Utility of Industry-Sponsored Oncology Registries For Clinical Trials – A Perspective

CTTI Experts Meeting

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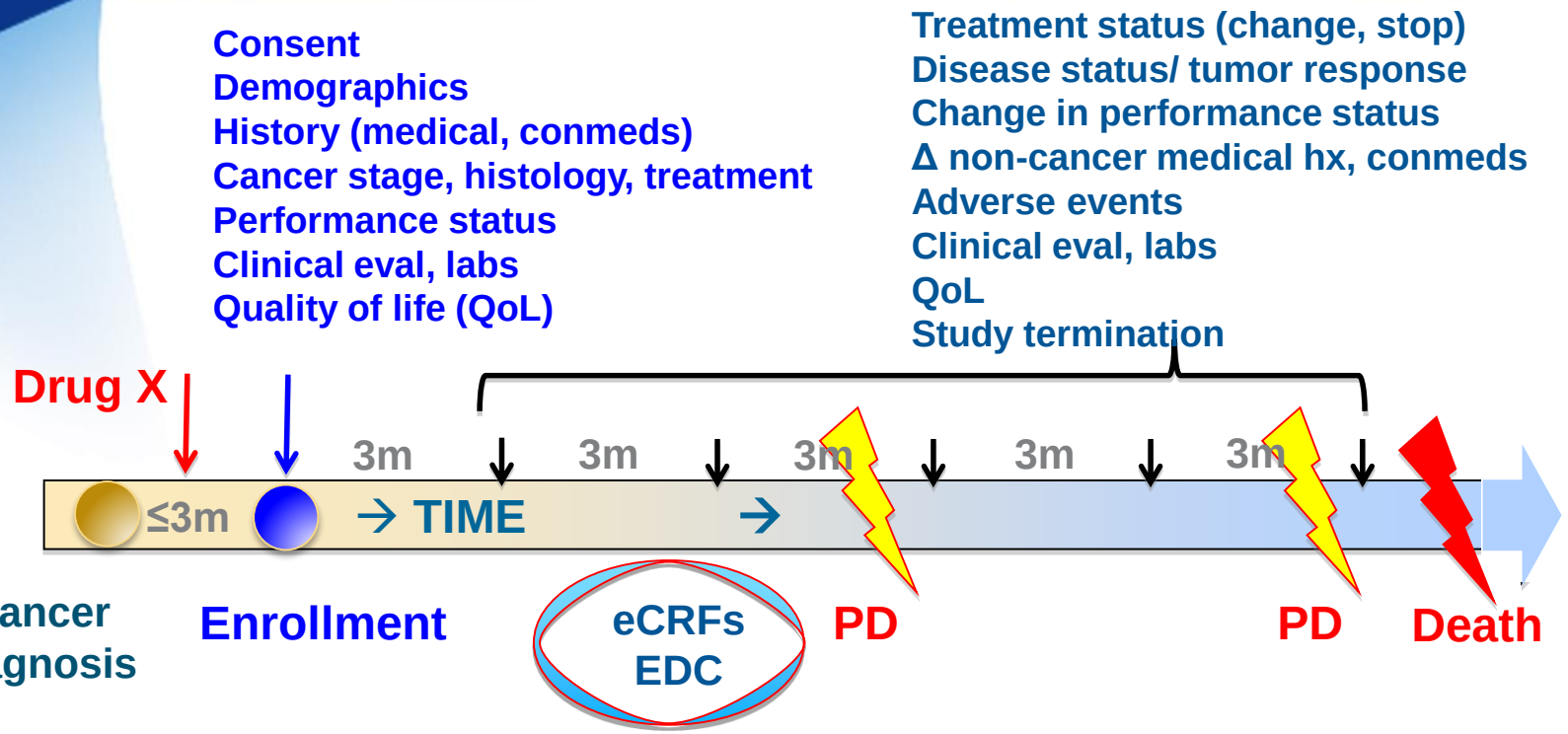
Disclaimer

- I am a current employee of Celgene Corporation
- Prior to Celgene, I was an employee of Genentech, A Member of the Roche Group, for 7 years
- Prior to Genentech, I conducted prospective observational cohort study research at Kaiser Permanente's Division of Research for 2 years
- All views shared today are my own and not those of my current or past employers

"Registry" Definition in This Talk

- Prospective observational cohort study conducted in U.S.
- Sponsored by a pharmaceutical/biotech company
- Treatment and disease registries
- Settings: advanced cancers, primarily solid tumor
- *Not* post-marketing commitments
- Primarily community settings; > 200 sites across U.S.
- N = 1,000 - 4,000 patients

Example Study Design: U.S. Oncology Disease Registry With 3-Month Enrollment Window From Time of Diagnosis



- Study protocol with broad study objectives and broad inclusion criteria. IRB approval and informed consent required.
- Patients treated and followed per standard of care (MD's discretion).
- Data cleaned/queried throughout the course of study. Minimal SDV/monitoring.
- Analyses and publications generated throughout the course of the study and beyond.
- An external Scientific Steering Committee (SSC) provides guidance on study conduct, analyses and publications.

eCRF = electronic case report forms; EDC = electronic data capture system; PD = disease progression

Are These Types of Registries Conducive to Embedding Clinical Trials?

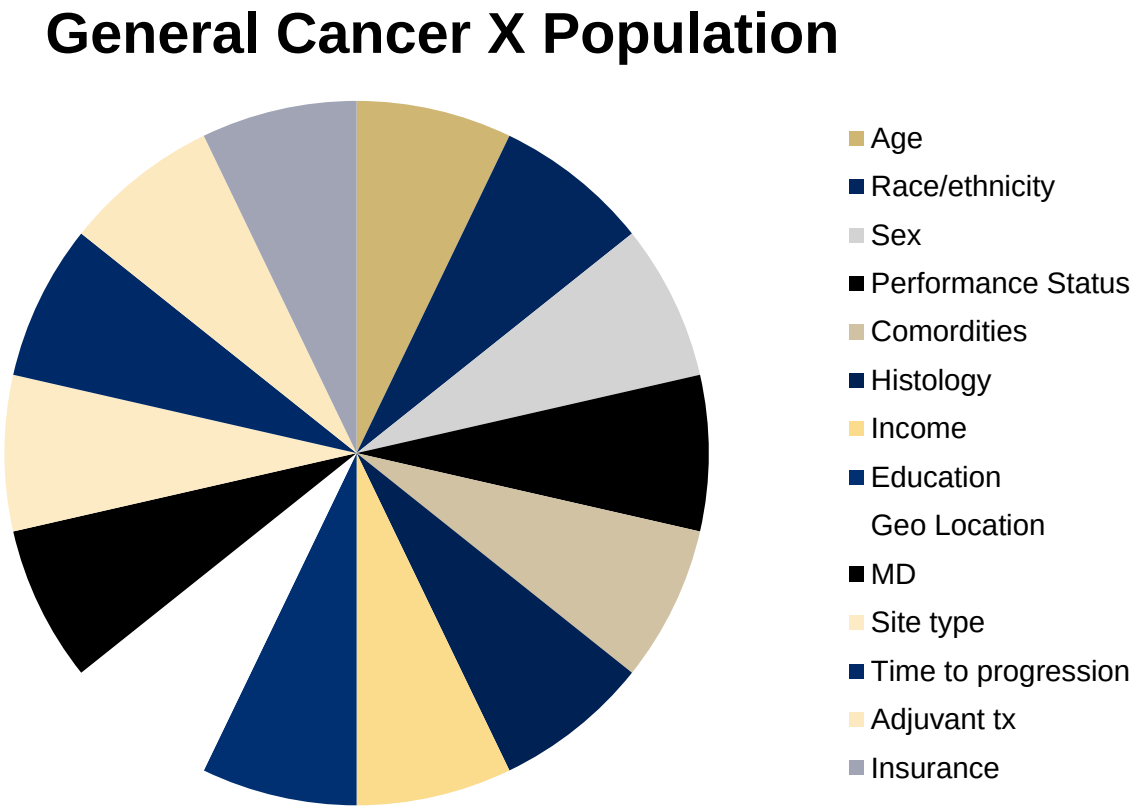
Considerations:

- Institution/site may not be trained, staffed or set up for conducting clinical trials
  - Community sites may be less experienced and fewer staff for clinical research
  - Increased paperwork and monitoring required for trials
  - Enrollment process would need to be expedited
  - IRB re-approval needed for each trial
  - Active patients would need re-consent for each trial
  - Follow-up visits, types of procedures, diagnostic tests would be protocol specified for trials
  - Clinicians would be required to follow formal/protocol-specified response criteria (e.g., RECIST) for trials
  - Trials require comprehensive safety collection with expedited reporting requirements
- Budget adjustments: site fees (for data entry) are generally lower for a registry than for a clinical trial
- ***Most importantly, registry study design can allow certain biases to be inadvertently introduced in the patient population and the data collection***

Potential Types of Bias in Oncology Registries To Consider For Embedded Clinical Trials

- Selection Bias: biased sampling of study population
- Information Bias: missing or erroneous information
- Confounding Bias: *out of scope here, reduced in trials via randomization and/or strict protocols*

Selection Bias - Sampling Considerations



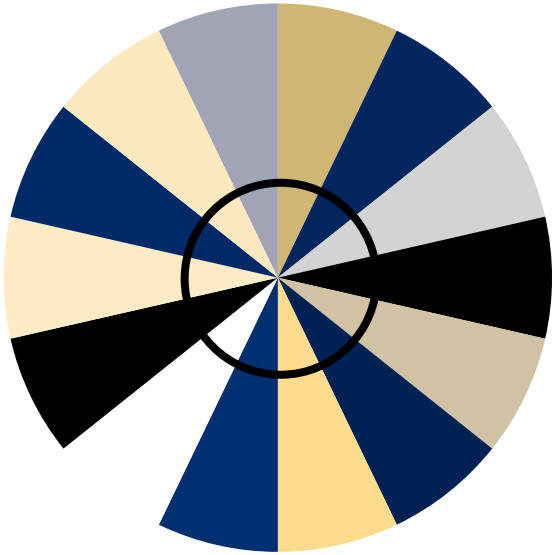
Registry study inclusion criteria are generally broad to get heterogeneous patient population.

Ideal Sampling of An Oncology Registry Study Population

General Cancer X Population

Enrollment Time

General Cancer X Population



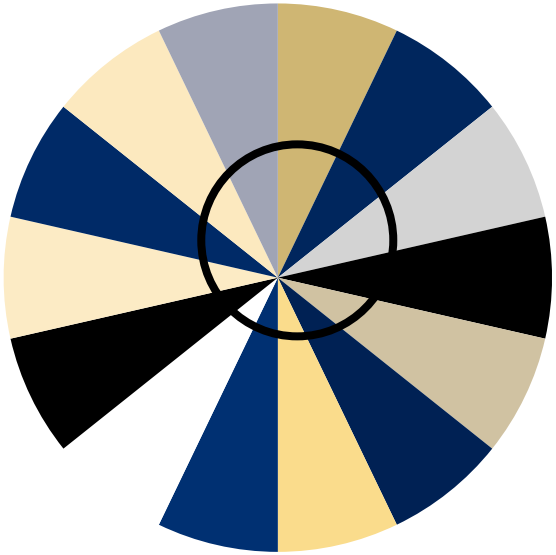
Ideal Scenario: "On target" sampling over time (several years, usually). General popn characteristics stay relatively constant during enrollment phase and study popn is representative of general popn.

Selection Bias Concern 1 – Population-Level Off-Target Sampling

General Cancer X Population

Enrollment Time

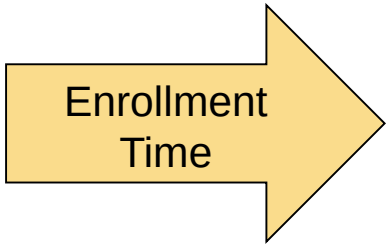
General Cancer X Population



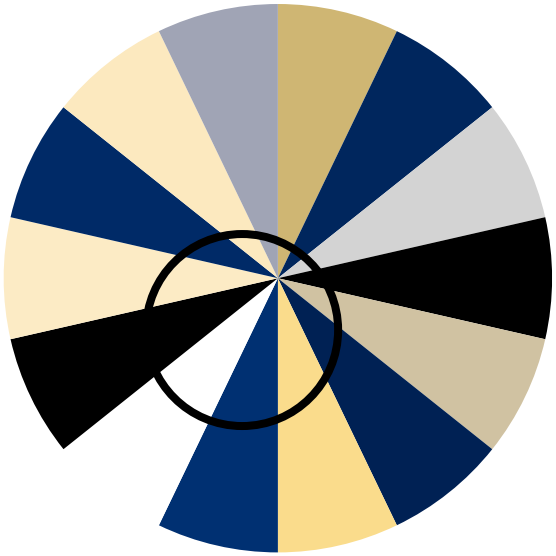
General population characteristics stay constant during enrollment period, but sampling is off target from the start [e.g., low number of sites; limited geographic distribution; high % academic site patients].

Selection Bias Concern 2 – Population Shift/Time Period Bias

General Cancer X Population

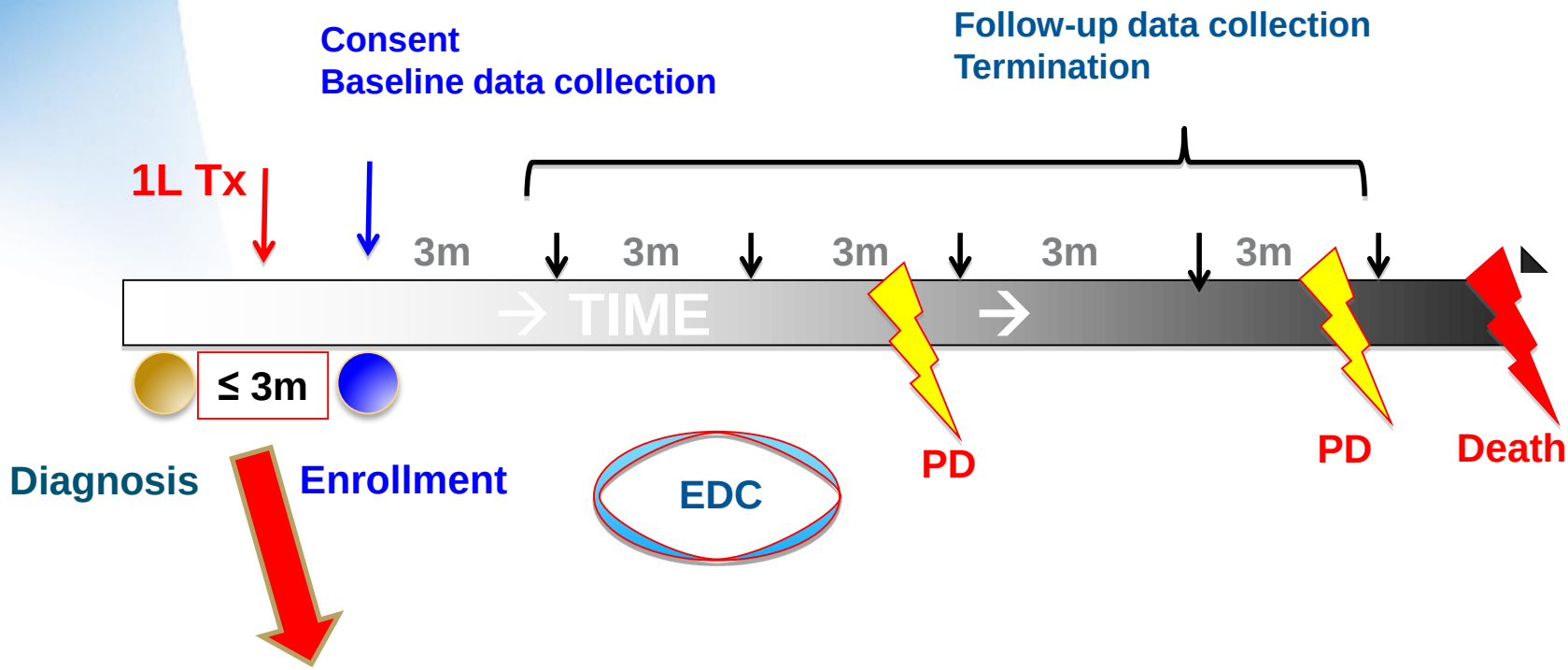


General Cancer X Population



Sampling starts on target, but as enrollment time lengthens, general cancer popn characteristics change during the enrollment period even though sampling methods and rates stay relatively consistent [e.g., median survival lengthens in certain subgroups (age, new treatments), new diagnostic criteria or new diagnostic tests emerge].

Selection Bias Concern 3 – Patient Level Survivorship/Participation Bias



CONCERN: Patient-Level Selection Bias

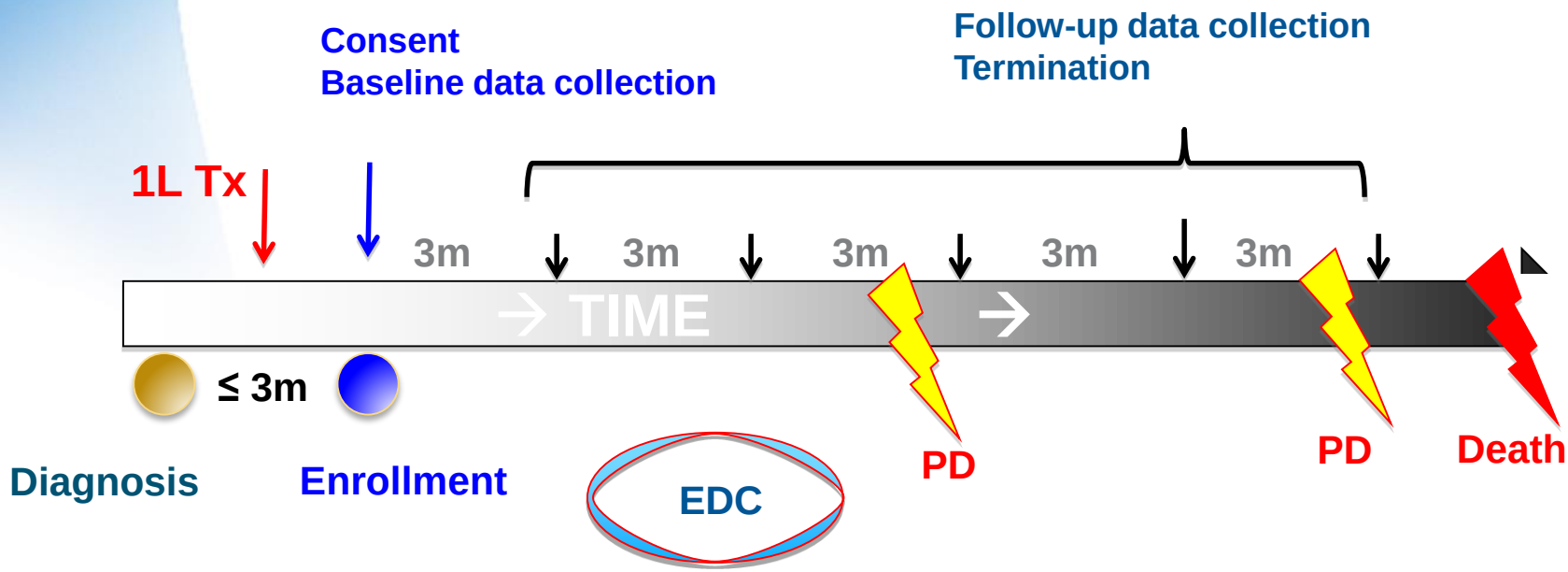
It generally takes longer to enroll a patient into a non-interventional study. This window of time can introduce "survivorship" bias. Additionally, informed consent requirement can introduce a "participation" bias. Oncology registries involving very aggressive cancers are more prone to these types of selection bias.

EDC = data collection in electronic data capture system; Tx = treatment; PD = disease progression

Information Bias

- Missing data
  - Loss to follow-up (LTFU)
  - Variable time between clinic visits and reporting frequency
  - Underreporting/overreporting
    - E.g., - Not ALL adverse events are collected in registry studies
- Erroneous data
  - Recording errors/Reporting errors
- Unresolved queries
- May result in differential exposure and outcome misclassification

Industry-Sponsored Registries – High Costs For High Quality Data



Site personnel transfers data to separate registry electronic data capture system

CONCERN: High costs!

Site fees, CRO/operational costs and resources are high for industry and increasing over time

EDC = data collection in electronic data capture system; Tx = treatment; PD = disease progression

Current Situation: The Industry-Sponsored Oncology Registry Model Needs To Evolve

Situation	Needs
Increasingly complex cancer disease and treatment landscapes	Large patient populations, possibly from multiple data sources
Rapidly emerging new therapies	Real-time data to address current questions for approved and future products
Questions rapidly changing	Study design flexibility to: •START and STOP quickly •Phase (sub)studies in and out over time •Gate on milestones and data availability
High costs of large, sponsored registries are not sustainable for *every cancer type or every new treatment*	More resource efficiencies; more external collaboration

What Changes Are Needed For This Evolution?

- Provide means to sites to increase resources/staff quickly.
- Provide mechanisms to enroll quickly.
- Continually accrue patients for long period of time.
- Implement a user-friendly process for submitting clinical trial proposals to a governance body, like a Steering Committee, for review, approval and prioritization.
- Prepare sites early in the registry for higher safety reporting and study monitoring requirements for trials.
- Consider RCTs, if feasible, as randomization can improve internal validity.
- Develop company SOPs/guidance documents specifically for registries designed for conducting trials.
- Engage stakeholders, customers (e.g., FDA) early in registry study planning and design.
- Consider industry-supported studies, rather than industry-sponsored.
  - External collaborations, multiple partners.

Thank You!