



## PHUSE US Connect 2023

*Submission Experience with  
Real-Time Oncology Review,  
Project Orbis, and Priority Review*



**Anna Liu**  
**Sai Ma**





# Background

## FDA Existing Expedited Programs

- ❖ Breakthrough Therapy: designed to expedite the development and review of drugs which may demonstrate substantial improvement over available therapy.
- ❖ Accelerated Approval: allowed drugs for serious conditions that filled an unmet medical need to be approved based on a surrogate endpoint. Additional results from controlled trials with hard clinical endpoints are required to confirm clinical benefit.
- ❖ Fast Track: a process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need. Rolling submission of completed sections of the New Drug Applications (NDA), original Biologics License Applications (BLA), and supplemental applications.
- ❖ Priority Review: FDA's goal is to take action on an application within 6 months, compared to 10 months under standard review.



# Background

Program and Project initiated by the Oncology Center of Excellence (OCE)

- ❖ Real-Time Oncology Review [1]: earlier submission of topline efficacy and safety results, prior to the submission of the complete application, to support an earlier start to the FDA's evaluation of the application
- ❖ Project Orbis [2]: a framework for concurrent submission and review of oncology products among international health authorities
- ❖ Bayer sNDA of Darolutamide (ARASENS study) submission in 2021-2022 under
  - Real-Time Oncology Review (RTOR)
  - Project Orbis
  - Priority Review



# Outline

- ❖ Background
- ❖ Real-Time Oncology Review (RTOR)
  - Purpose and Benefit
  - Scope
  - Timeline
- ❖ Project Orbis
  - Purpose and Benefit
  - Application and Pre-submission Process
  - Operation Mode
- ❖ Bayer RTOR, Project Orbis, and Priority Review Experience
- ❖ Recommendations and lessons learned
- ❖ Conclusion
- ❖ Q & A



# Real-Time Oncology Review (RTOR)

## Purpose and benefit

- ❖ Initiated by OCE in Feb. 2018
- ❖ Aims to explore a more efficient review process.
- ❖ Early iterative engagement with the applicant –
  - Allows the FDA to review **much** of the *key* data earlier, for sufficiency and integrity, before the applicant formally submits the complete application.
  - Early opportunity to address data quality and potential review issues.
  - Early feedback from FDA to applicant.
- ❖ NOT the same as rolling review – only fully completed modules can be submitted and not individual components of a module.
- ❖ *Possible early approval – a win-win situation across the board for industry, FDA, HC providers and patients.*



# Real-Time Oncology Review (RTOR)

## Scope

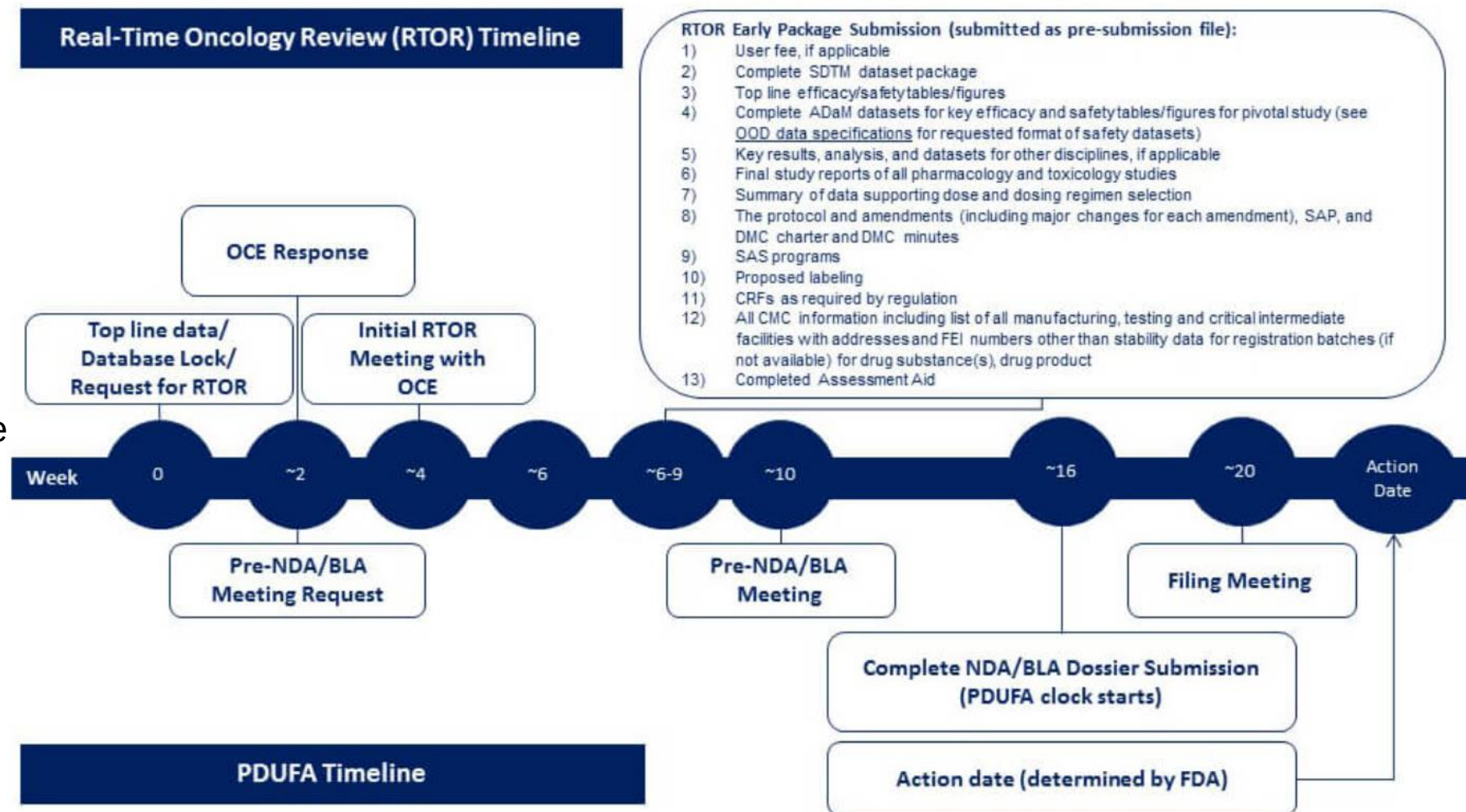
- ❖ Voluntary participation
- ❖ New Drug Applications (NDA), original Biologics License Applications (BLA), and supplemental applications for oncology indication
- ❖ Consideration criteria –
  - Drugs likely to demonstrate substantial improvements over available therapy or meeting criteria for Expedited Programs (*e.g. fast track, priority review*)
  - Straightforward study designs
  - Endpoints that can be easily interpreted
- ❖ Possible for Therapeutic Areas other than Oncology?
  - Started with two pilot programs for supplemental applications, later expanded to original NDA and BLA for new molecular entities (NME)
  - Experience and core principles of RTOR has been shared with non-oncology review divisions from CDER and CBER for potential adaption to other applications [4]



# Real-Time Oncology Review (RTOR)

## General RTOR Timeline [1]

- ❖ **Week 0**, any of –
  - **Topline data readout.**
  - DB release/lock.
  - Request for RTOR.
- ❖ Week ~6-9: early package.
- ❖ Week ~16: complete package review clock starts.



\* The diagram reflects a general timeline suggestion. Companies should discuss with FDA their submission proposal.



# Real-Time Oncology Review (RTOR)

## Key deliverables

- ❖ Early package (week 6 ~ 9)
  - User fee, if applicable.
  - Complete SDTM dataset package.
  - Top line efficacy/safety tables/figures.
  - Complete ADaM datasets for key efficacy and safety tables/figures for pivotal.
  - Key results, analysis, and datasets for other disciplines (*e.g. clinical pharmacology*), if applicable.
  - Final study reports of all pharmacology and toxicology studies.
  - Summary of data supporting dose and dosing regimen selection.
  - The protocol and amendments (a list of major changes for each amendment), SAP, and DMC charter and DMC minutes.
  - SAS programs
  - Proposed labeling.
  - CRFs as required by regulation.
  - All CMC information including list of all manufacturing, testing and critical intermediate facilities with addresses and FEI numbers other than stability data for registration batches (if not available) for drug substance(s), drug product.
  - Completed AAid – Assessment Aid (AAid) document is “preferred” by FDA for RTOR.
- ❖ Full package (week 16) – complete marketing application includes any remaining components previously not submitted in the pre-submission/early package.



# Project Orbis

## Purpose, Benefit, and Scope

- ❖ Initiated by OCE in May 2019
- ❖ Give patients faster access to promising cancer treatments across the globe
- ❖ New Drug Applications (NDA), Biologics License Applications (BLA), and supplemental applications for oncology indication
- ❖ Provide a framework for concurrent submission and review of oncology products among international health authorities, Project Orbis Partners (POPs):
  - Australian Therapeutics Goods Administration (TGA)
  - Brazil's National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária [ANVISA])
  - Health Canada (HC)
  - Israel Ministry of Health (IMOH) Pharmaceutical Administration
  - Singapore Health Sciences Authority (HSA)
  - Switzerland Swissmedic
  - United Kingdom Medicines and Healthcare Products Regulatory Agency (UK MHRA)



# Project Orbis

## Application and Pre-submission Process

**Applicant sends the query for Project Orbis to the respective Office of Oncologic Diseases review divisions. The query should include topline efficacy and safety results and a global submission plan (GSP).**



**FDA review team consider the eligibility based on following criteria: high impact, clinically significant applications, general qualification for priority review because of improvement in safety/efficacy.**



**FDA review team notifies the OCE global team about the proposed Project Orbis application. The OCE global team will then reach out to the Project Orbis Partners (POPs) to confirm the participation of collaborative review.**



**The FDA team notify the applicant regarding the acceptance into Project Orbis and indicate which POPs will be involved.**



**The applicant sends the Sponsor Authorization Letter (SAL) for POPs involved in review, and work with each country to confirm the regulatory requirements for each agency, and to negotiate pre-submission and submission timelines.**



# Project Orbis

## Operation Mode

### ❖ Collaboration

- POPs have regularly scheduled conference calls to collaborate and discuss evaluation of the application.
- POPs share the information requests (IRs) for comment and review prior to sending to the sponsor company/local affiliate.
- The sponsor teams should send the IR response(s) to all HAs that have received the application.
- The FDA shares review analyses with the other Health Authorities

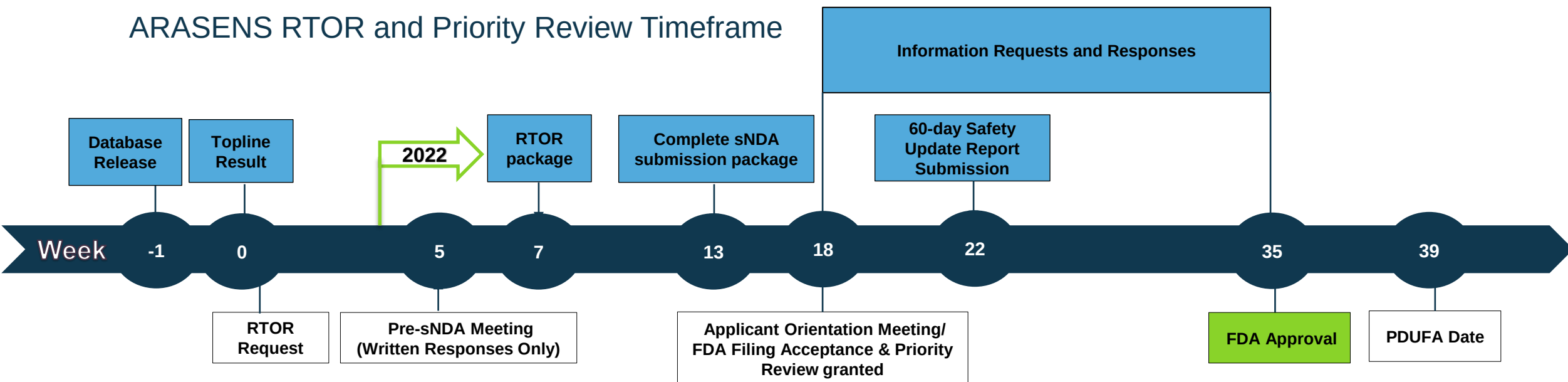
### ❖ Independence

- each agency conducts their own review and retains independence of their final regulatory decision, labeling negotiations, and timelines



# Bayer RTOR, Project Orbis, and Priority Review Experience

## ARASENS RTOR and Priority Review Timeframe



- RTOR package (Week 7)
  - FDA Assessment AID
  - Draft US-PI (Proposed Label)
  - **Topline Efficacy/Safety Tables and Figures**
  - **SDTM and ADaM datasets package**
  - **Analysis Result Metadata (ARM)**
  - **SAS programs for selected key tables, and all ADaM datasets**
  - Protocol and amendments, SAP-Amended,
  - DMC Charter and DMC minutes
  - FDFs
  - 3 Clinical Pharmacology Reports
  - **BIMO package**
  - ARASENS CRFs

- sNDA submission complete package – remaining components previously not submitted in RTOR early package (Week 13), Statistical programming related elements
  - Complete CSR (in-text tables)
  - Complete section 14 and section 16 TLFs
  - Complete post-hoc TLFs for CSR
  - COVIDMOD dataset

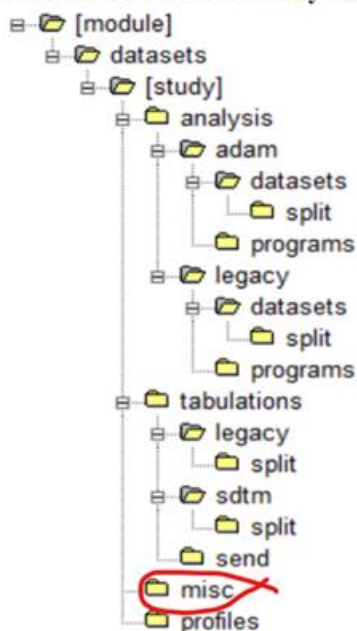


# Bayer RTOR, Project Orbis, and Priority Review Experience

## COVID-19 Pandemic Related Contents

- ❖ Pandemic specific tables
- ❖ Patients who had their data collection affected by the COVID-19 pandemic should be flagged in the datasets
- ❖ COVIDMOD dataset: Document the date that remote assessments were permitted at the patient and site level.

Figure 1: Folder Structure for Study Datasets



| Variable Name | Variable Label                              | Type | Length | Format<br>Codelist/<br>Controlled<br>Terms | Source / Computational Method                                                                                                                                                                                                          |
|---------------|---------------------------------------------|------|--------|--------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PatientID     | Unique Subject Identifier                   | C    | 20.    |                                            | USUBJID                                                                                                                                                                                                                                |
| Site          | Study site identifier                       | C    | 10.    |                                            | SITEID in ADSL domain                                                                                                                                                                                                                  |
| ModType       | Standardize categories of ModType - derived | C    | 29.    |                                            | Modtype=' Telemedicine visits' if SVCONTYP = "Phone contact" or "Video contact" in ADSV domain<br>Modtype=' Remote labs' if LBEPRELI = 'Y' in ADLB domain<br>Modtype=' Other - Remote Questionnaires' if QSEPRELI = 'Y' in ADQS domain |
| DateModStart  | Start date                                  | N    | 8.     | Date9.                                     | SVSTDT if SVCONTYP = "Phone contact" or "Video contact" in ADSV domain.<br>QSDT if QSEPRELI = 'Y' in ADQS domain<br>LBST if LBEPRELI = 'Y' in ADLB domain                                                                              |
| DateModStop   | End date                                    | N    | 8.     | Date9.                                     | SVENDT if SVCONTYP = "Phone contact" or "Video contact" in ADSV domain<br>QSDT if QSEPRELI = 'Y' in ADQS domain<br>LBST if LBEPRELI = 'Y' in ADLB domain                                                                               |



# Bayer RTOR, Project Orbis, and Priority Review Experience

Timeline comparison with summarized RTOR experiences

Submission and review timelines of 20 oncology applications under RTOR from February 2019 to April 2020 were summarized in [4]

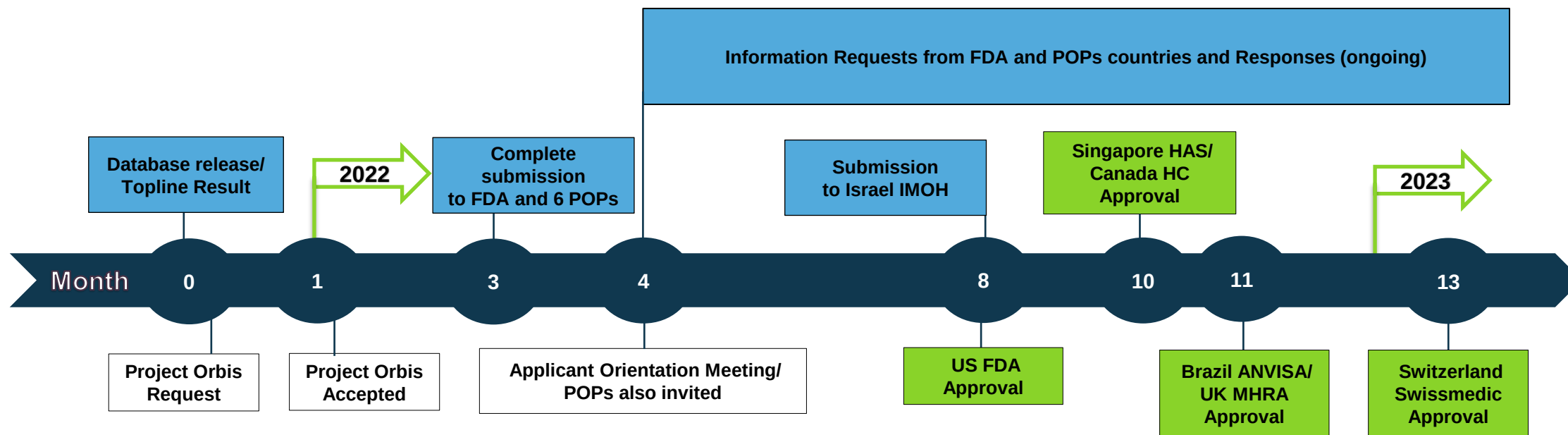
[4] *de Claro RA, Gao JJ, Kim T, Kluetz PG, Theoret MR, Beaver JA, Pazdur R*. U.S. Food and Drug Administration: Initial Experience with the Real-Time Oncology Review Program. Clin Cancer Res. 2021 Jan 1;27(1):11-14. doi: 10.1158/1078-0432.CCR-20-2220. Epub 2020 Aug 19. PMID: 32816899.

<https://aacrjournals.org/clincancerres/article/27/1/11/83387/U-S-Food-and-Drug-Administration-Initial>

| Timeframe            |                    | ARASENS submission experience | RTOR experience summarized in [4] |            |             |
|----------------------|--------------------|-------------------------------|-----------------------------------|------------|-------------|
| From                 | To                 |                               | Median                            | Min        | Max         |
| RTOR package         | Full application   | 6.3 weeks                     | 5.7 weeks                         | 1.7 weeks  | 16.2 weeks  |
| Full application     | Approval           | 5.1 months                    | 3.3 months                        | 0.4 months | 5.9 months  |
| Clinical data cutoff | RTOR early package | 2.8 months                    | 4.2 months                        | 2.1 months | 14.6 months |
| Clinical data cutoff | Full application   | 4.3 months                    | 6.1 months                        | 2.7 months | 15.7 months |



# ARASENS Global Submission under Project Orbis Timeframe





# Recommendations and Lessons Learned

- ❖ Frontloading Programming Activities
- ❖ Accelerated Submission Documents Completion
  - Cross-functional collaboration and alignment
    - Early team review of draft TLFs on blinded data
    - A stable draft of CSR before database release
  - Good company standardization
  - The extensive internal macro library can support generating tables, complex figures and submission data documents (e.g., define.xml).
- ❖ Resource Planning for Expedite Global Submissions
  - Simultaneous IRs from POPs with overlapping timelines under Project Orbis
  - Global team support
  - Cross functional alignment and coordination
  - Support and early involvement of local team for submissions in countries/regions with specific requirements



# Conclusion

- ❖ RTOR allows early submission of the efficacy and safety topline results and datasets to the agency prior to complete submission
- ❖ RTOR can also be combined with other review programs including the Project Orbis, Priority Review, and BTDL
  - Possible for the accelerated submission and review
  - Contribute to the chance of early access of the approved drugs globally
- ❖ With RTOR and Project Orbis as part of submission planning
  - Alignment of the cross functional team on the analyses is very necessary to avoid late-stage changes and consequent impact on the statistics and programming
  - An approved draft CSR would be recommended. Statistical programming activities need to be planned and started early with country specific submission requirements taken into consideration
  - Resources need to be planned carefully for the busy requests and responses between different HAs with overlapping timelines.



# *Thank you!*



Questions?





# Reference

- [1] U.S. Food and Drug Administration. Real-Time Oncology Review Pilot Program. From: <https://www.fda.gov/about-fda/oncology-centerexcellence/real-time-oncology-review-pilot-program>
- [2] U.S. Food and Drug Administration. Project Orbis. From <https://www.fda.gov/about-fda/oncology-center-excellence/project-orbis>
- [3] Real-Time Oncology Review and the Assessment Aid: Increasing Review Efficiency through Standardization and Earlier Data Access  
<https://www.focr.org/sites/default/files/pdf/ROTR%20White%20Paper%201.pdf>
- [4] *de Claro RA, Gao JJ, Kim T, Kluetz PG, Theoret MR, Beaver JA, Pazdur R.* U.S. Food and Drug Administration: Initial Experience with the Real-Time Oncology Review Program. Clin Cancer Res. 2021 Jan 1;27(1):11-14. doi: 10.1158/1078-0432.CCR-20-2220. Epub 2020 Aug 19. PMID: 32816899.  
<https://aacrjournals.org/clincancerres/article/27/1/11/83387/U-S-Food-and-Drug-Administration-Initial>
- [5] U.S. Food and Drug Administration. Project Orbis Approvals  
<https://www.fda.gov/media/157082/download> extracted on 17JAN2023.
- [6] *Durve K, Varghese A.* Real Time Oncology Review – Applicant Experience. Phuse US-Connect 2020 SA01 <https://www.lexjansen.com/phuse-us/2020/sa/SA01.pdf>