Developing Drugs for Rare Diseases: Manufacturer's Perspective

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Agenda

Why develop drugs for rare diseases?

- What is Missing Beyond the Cost and Headlines?
- Why should we think about this differently?
- Possible solutions? Next steps?

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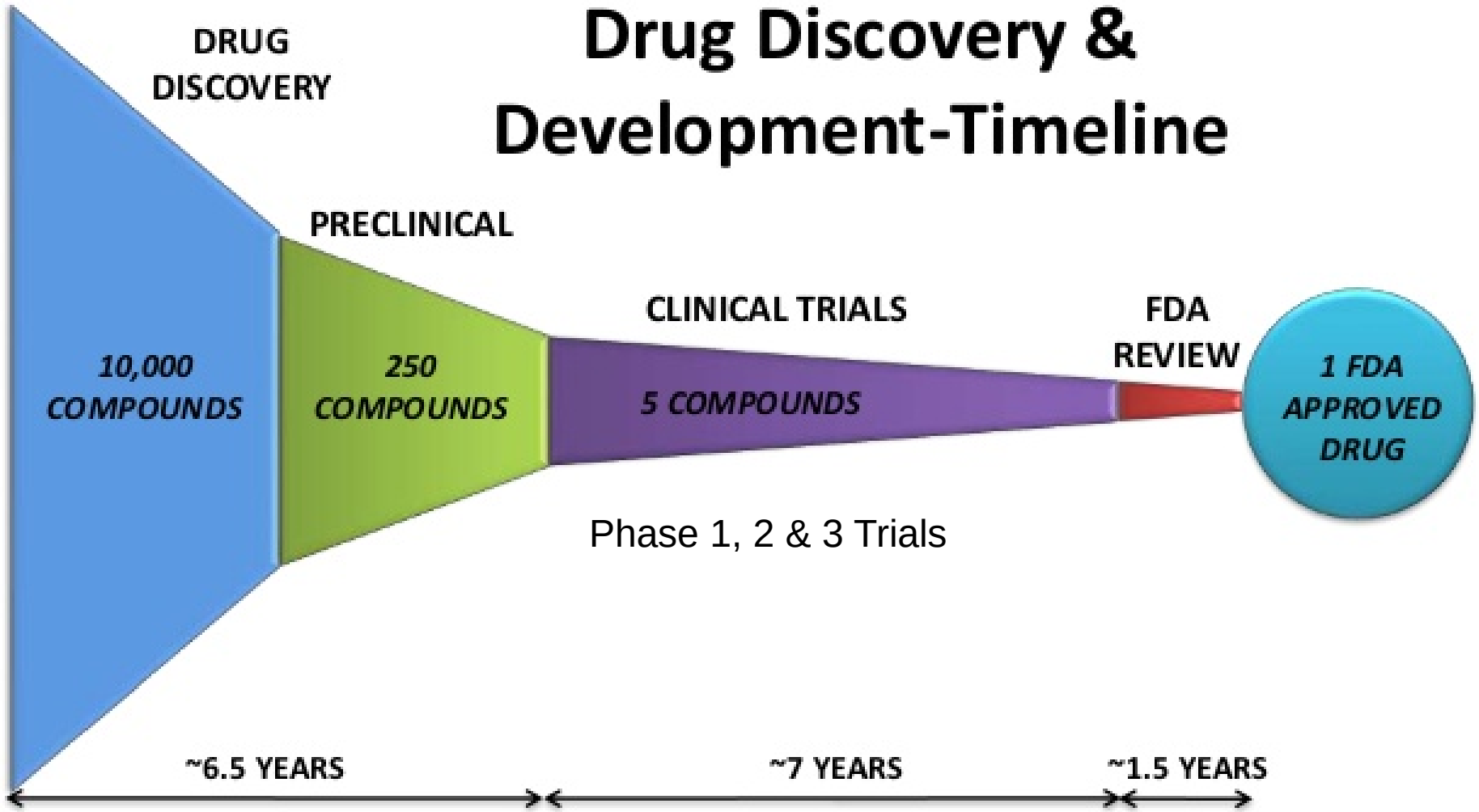
Unmet Need Rather Than Prevalence Guides Strategy

The **Novartis Mission** and Vision. Our **mission** is to discover new ways to improve and extend people`s lives. Our vision is to be a trusted leader in changing the practice of medicine.

Drug discovery and development timelines are lengthy



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Assessment of Safety and Efficacy are Central to RCT[1] Programs

Phase 1

- First-in-human
- Evaluate safety and pharmacological effects
- 20 - 80 healthy volunteers
- establish safe dosage range; and mechanism of action
- Duration - 6 mos to 1 yr
- Only 70% of submitted INDs reach Phase 1 Clinical trials

Phase 2

- Evaluate additional safety, tolerability and efficacy
- 50 - 300 patient volunteers with the disease / symptoms
- Provide data for the design of the Phase 3 clinical trials
- End-of-Phase 2 FDA meeting – to discuss Phase III plans
- Duration: about 2 years
- 33% of new drugs complete Phase II CT

Phase 3

- Assess effectiveness and safety and the appropriate dose/dosage range for the drug – for the specific indication
- Large trials - 200-3000 patients with disease/symptoms
- Two positive well controlled clinical trials
- In outpatients and hospital settings
- Duration: ≥3 years
- Only 27% of new drugs complete Phase III CT

[1]RCT – Randomized Controlled Clinical Trial

Evidence Needs Continue Beyond Registration

Satisfying critical needs from multiple stakeholders

Clinical Trials are not representative of all patients with the disease
Only 3 – 5 % of eligible patients participate in oncology clinical trials[1]

Recruitment challenges for rare disease patients include:

- Poor understanding of the natural history of the condition
- Heterogeneous patient populations
- geographic dispersion regulatory uncertainties
- Small populations at limited tertiary care centers.

- Drug development & registration needs:
  - Deeper understanding of target population and unmet needs, informing RCT design
  - Selecting endpoints that matter to patients
- Payer needs:
  - Addressing critical payer questions for market access: Does it work in real-life? Is it worth the money?
- Clinician needs:
  - Understand how patients with real-life conditions and lifestyle factors respond to medications

1. Institute of Medicine (US) Forum on Drug Discovery, Development, and Translation, 2010

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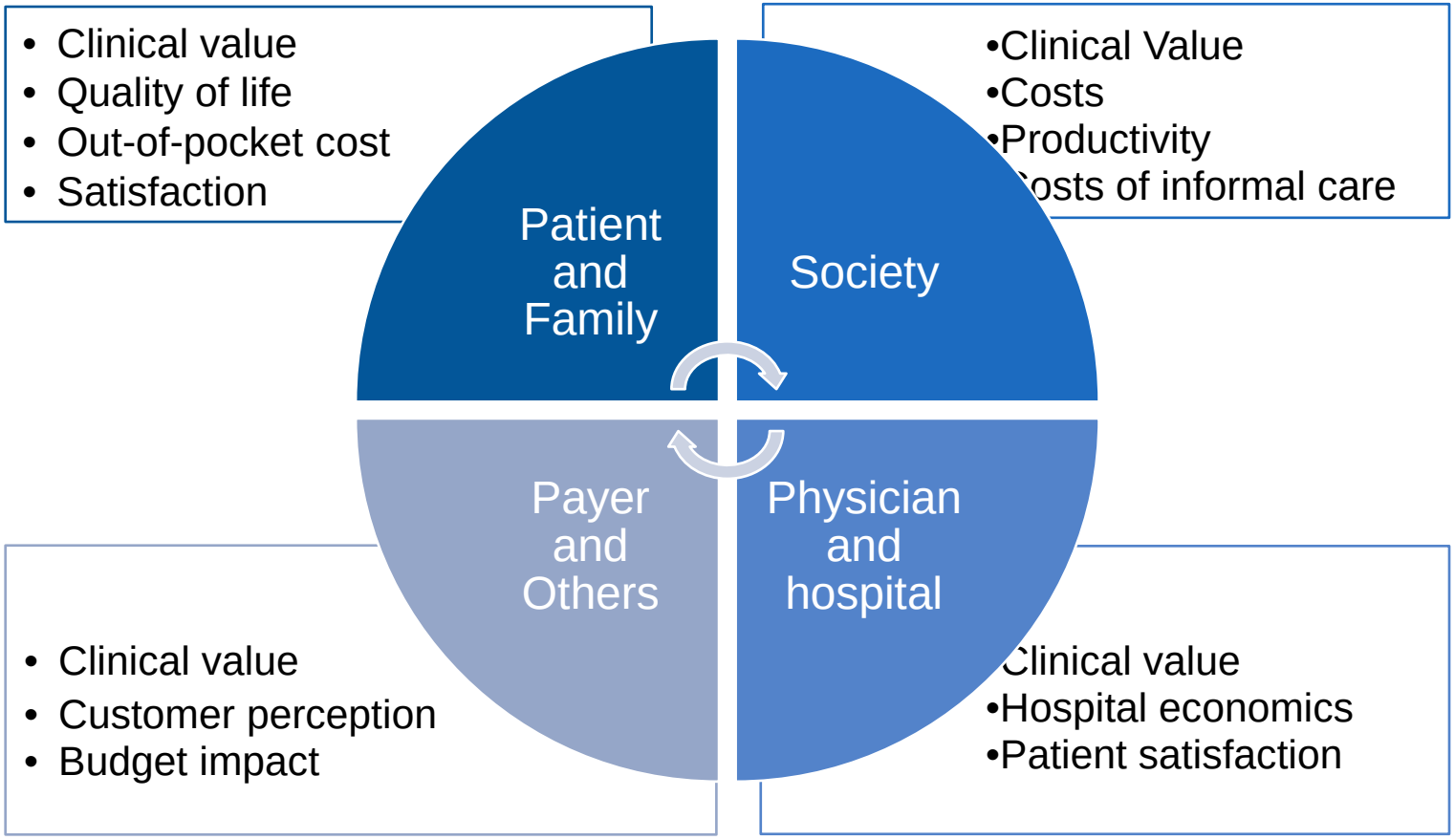
What do external stakeholders not know?

- Hurdles for regulatory approval are high
  - Time
  - Economic investment
- The number of patients treated may be low
  - Yescarte example
- Evidence demands to not end after registration
- Patient assistance programs
- Areas of discounting
  - 340B
  - Outcomes based contracting
  - Alternative payment models
    - OCM

Evaluate the Value of an Intervention Extends Beyond the Clinical Trial



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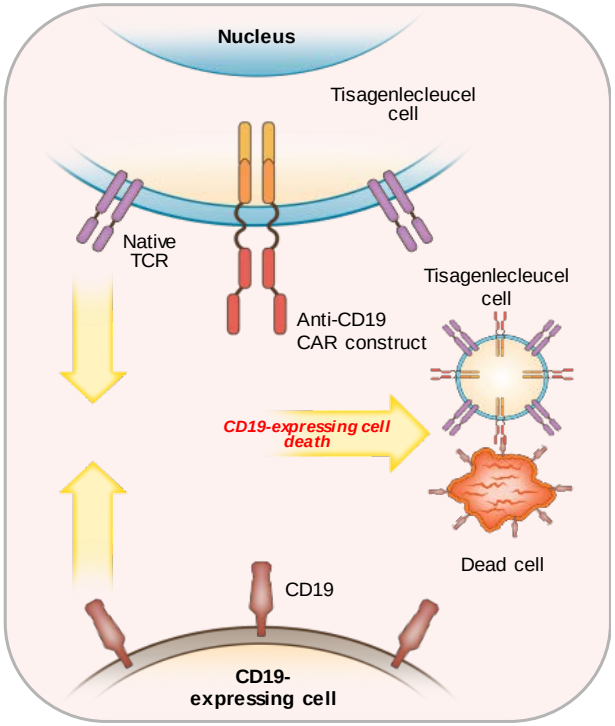
Example: Kymriah™ as a Promising New Treatment Option for Relapsed/ Refractory B-Cell ALL

- Kymriah™ (tisagenlecleucel), a chimeric antigen receptor T-cell (CAR-T) therapy, was approved by FDA for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse[1]

For the total US population (per the 2016 US Census), the number of pediatric and young adult patients with ALL likely to access tisagenlecleucel is 142 based on market uptake of 33%, with a range of market uptake between 26%-40% the corresponding eligible population for tisagenlecleucel is 111-171, all consistent with expectations for a rare disease.[2]



[1] Kymriah Product Insert
[2] Estimates are based on published literature and Novartis market forecast data

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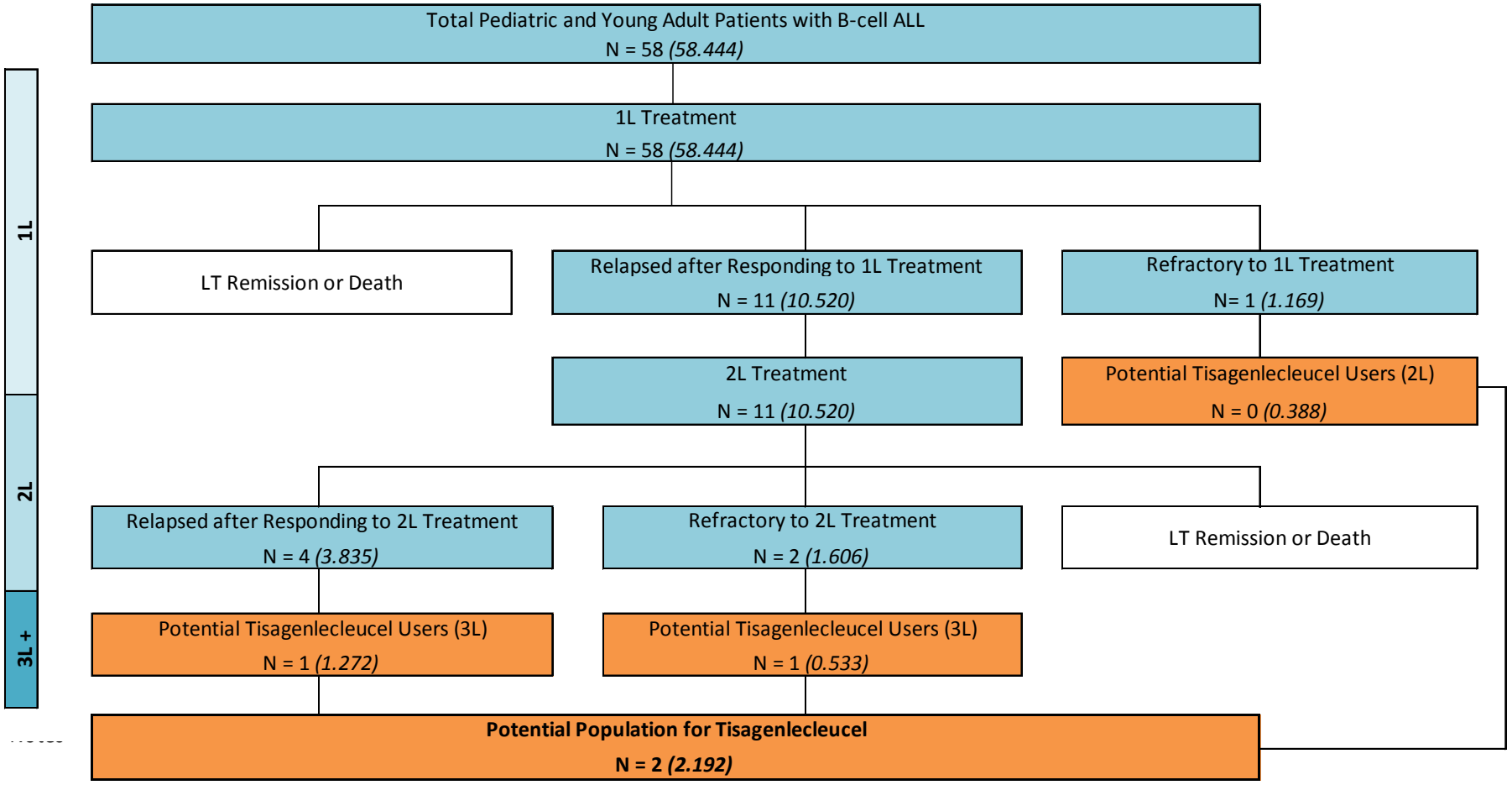
The Relevant Population is Small

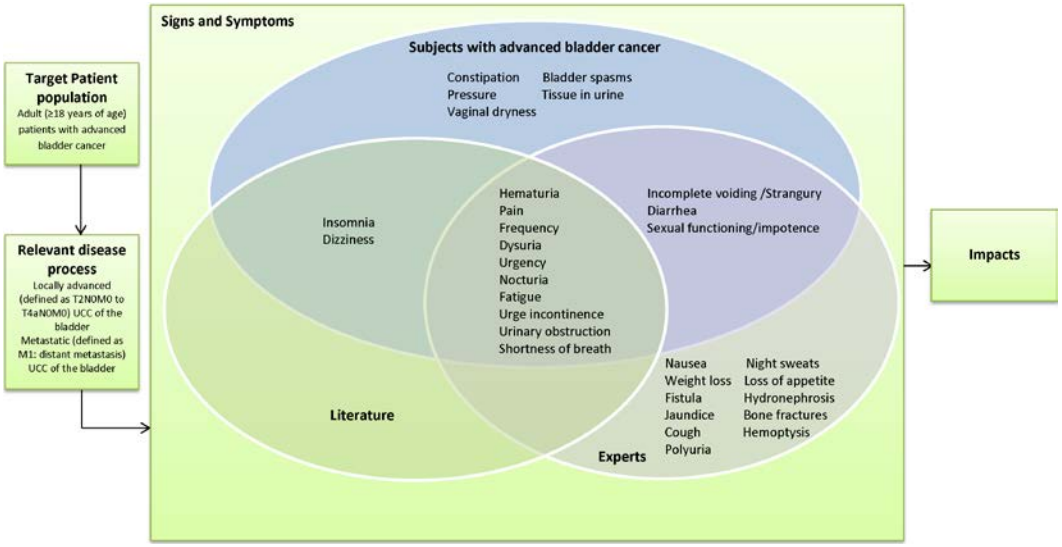


Note: Totals may not add up due to rounding (unrounded values shown in parentheses and italicized).
1L, first-line; 2L, second-line; 3L, third-line; ALL, acute lymphoblastic leukemia; LT, long-term.

Opportunities to Enhance Evidence for Regulatory Decision Making

- FDA increasing focus on RWE
  - 21st Century Cures
  - FDA - Friends of Cancer Research workshop
- RWE has potential to inform patient safety, continuum of care, treatment efficacy and management of care
- Areas of RWE analyses include
  - Pragmatic Trials
  - Natural History of Disease
  - Treatment Patterns and Monitoring
  - Sequencing of Treatment Options
  - Treatment Free Remission

A Potential Solution – Example #1 Patient Narratives For Efficient Enrollment



- A narrative analysis was used to illuminate patient-centered processes that may mediate relationships between disease and treatment related symptoms and their more distal impact
- Identified important distal impacts which have the potential to inform shared decision making.
  - Clinical Trial design and recruitment
  - Evidence development beyond approval
  - Outcomes based contracting

Shields *et al*. Exploring the Experience of Advanced Bladder Cancer from Three Perspectives: Literature, Clinical Experts, and Patients. *Under review*

Treatment Sequencing: Example - Metastatic Melanoma

Background

- Melanoma now has multiple treatment options from IOs to targeted therapies
  - One drug approved over 25 year period vs. now 10 new approved regimens either in monotherapy or in combination as part of treatment continuum
- Recent availability of multiple therapeutic options in metastatic melanoma necessitates collection of RWE across the treatment continuum including:
  - patient characteristics
  - reasons for change in therapy
  - effectiveness and adverse effects (specifically those related to dosing changes/discontinuation)

Approach

- Retrospective, observational study using electronic medical records (EMR)

Study Findings

- In disease areas with limited understanding on physician decision making, toxicities and disease progression remain the major reasons for treatment discontinuation[1-3]
- Lack of data on optimal sequencing in mutated sub-population remains an important unanswered question

Lessons Learnt

- Clinician interview necessary to inform and validate reasons for treatment discontinuation

Application

- Provide supportive evidence for a submission and/or to inform label
- Inform next steps in drug development

Treatment-Free Remission (TFR) Example: Chronic Myeloid Leukemia

Background

- Conducted two clinical studies to evaluate TFR for CML patients treated with nilotinib
- Hematologists/oncologists treating CML-CP patients recommending discontinuation of TKIs for certain patients
- NCCN CML guidelines recently updated to provide guidance for physicians considering TKI discontinuation in routine clinical practice

Approach

- Study: Web based survey of 300 US oncologists/hematologists

Study Finding

- Significant variability in testing, minimum response needed, follow up time, frequency of monitoring post discontinuation

Lesson Learned

- Metrics for TKI discontinuation used in the Novartis trials differ from NCCN guidelines and real world practices

Application

- RWE survey results demonstrate need for providing further direction for physicians on identifying appropriate patients for TKI discontinuation, monitoring, and to inform timing for re-initiation of therapy
- Adapt clinical studies section of the label to clearly define depth and duration of response and monitoring requirements before attempting TFR

Summary: Utilization of RWE to Enhance Patient Outcomes

- Additional indications for rare diseases where clinical trials may not be feasible
  - Post-marking commitments
- Populations with enhanced benefit/risk for an already approved therapy to inform clinical practice
- Strengthen how we demonstrate value to the healthcare ecosystem
- Utilize RWE to enhance our understanding of patient journeys
  - Understanding treatment patterns
- Applications to augment clinical trials
  - Feasibility
  - Matching

What do we still need to know to proceed?

- What are some of the attributes of either the disease or drug candidate that support an ideal RWE study to inform regulatory decision making?
- Are current claims and EHR sources sufficient for rare diseases?
- Are current methodologies sufficient?
  - What are key gaps that should be addressed?

Thank you

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