Real Time Oncology Review Janssen Experience

Ketan Durve
Integrated Data Analytics and Reporting
Janssen R&D

janssen
PHARMACEUTICAL COMPANIES
OF Johnson&Johnson

Disclaimer

Presentations are intended for informational purposes only and do not replace independent professional judgment.

Statements of fact and opinions expressed are those of the presenters individually and are not the opinion or position of Janssen Pharmaceuticals or its affiliates.

Accelerated Approval, Priority Review, Fast Track, Breakthrough Therapy[1]

- Accelerated approval
  - Conditional approval granted using surrogate endpoints or intermediate clinical endpoints additional results from controlled trials with hard clinical endpoints required to confirm clinical benefit
- Priority review
  - Action on an application within 6 months; compared to 10 months under standard review
- Fast track
  - Rolling submission of completed sections of the (s)NDA / (s)BLA. Eligible for priority review if criteria are met
- Break through Therapy
  - Abbreviated development plan eg: Accelerated approval standard
  - Frequent agency interactions and guidance on development program
  - Eligible for fast track and thereby priority review if criteria are met

[1] https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review retrieved Sep 10 2019

Real Time Oncology Review (RTOR)[2]

- A Pilot Program
- Initiative by the Oncology Center of Excellence
  - OCE works with CDER/CBER/OHOP/CDRH
- Purpose of the Pilot
  - Ensure Safe, Effective Treatments Available to Patients as Early as Possible
  - Improve Review Efficiency
  - Maintain/Improve Review Quality
  - Balance Reviewer's Workload
  - Early Iterative engagement with applicant

[2] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program retrieved Sep 10 2019

Real Time Oncology Review (RTOR)

In scope

- **Supplemental New Drug Application** (sNDA) and **supplemental Biologic License Application** (sBLA) submissions
- Drugs likely to demonstrate **substantial improvements over available therapy**, which may include drugs previously granted Breakthrough Therapy Designation for the same or other indications
- Drugs meeting other criteria for other expedited programs (e.g. fast track, priority review) may also be considered
- **Straight forward study designs**, as determined by the review division and the OCE
- **Endpoints that can be easily interpreted** (for example, overall survival in a randomized trial)

Out of Scope

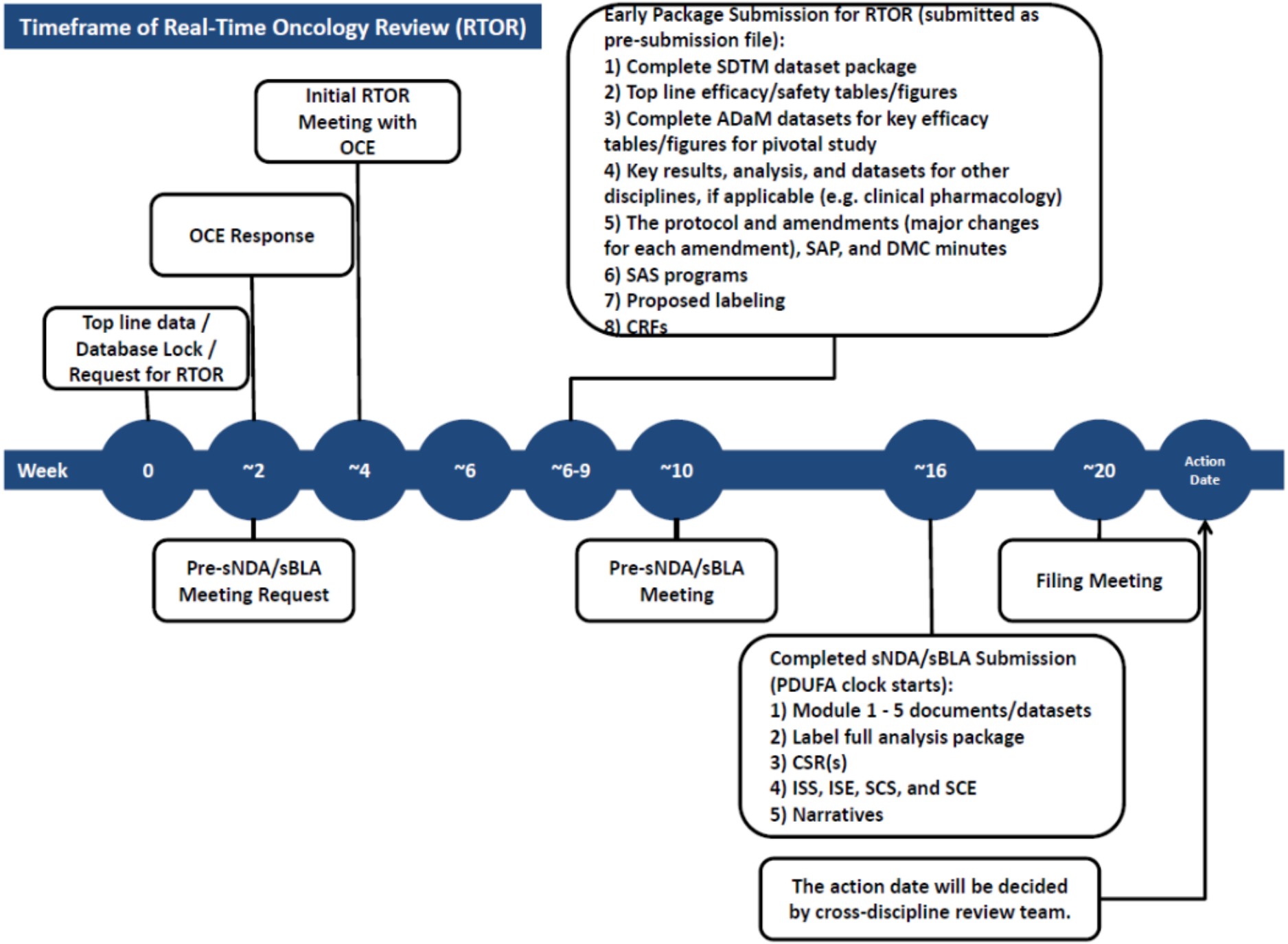
- Supplements with CMC formulation changes and supplements with pharmacology/toxicology data will be excluded
- Submissions with greater complexity, including those with companion diagnostics
- Studies conducted exclusively outside the United States and adjuvant, neoadjuvant, and prevention studies will be excluded

Real Time Oncology Review (RTOR)

At the time of top-line results of a pivotal trial an applicant can apply for the RTOR pilot by notifying the appropriate division Regulatory Manager.

The clinical division director/deputy director, the review team (including reviewers, team leaders and management from all relevant review disciplines) and OCE Management will jointly decide whether the application can be selected for the RTOR pilot program.

Acceptance into the RTOR pilot does not guarantee or influence approvability of the supplement, which is subject to the usual benefit-risk evaluation by FDA scientists.


Timeframe of Real-Time Oncology Review (RTOR)
Initial RTOR Meeting with OCE
OCE Response
Top line data / Database Lock / Request for RTOR
Early Package Submission for RTOR (submitted as pre-submission file):
1) Complete SDTM dataset package
2) Top line efficacy/safety tables/figures
3) Complete ADaM datasets for key efficacy tables/figures for pivotal study
4) Key results, analysis, and datasets for other disciplines, if applicable (e.g. clinical pharmacology)
5) The protocol and amendments (major changes for each amendment), SAP, and DMC minutes
6) SAS programs
7) Proposed labeling
8) CRFs
Week
0
~2
~4
~6
~6-9
~10
~16
~20
Action Date
Pre-sNDA/sBLA Meeting Request
Pre-sNDA/sBLA Meeting
Filing Meeting
Completed sNDA/sBLA Submission (PDUFA clock starts):
1) Module 1 - 5 documents/datasets
2) Label full analysis package
3) CSR(s)
4) ISS, ISE, SCS, and SCE
5) Narratives
The action date will be decided by cross-discipline review team.

RTOR Pilot - Participating Sponsor Experiences and Key Takeaways[3]

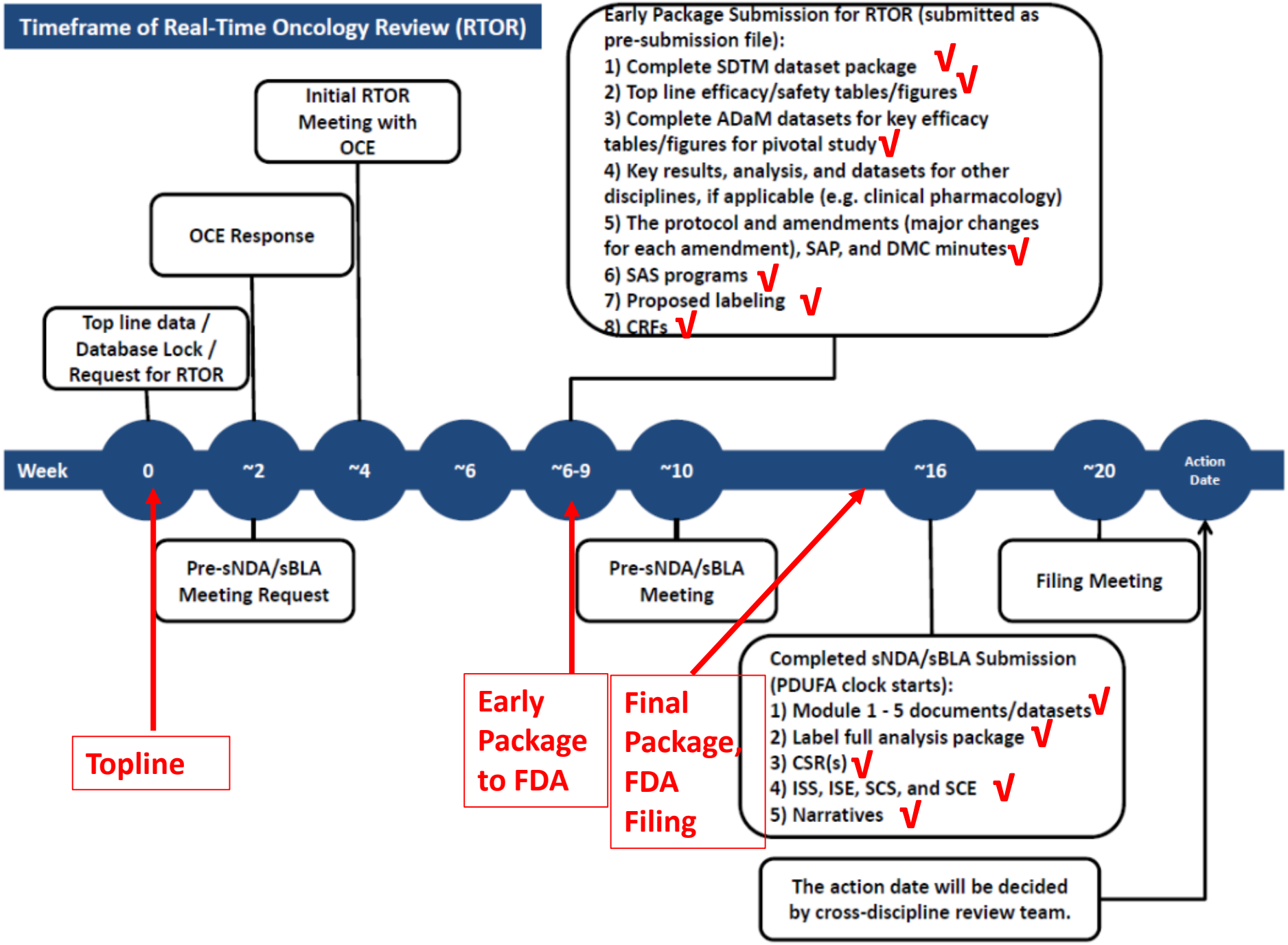
- Early engagement and clear communication with FDA on what type of information is needed and when is key
- Earlier submission of the following may help facilitate FDA review
  - General information/comments related to data derivation (i.e. grouped terms provided in draft USPI)
  - Documentation to accompany datasets
  - Data definition files
- Information Requests (IRs) should be expected after submission of the “Pre-Submission Package”
  - Quick response/submission is expected
  - Team may be simultaneously working on deliverables for the “Full Dossier Submission” and IRs

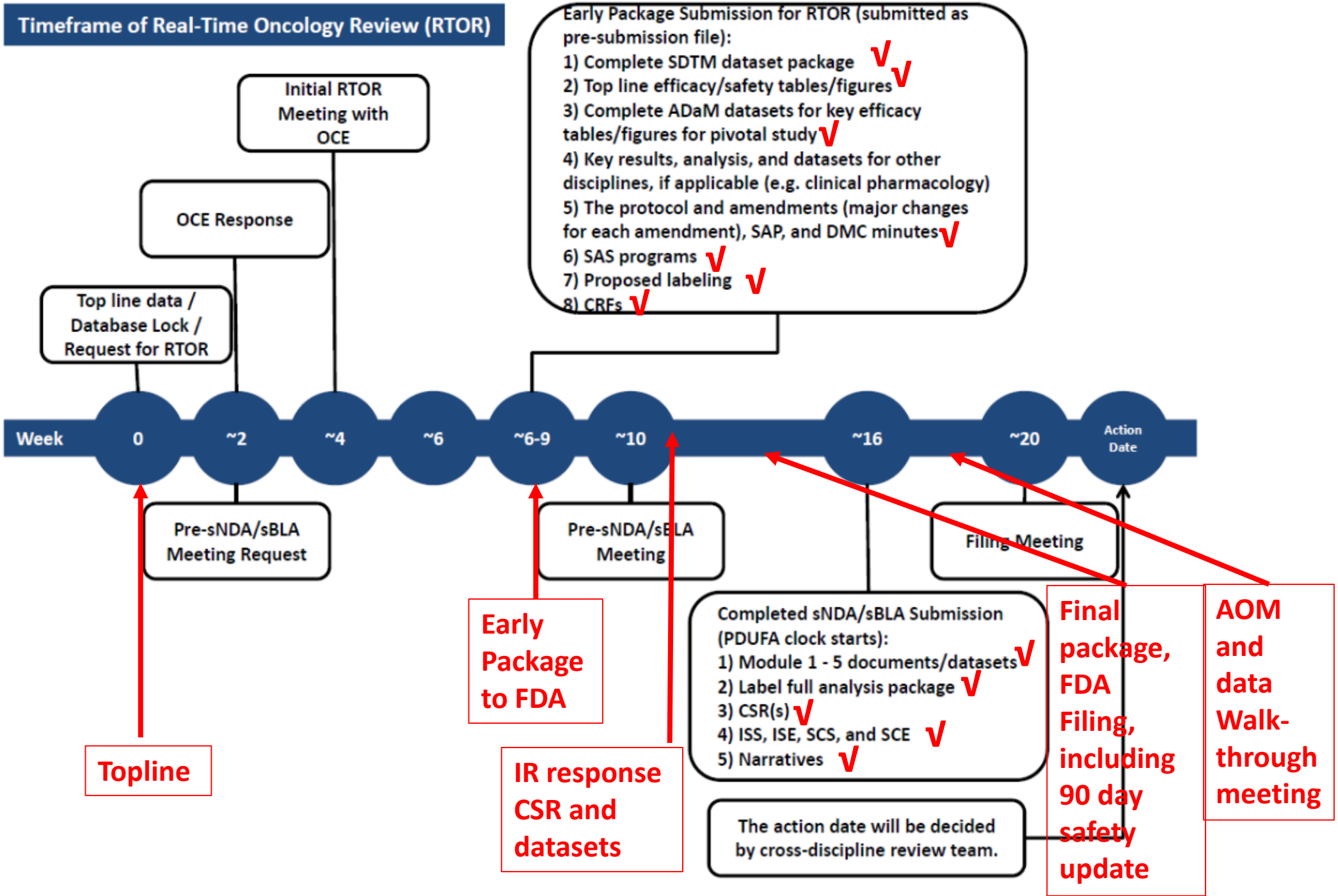
[3]Friends of Cancer Research. (2018). Real-Time Oncology Review and the Assessment Aid: Increase Review Efficiency Through Standardization and Earlier Data Access [White paper] Retrieved Nov 20, 2018, from Friends of Cancer Research: https://www.focr.org/sites/default/files/pdf/ROTR%20White%20Paper%201.pdf

RTOR Pilot - Potential Future Expansion[3]

- Pilot could ultimately be converted to permanent program, however there is no set timeline
- Expansion of the pilot would be in a stepwise approach
- Current pilot only includes straightforward supplemental applications
  - Expansion would first move to more complex supplemental applications, then simple new molecular entities (NMEs)

[3]Friends of Cancer Research. (2018). Real-Time Oncology Review and the Assessment Aid: Increase Review Efficiency Through Standardization and Earlier Data Access [White paper] Retrieved Nov 20, 2018, from Friends of Cancer Research: https://www.focr.org/sites/default/files/pdf/ROTR%20White%20Paper%201.pdf


Timeframe of Real-Time Oncology Review (RTOR)
Initial RTOR Meeting with OCE
OCE Response
Top line data / Database Lock / Request for RTOR
Early Package Submission for RTOR (submitted as pre-submission file):
1) Complete SDTM dataset package √
2) Top line efficacy/safety tables/figures √
3) Complete ADaM datasets for key efficacy tables/figures for pivotal study √
4) Key results, analysis, and datasets for other disciplines, if applicable (e.g. clinical pharmacology)
5) The protocol and amendments (major changes for each amendment), SAP, and DMC minutes √
6) SAS programs √
7) Proposed labeling √
8) CRFs √
Week
0
~2
~4
~6
~6-9
~10
~16
~20
Action Date
Pre-sNDA/sBLA Meeting Request
Pre-sNDA/sBLA Meeting
Filing Meeting
Topline
Early Package to FDA
Final Package, FDA Filing
Completed sNDA/sBLA Submission (PDUFA clock starts):
1) Module 1 - 5 documents/datasets √
2) Label full analysis package √
3) CSR(s) √
4) ISS, ISE, SCS, and SCE √
5) Narratives √
The action date will be decided by cross-discipline review team.


Timeframe of Real-Time Oncology Review (RTOR)
Initial RTOR Meeting with OCE
OCE Response
Top line data / Database Lock / Request for RTOR
Early Package Submission for RTOR (submitted as pre-submission file):
1) Complete SDTM dataset package √
2) Top line efficacy/safety tables/figures √
3) Complete ADaM datasets for key efficacy tables/figures for pivotal study √
4) Key results, analysis, and datasets for other disciplines, if applicable (e.g. clinical pharmacology)
5) The protocol and amendments (major changes for each amendment), SAP, and DMC minutes √
6) SAS programs √
7) Proposed labeling √
8) CRFs √
Week
0
~2
~4
~6
~6-9
~10
~16
~20
Action Date
Pre-sNDA/sBLA Meeting Request
Pre-sNDA/sBLA Meeting
Filing Meeting
Topline
Early Package to FDA
IR response CSR and datasets
Completed sNDA/sBLA Submission (PDUFA clock starts):
1) Module 1 - 5 documents/datasets √
2) Label full analysis package √
3) CSR(s) √
4) ISS, ISE, SCS, and SCE √
5) Narratives √
The action date will be decided by cross-discipline review team.
Final package, FDA Filing, including 90 day safety update
AOM and data Walk-through meeting

Lessons Learned and Recommended Best Practices

- Create **submission compliant datasets and documentation upfront** rather than after finalization of submission documents.
  - Submitted complete data package and documentation instead of just Tables, listings and graphs or Analysis data without documentation for RTOR early package.
  - Submitted key efficacy analysis datasets and complete SDTM in RTOR early package. Complete Analysis dataset package submitted at filing.

Lessons Learned and Recommended Best Practices

- **Accelerate completion of the CSR** allowing for stable approval draft to be available by the time of RTOR early package delivery. Enables finalization of the datasets to be sent as part of the RTOR early package.
  - Cross functional teams have to understand the impact of analysis updates after submission of the RTOR early package datasets.
  - Early and robust definition, programming and interpretation of adhoc analyses is required.
  - CSR was finalized shortly after RTOR early package delivery which allowed for submission of the complete analysis dataset package along with the CSR in response to Information request (IR) between early and final package submission.

Lessons Learned and Recommended Best Practices

- **Minimize re-submission** of datasets already provided in prior submission sequence as part of RTOR early package.
- **Only submit new or changed information** (datasets and documentation) in final package.
  - With datasets submitted via different sequences as part of RTOR early package, final package and IR responses, agency reviewers may have difficulty finding the correct location for these datasets in the eCTD if viewed by submission sequence.
  - As all datasets are not submitted in one package, this might lead to some confusion regarding the availability of all analysis datasets for the study.

Lessons Learned and Recommended Best Practices

- Consider establishing a **Response Team alongside the core Submission Team** to manage IR responses concurrent with submission document finalization.
- Regularly scheduled meetings with FDA to discuss RTOR package findings and questions.
  - Biweekly teleconferences (agenda driven) + Face to face Application orientation meetings and data walkthrough, provide opportunities for robust and focused discussions with review team given their familiarity with the data submitted earlier.

Lessons Learned and Recommended Best Practices

- RTOR differs from other accelerated submission approaches as topline results and datasets to support key analysis are submitted to the agency prior to corresponding study reports.
- Considerations on dataset submission need to be addressed both from a statistics and programming operational process perspective as well as regulatory submission management and publishing perspective.
- Enables early engagement with FDA where FDA reviewers were able to review the data for completeness, send IRs for clarifications and additional analysis and sponsor was able to respond to these in advance of sNDA filing.
- Provides an opportunity to address any data quality and potential review issues early on.
- Provides early feedback regarding the most effective way to analyze data to properly address key regulatory questions.
- Enables early scheduling of application orientation meeting and a more robust and focused discussion given the FDA review team has good understanding of the submission components.

Questions ?