease) • Established relationships with other site staff. • Understanding of the importance of sample completeness e.g. biomarker, PK/PD, tissue • Flexible and accessible for regular communication with study team	• Stakeholders in key departments that will readily support the trial e.g. pathology, radiology • Pharmacy capabilities that can cope with protocol • Professionally resourced – PI to Study coordinator - resources to cope with high data flow • Sample preparation and storage facilities
Regulatory/IRB	**Other**
• Clear and established committee and review process (protocol and amendments) experienced in early phase • Predictable timelines	• Strong engaged relationship • Open and able to cope with frequent monitoring visits • Long term focus

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Investigators' Handbook for Clinical Investigators Conducting Therapeutic Clinical Trials Supported by Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI) | NCI

Conducting Clinical Trials: Information for Investigators, Tools for Managing Trials, Registration/Reporting and Ensuring Patient Safety | NCI

Requirements for oncology studies

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Facilities

- Synchronised clocks in wards.
- Access only to authorised personnel. Trial subjects should not be allowed access to certain areas. Access to toilets should be controlled in case of urine collection.
- Temperature-monitored fridges/freezers for IMP and sample storage.
- Equipment maintained, validated, and calibrated regularly. Evidence of maintenance.
- Ability to prepare the onco drugs
- Access to Pharmacy (GMP)
- Access to Pathology Lab
- Sample handling facilities (e.g. ward lab, centrifuge)

Medical Emergency

- Access to 24-hour medical cover.
- Emergency crash carts in each ward.
- Proximity to a critical care unit.
- Contractual arrangements.
- An alarm system to call for assistance in case of a medical emergency: bedside, bathrooms, recreational areas.
- Continuous monitoring of vital signs, such as ECG and pulse oximetry.

Staff

- Full-time clinical research physicians and registered nurses with life support training on each ward.
- GCP training for all staff
- A member of staff who will act as a study coordinator.
- Physicians / PIs with experience in phase I studies.

Operational

- Fast recruitment of patients with full range of Hema-Oncology and Solid Tumors
- Hospital based unit, exclusively dedicated to challenging protocols in oncology patients
- Complex biomarker assays
- On-site modern diagnostics: radiology, CT, MRI, biopsies
- On-site therapies including high-dose chemotherapy

Medical overview of Early Phase Oncology trials

Type of population and drugs

Study designs include a **dose escalation** cohort to determine the maximum tolerated dose (**MTD**) of the optimal biological dose (**OBD**), followed by a **dose expansion** cohort with narrower eligibility criteria with focus on specific biomolecular features to confirm the **recommended Phase II dose (RP2D)** and to obtain preliminary evidence of the anticancer efficacy in selected patient subgroups.

The type of new drugs tested in early phase oncology trials includes the following:

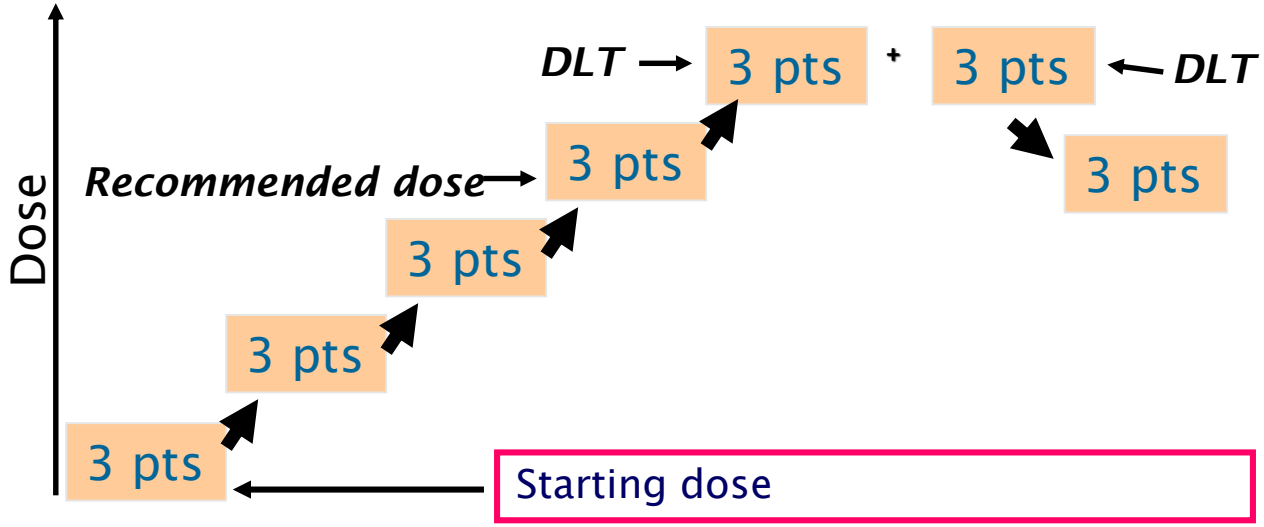
- A **completely novel agent, never tested** (or with limited experience) in humans
- An agent already in clinical development
- An agent belonging to a class of drugs already studied in humans
- The **first administration to a specific population, such as elderly people or those with hepatic or renal impairment**
- A combination **of a new and approved drug(s)**
- A new combination of approved drugs
- A new dose of an approved drug
- Potentially **high-risk products**

The study populations of early oncology trials include the following:

- **Multi-tumor unselected population**
- **Single type of tumor**, unselected patients
- **Histology- and/or biomarker-selected** population
- Patients with global **liver impairment**
- Patients with **renal impairment**
- **Restricted to age classes** (elderly, children) or to one sex

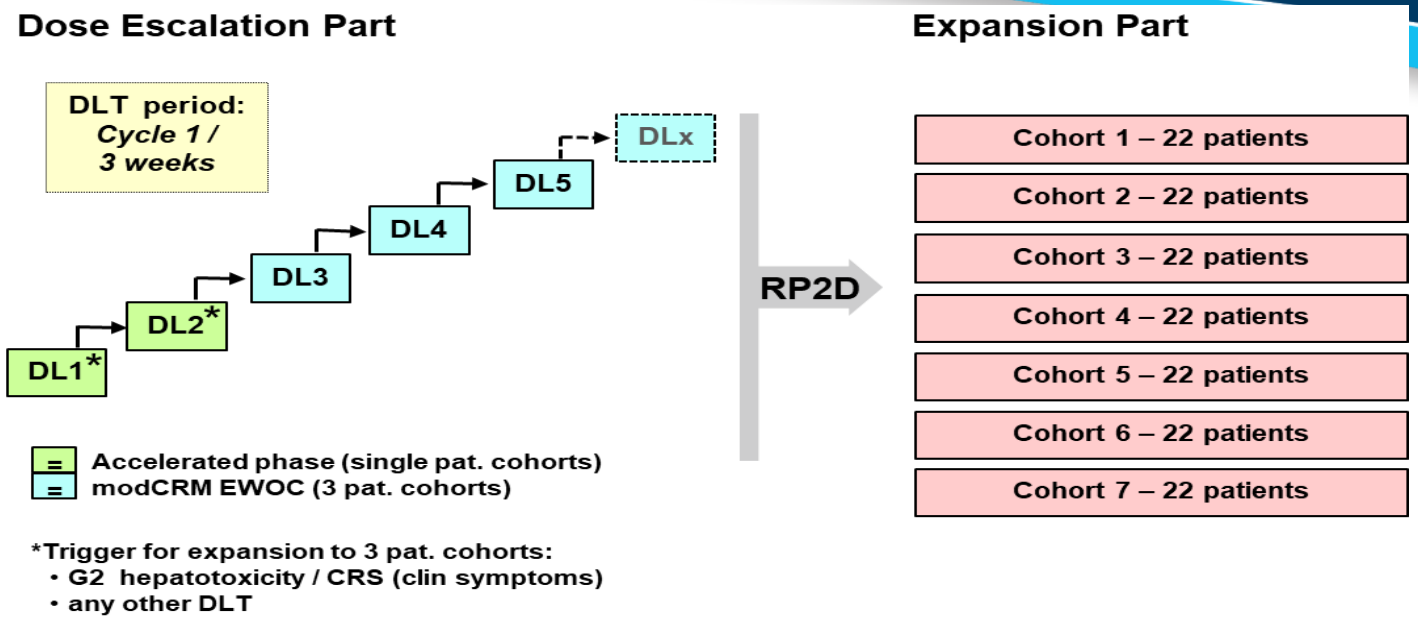
Phase I trial design: standard 3+3 design

- DLT - **dose-limiting toxicity**



Eisenhauer et al.

Study XXX SOLID TUMOR design



Continual reassessment method (CRM) designs

Recommended Phase II Dose

Cohort management success factors for clinical trial execution

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Close communication among PL, CRA, site, project team

- Regular emails, site calls, TCs, 1:1 communications
- CRAs to be primary contacts with sites
- Active communication with Study Physician / Prevent Protocol Deviation rather than to report it

Management of cohort and transition to expansion

- Cohort Management Plan with agreed expectations and communications flow
- Regular site communication to confirm slot availability, patient "waiting list," and any key decision, including progress and when/how transition to expansion will occur
- Cohort enrollment "rules": make clear and be fair
- Slot allocations to flow through one person (Study Project Leader), wait list accessible to all
- Use screening window to minimize gaps and fasten timelines
- Communication once transition is completed and expansion is ready to start

Cohort Review Committee (CRC) meeting / Minimize "white space"

- Agreed CRC meeting timelines and meeting requirements
- Proactively schedule meetings to occur based on Last Patient Out in each cohort
  - Send site reminders and provide deadlines
  - Enter patient data into eDC prior to the CRC meeting; specify priority/key data fields
  - Ship lab samples to central labs
  - Availability of results required at each CRC meeting
- Distribute minutes and cohort approval memo immediately after CRC meeting

Common challenges:

- **Risks** and uncertainties relevant **to a drug with limited exposure in humans both from safety and efficacy perspective**.
- **The selection of an appropriate starting dose** and the anticipated dose level **leading to a minimal biological effect in humans.**
- It may **require a long dose escalation phase**.
- For Phase I/II designs, **investigators may be not keen to recruit until an RP2D is established**.
- Inclusion of refractory / heavily **pre-treated patients that are less likely to respond may lead to frustration from efficacy failures with the perception of an ineffective drug and loss of enthusiasm for the study.**
- **Administration** of the investigational **drug may be uncomfortable**.
- The rigors of early phase studies to patients **include intense pharmacokinetics sampling, and an overnight stay in the hospital may be also required**.
- It may involve **exploratory imaging**.
- There is little or **no flexibility for visits window and schedule of assessments** (e.g.,holidays, weekends).
- **The study design may involve the untargeted use of a targeted agent**, **with Ethics Committee concerns and/or investigator and patient concerns.**
- **Change of study design and/or study population may be required** according to the emerging data.

Early Phase Oncology Network (EPON)

IQVIA Early Phase Oncology Network (EPON)

Established network of qualified Phase I oncology sites working in close alignment to achieve goals, mitigate risk, and increase efficiency

Deliver consistently

- Consult on design to **reduce risk of amendments and delays**
- Using deep experience to **streamline start-up**

Deliver differently

- Network of sites working together for optimal outcomes
- **Earlier engagement with compound and protocol**
- Fewer sites delivering more patients to **reduce variability**

Deliver high quality

- Productivity leaders in early phase oncology
- **Adds value to study planning and conduct**

France

Belgium

The Netherlands

Spain

United Kingdom

Italy

EPON - Adaptive Site Strategies

Our innovative applications

EPON Sites/KOLs → **Additional IQVIA relationships**
- Prime/Partner
- Precision Enrollment Network

→ **Additional tactical sites if necessary**

Phase I	Phase Ib/II

FIH & Dose Escalation → **Dose and cohort expansion** →

IQVIA Early Phase Oncology Network (EPON)

High touch, high efficiency operational model

Strong Site Engagement

- **Tailored group of ECD oncology specialized Sites/Investigators** *Early and ongoing engagement from concept to POC*
- **Established relationships with non-investigator site staff** *(Research Directors, Nurse Managers, Contract Specialists, Regulatory, etc.)*

"High Touch" Delivery Model

- **Early Phase Oncology Specialists:** Strategic resourcing of experienced staff
- **Site relationship managers on hand** to support communication and escalations
- **Specialized resourcing in startup**

Operational Efficiency

- **Streamlined feasibility and expedited site selection**
- **Master Confidentiality agreements** and contract/budget efficiencies to leverage
- **Better site selection & qualification**


USA


United Kingdom


Netherlands


Spain


Taiwan


Belgium


Italy


France


Australia


Malaysia

Precision Enrollment Network (PEN)

IQVIA Precision Enrollment Network

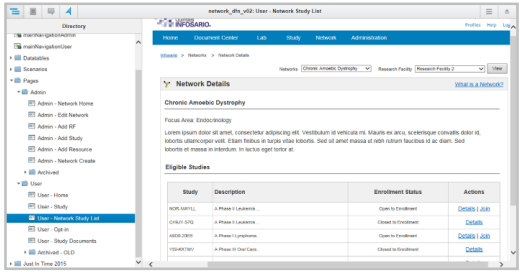
A new approach to patient recruitment through a proactive site network

Large Site Network

Oncology-aligned network of 100+ sites ready on-demand

Expose Network to Studies

Sites search studies through an online portal

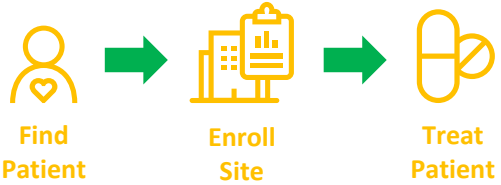


Eligible PEN Studies

Acme Phase 3 HCC	Join
Acme Phase 2 Lung	Join
Acme Phase 2 Melanoma	Join
Acme Phase 2 Solid Tumor	Join
Company X Phase 2 Breast	Join
Company Y Phase 2 CRC	Join

Implement Rapid Site Start-Up

Enroll site and begin treatment within 14-21 days of patient identification

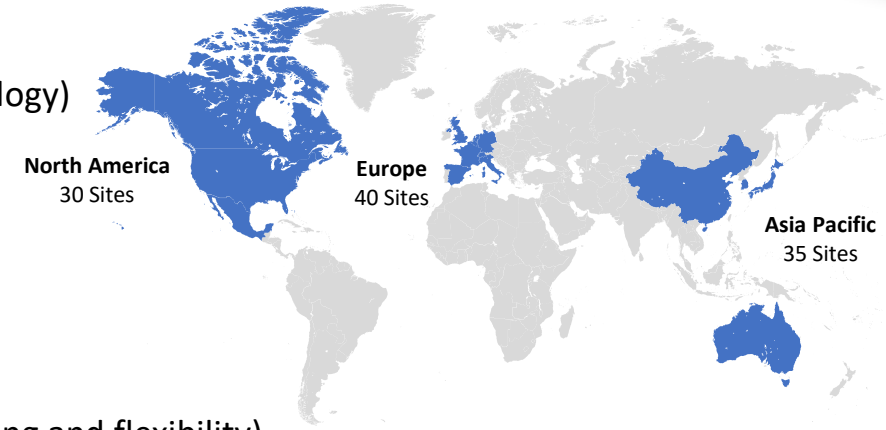


Cell and Gene Therapy Network (CAGTN)

IQVIA Global Site Network for Cell and Gene Therapy Studies

By early 2020, IQVIA will have >100 qualified CAGT sites across 14 countries

- Quality check
- Start-up efficiencies (IRB/EC & contracts)
- CAGT trial experience
- Access to Patients (Hem/Onc, Cardio, Neuro, Ophthalmology)
- Country and/or State license
- SOPs for routing cell therapies
- Appropriate surgical capabilities
- Apheresis capability
- Onsite cell therapy lab
- Cold-chain sub-contractors
- Pharmacy, Lab and Radiology support (including scheduling and flexibility)



Once sites meet the pre-qualification criteria, a CAGT SME and site specialist meet with investigators and their staff to discuss the enrollment potential of their referral network and investment into proactive development of these patient pathways.

Q&A

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