

PharmaSUG 2020 – Paper SS-54
RTOR: Our Side of the Story
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ABSTRACT

FDA's **Real-Time Oncology Review (RTOR)** pilot program was initially introduced in June 2018 for supplemental New Drug Applications (NDA) and supplemental Biologics License Applications (BLA) and more recently extended to original NDAs and BLAs. This presents a new ray of hope for cancer patients, as the program aims to **expedite review of oncological submissions** with improved efficiency and quality by allowing FDA earlier access to clinical safety and efficacy data and results, especially those related to Biometrics. This in turn may help expedite availability of novel treatments to cancer patients.

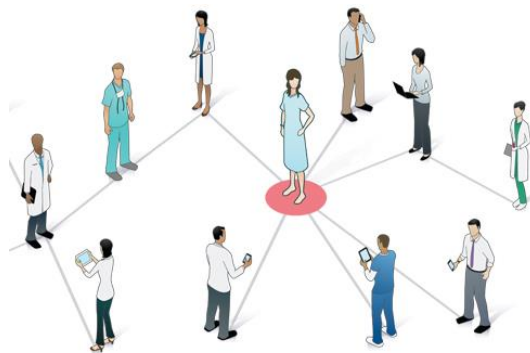
Seattle Genetics participated in the RTOR pilot program for the **supplemental BLA for ADCETRIS®** based on the **ECHELON-2 trial in the frontline treatment of patients with CD30-expressing PTCL**, which received **approval in an unprecedented 11 days** from sBLA submission. Against the backdrop of our positive RTOR experience, this paper will provide a background of the program, its eligibility criteria, and its success so far.

We will give you insights into:

- **How and why** a submission can be accepted into this program
- FDA's **RTOR expectations** and how they have evolved since our sBLA to now
- Effective **communication and collaboration** within our organization and with FDA
- Seamless **preparation and planning** to enable rapid submission and review
- **Post-submission activities** and efficient responses to information requests from FDA
- The pivotal **role of Statistical Programming and best practices** towards perpetual submission-readiness

We are excited to share **our story** as well as insights into more recent RTOR developments to help colleagues in industry be optimally prepared to **get drugs to cancer patients faster!**

INTRODUCTION



Patient centricity is about being focused on putting patients first and making our patients the “center” of the health care experience. The health care industry is constantly striving to discover and enable new and innovative solutions to provide improved healthcare technologies and benefits to our patients. This also involves expediting and empowering the decision-making process at FDA, with the help of collaborative strategies with sponsors and healthcare providers. One of the most recent efforts in that direction is the introduction of FDA's RTOR pilot program.

This paper will highlight the background of the highly reputed FDA RTOR program and share some of the best practices and techniques adapted by Seattle Genetics to support this program in order to help improve efficiencies and to provide access of novel drugs and treatments to the patients in a more expedited manner.

USEFUL RTOR PROGRAM SUBMISSION GUIDELINES

Per the [FDA Website](#), submissions to be considered for the RTOR pilot program should meet the following criteria:

- Drugs likely to demonstrate substantial improvements over available therapy, which may include drugs previously granted Breakthrough Therapy Designation (BTD) for the same or other indications.
- Straightforward study designs, as determined by the review division and the FDA Oncology Center of Excellence (OCE).
 - Studies conducted exclusively outside the United States and neoadjuvant and prevention studies will be excluded.
- Endpoints that can be easily interpreted (for example, overall survival in a randomized trial).
- Supplements with CMC formulation changes will be excluded.

Submissions with greater complexity, including those with companion diagnostics, may also be excluded for the purposes of the pilot program.

At the time of top-line results of a pivotal trial, if the eligibility criteria above are met, applicants can apply for RTOR.

More information can be found on the [FDA Website](#).

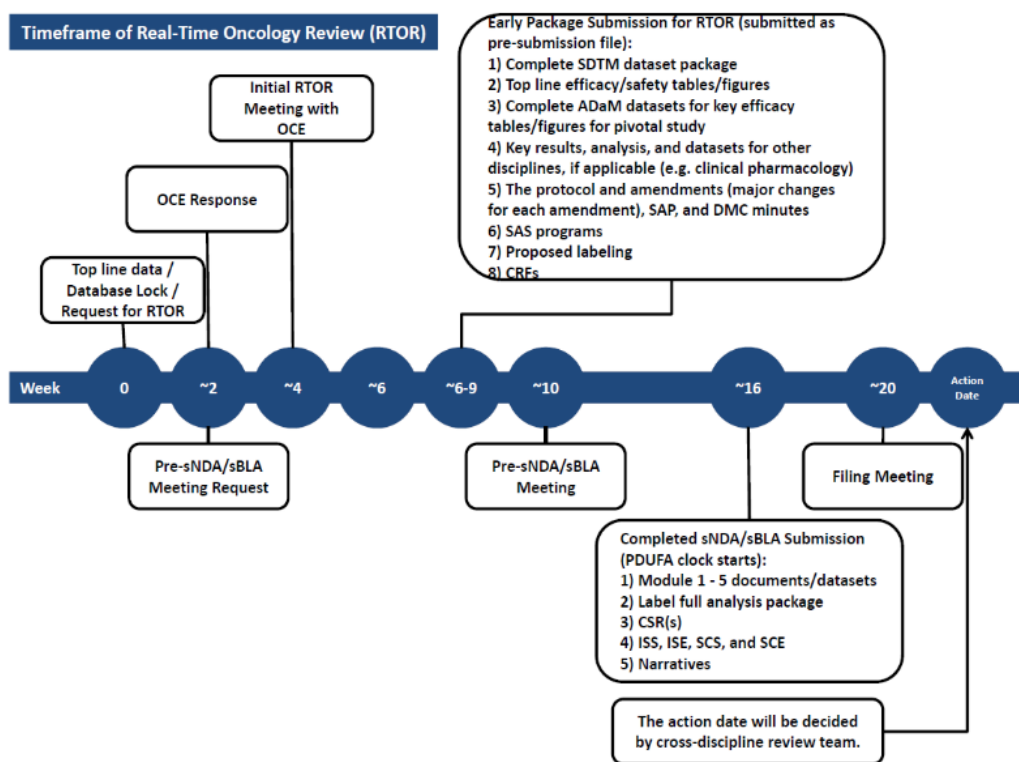


Figure 1: sNDA/sBLA Timeframe of Real-Time Oncology Review (RTOR)

RECENT RTOR APPROVALS

The RTOR program has been successful in several sBLA submissions and more recently in original BLAs and NDAs as well.

[Table 1](#) provides a summary of approvals through the RTOR pilot program since its inception in 2018. The first approval made via RTOR was Kisqali® on July 18, 2018. There have been a number of subsequent approvals via RTOR since then, including the Seattle Genetics ADCETRIS ECHELON-2 (PTCL) approval on November 16, 2018. At the time of writing, the ADCETRIS ECHELON-2 approval holds the record time of 11 days after the submission was completed on November 5, 2018.

Noticeably, the most recent approval of Piqray® for breast cancer was a full original NDA with a companion diagnostic, which was considered a more complex submission than the rest of the approvals listed (supplemental submissions). This may suggest the thinking at the Agency is evolving such that admission to the RTOR program is heavily driven by the top-line results of a pivotal trial.

Table 1. Recent Approvals Under FDA's RTOR Pilot Program

Name (Disease Area)	Submitted	Approved	Review Time* (Months)
Keytruda® (NSCLC)	23 Mar 2018	20 Aug 2018	4.9
Kisqali® (BC)	28 June 2018	18 July 2018	0.7
Kyprolis® (MM)	24 Aug 2018	28 Sep 2018	0.9
ADCETRIS® (PTCL)	04 Nov 2018	16 Nov 2018	0.4 (11 days)
Piqray® (BC)**	18 Dec 2018	24 May 2019	5.3
Tibsovo® (AML)	21 Dec 2018	02 May 2019	4.4
Kadcyla® (BC)	04 Feb 2019	03 May 2019	3
Xospata® (AML)	22 Feb 2019	29 May 2019	3.2
Venclexta® (CLL)	06 Mar 2019	15 May 2019	2.3
Darzalex® (ASCT)	12 Mar 2019	27 June 2019	3.6
Erleada® (mCSPC)	29 Apr 2019	17 Sep 2019	4.7
Lenvima/Keytruda® (AEC)	17 June 2019	17 Sep 2019	3.1
Calquence® (CLL/SLL)	24 Sep 2019	21 Nov 2019	1.9

Note: the list of approvals is sorted by submission dates, and is current as of the time of writing.

* Following submission of last component/complete package

** Full original NDA with companion diagnostic

AEC: advanced endometrial carcinoma; **AML:** acute myeloid leukemia; **ASCT:** autologous stem cell transplant;

BC: breast cancer; **CLL:** chronic lymphocytic leukemia; **mCSPC:** metastatic castration-sensitive prostate cancer;

MM: multiple myeloma; **NSCLC:** non-small cell lung cancer; **PTCL:** peripheral T-cell lymphoma; **SLL:** small lymphocytic lymphoma

FIRST SEATTLE GENETICS ENTRY FOR RTOR: ADCETRIS® (ECHELON-2)

CD30-Expressing PTCL (Peripheral T-Cell Lymphoma) Indication Being Considered for RTOR

Seattle Genetics' ADCETRIS is a well-established product with 5 approved indications before the 2018 ECHELON-2 submission.

ADCETRIS is a CD30-directed antibody-drug conjugate (ADC) with the microtubule disrupting agent MMAE. ADCETRIS was originally approved in 2011 for two types of blood cancer, relapsed classical HL and relapsed systemic ALCL. Three new blood cancer indications were added in 2015, 2017, and 2018, respectively, based on three Phase 3 registrational trials.

The ECHELON-2 trial in patients with a CD30-expressing PTCL, met its primary (PFS) and all key secondary endpoints (including OS). There were no new safety signals in the already well-characterized safety profile of ADCETRIS®.

Median PFS was 48.2 months (95% CI 35.2–not evaluable) in the ADCETRIS+CHP group and 20.8 months (12.7–47.6) in the CHOP group (hazard ratio 0.71 [95% CI 0.54–0.93], $p=0.0110$, [Figure 2](#)), where CHP is the combination of cyclophosphamide, doxorubicin, and prednisone, and CHOP is the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone.

Furthermore, treatment with ADCETRIS+CHP reduced the risk of death by 34% compared with CHOP (hazard ratio 0.66 [95% CI 0.46–0.95], $p=0.0244$, [Figure 3](#)).

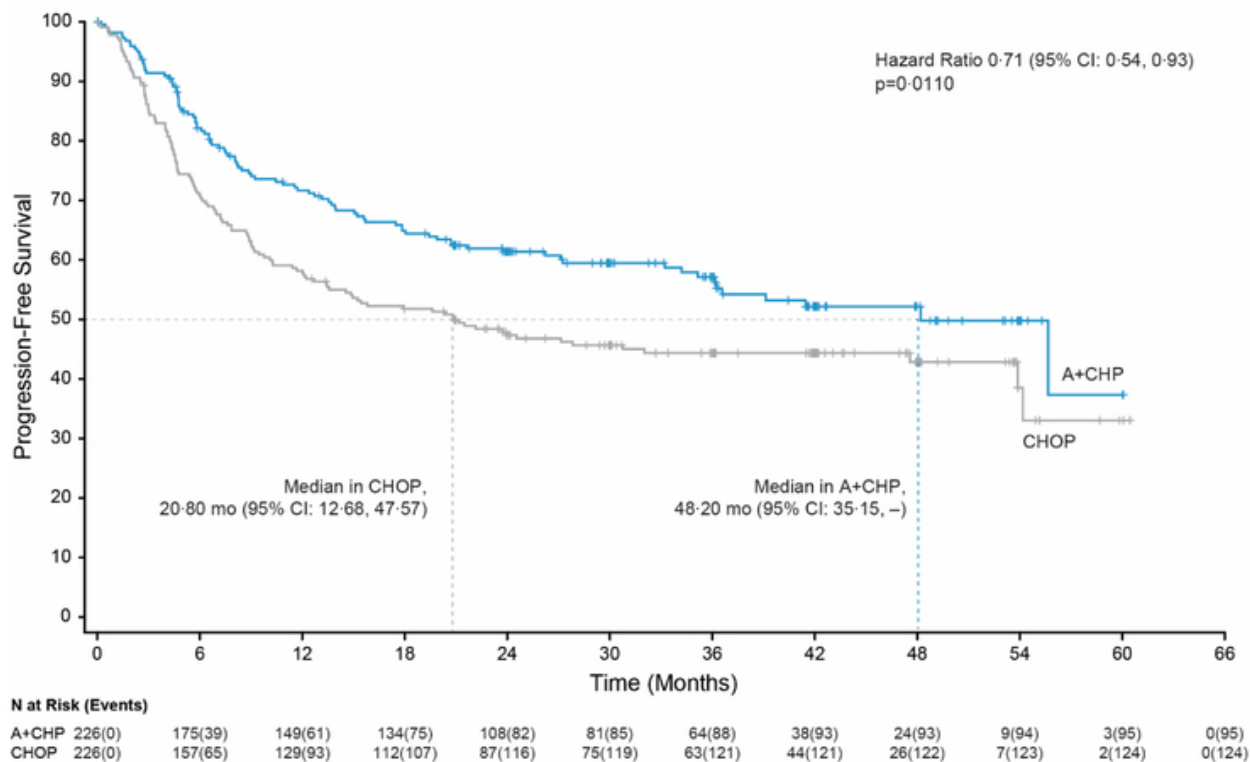


Figure 2: ECHELON-2 Progression-Free Survival

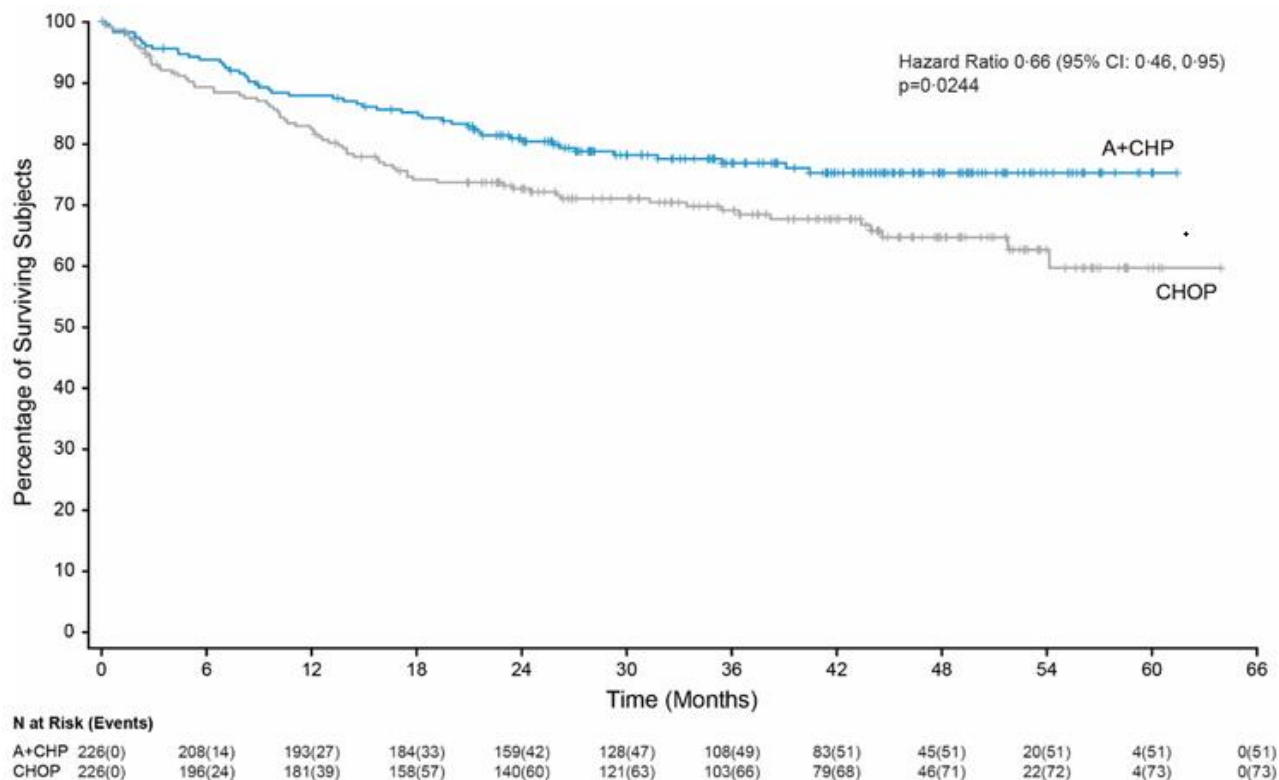


Figure 3: ECHOLON-2 Overall Survival

Study Conclusion: Front-line treatment with A+CHP is superior to CHOP for patients with CD30-positive peripheral T-cell lymphomas as shown by a statistically significant and clinically meaningful improvement in progression-free survival and overall survival with a manageable safety profile.

Requesting RTOR

Following the release of topline results, Seattle Genetics proactively pursued the option of requesting that the ECHOLON-2 study be accepted by the FDA for inclusion in its pilot RTOR program. The prospects of expediting the submission and review of application were highly desirable and advantageous for all parties (FDA, sponsor, and patients); however, the guidelines for the program were still evolving.

As a pilot, there was no template for requesting RTOR. Seattle Genetics submitted a topline report with a request for RTOR. Seattle Genetics submitted a topline report with a one-page description outlining why our application met the RTOR criteria, in parallel with a separate request for breakthrough therapy designation (BTD).

The submission timeline and contents were negotiated with FDA in order to streamline the review. At the time of initial RTOR communications with FDA, a mutual commitment was made to rapidly turn around all information requests (IRs), in general within 24 to 48 hours. FDA also provided a dedicated project manager to work closely with the Seattle Genetics submission team, which helped tremendously.

Early Data Package Submission

Since the RTOR program was at a nascent stage when it was utilized by Seattle Genetics, there was limited experience with the process. Considering those aspects, Seattle Genetics decided to provide a full and robust data package including pivotal study and supporting studies with the early RTOR submission.

Table 2 provides a summary of FDA's baseline expectations compared to Seattle Genetics' submission for the early RTOR components.

Table 2: Early RTOR Components by FDA vs. ECHELON-2 Submission

Early RTOR Components (per FDA Website)	What Seattle Genetics Submitted for ECHELON-2*
Complete SDTM data set package for pivotal study	Complete SDTM data set package for pivotal study (including define.xml, cSDRG, etc.)
Top-line efficacy/safety TLFs for pivotal study	All TLFs for pivotal study and 2 supporting studies
ADaM data sets for key efficacy tables/figures for pivotal study	All ADaM data set package for pivotal study and two supporting studies (including define.xml, ADRG, etc.)
Key results, analysis, data sets for other disciplines (if applicable)	N/A. No CMC, preclinical and PK data included.
Protocol, amendments, SAP, DMC minutes for pivotal study	Protocol and amendments, SAP for pivotal study and two supporting studies
SAS programs for pivotal study	SAS programs for pivotal study and 2 supporting studies <u>ECHELON-2</u> : All ADaM data sets program, top-line TLF programs, formats, library reference assignments, extensively used macros <u>Two supporting studies</u> : ADaM data set programs related to ISE analysis
Proposed labeling	Proposed labeling (clean and annotated)
CRFs for pivotal study	CRFs for pivotal study and two supporting studies
	Full CSRs for pivotal study and two supporting studies

* The example of ECHELON-2 is provided merely for illustration purposes. It is important to following FDA recommendations and confirm the submission scope through regulatory interactions.

RTOR Process

An agreement was made between FDA and Seattle Genetics to submit responses to information requests (IRs) via email followed by an official submission. Several IRs were received prior to the submission of the data, more focused on expectation-setting and confirmation of data formats and completeness. Seattle Genetics identified a dedicated team of cross-functional SMEs to focus on the frequently received IRs. To meet timelines and expectations, teams regularly worked beyond regular business hours to address several critical IRs.

The IR-focused team met twice a day with Senior Management to ensure timely feedback and approval. The FDA's commitment was also evident, and the FDA review team promptly responded to our questions, often within a few hours.

Some highlights of activities and timelines:

- Full data packages (SDTM and ADaM datasets, ADaM and TLF programs, aCRF, define.xml files, reviewer's guides, and other supplemental documents for the pivotal trial and two supporting studies, see [Table 2](#)) were submitted to FDA within 2.5 weeks of requesting RTOR
- 15 IRs were received in a period of 4 weeks
- Formal sBLA was submitted 2.5 weeks after the data package submission
- **sBLA approval was granted 11 days after the formal sBLA submission**

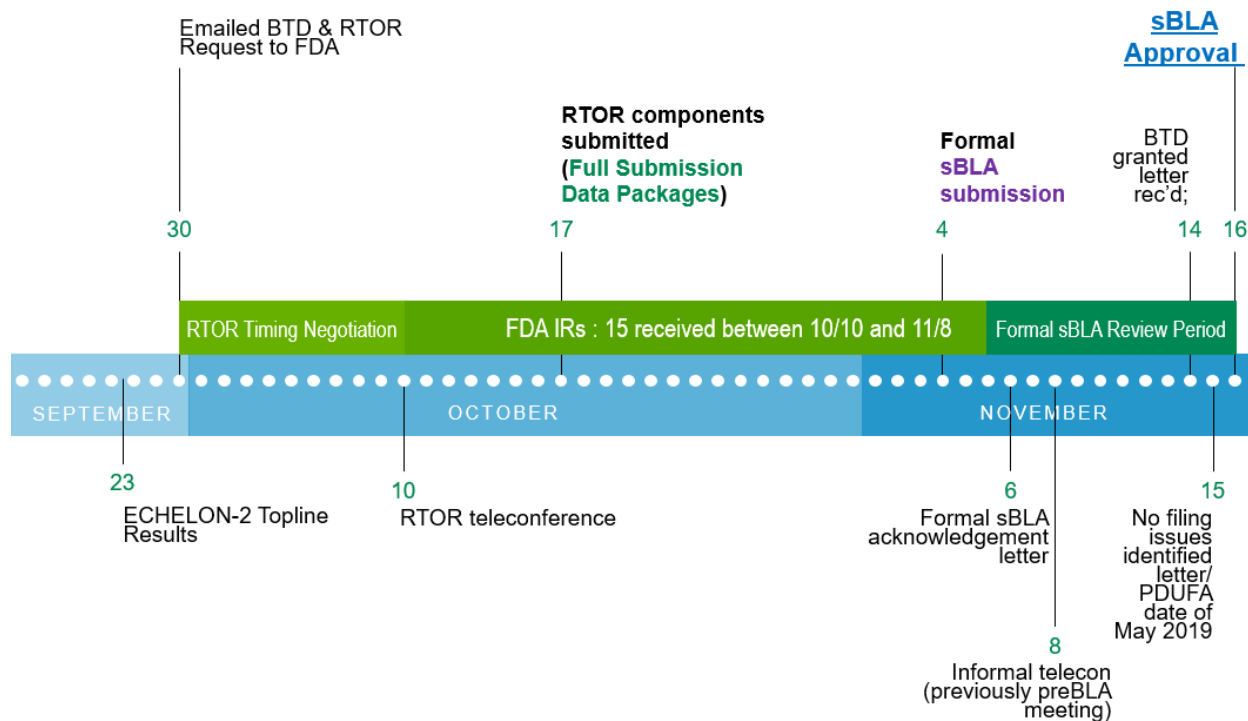


Figure 4. RTOR Journey: Milestones and Timelines

IR Overview

During the ECHELON-2 submission under RTOR, we received the first IR on Oct. 10, 2018, and the last one on Nov. 8, 2018, with a total of 15 IRs. Biometrics (Biostatistics and Statistical Programming) was an important contributor to most of the IRs. Within a duration of 20 business days, we received about 1 IR every other day. Given the intensity of the activities and the expected rapid turnaround time for each IR, we kept senior management informed on the proposed analyses for the responses early on to ensure alignment on the interpretation of the questions and endorsement on the response strategy proposed by the study team. Where feasible, table shells for review at the strategy planning meetings proved very helpful.

BEST PRACTICES FOR RTOR SUBMISSION FOR THE STATISTICAL PROGRAMMING GROUP

Proactive Preparation

Here are some guidelines that may help study teams prepare their project for potential RTOR submission.

Regular P21 validation checks: Ensuring CDISC compliance pre-DBL by running P21 checks on the ongoing data may help rectify challenges and issues at an early stage. This will also help avoid late changes with large downstream impact.

Submission Readiness:

- Maintain clear and concise data specifications which can be translated into define.xml with ease and efficiency
- Maintain a tracker to document any special data handling scenarios, and refer to it while preparing reviewer's guides (see [Table 3](#))

Dataset	Label	Dataset Description for ADRG
ADPN	Peripheral Neuropathy Analysis Dataset	ADPN is special purpose of occurrence data structure class based on ADaM guidelines. Dataset have one Peripheral Neuropathy event record per subject. It is basically subset of ADAE for only the Peripheral Neuropathy SMQ identified based on SMQ MedDRA dictionary v21.0. There are additional variables derived which will be utilized in the development of ADPNUSUM to support CSR analysis needs. The treatment emergent PN only includes the events that started within the safety analysis period. The detail definition of PN resolution/improvement is included in ADaM_Additional_definitions supplemental document
ADNTX	FACT/GOG-NTX Subscale Questionnaire Analysis Dataset	ADNTX summarize the FACT/GOG-NTX individual subscale scores and the summary score (PARAMCD=NTXSS). The analysis variables focus on the NTXSS records only. At each visit, a NTXSS record is derived using the individual subscale. For the visits that are planned to have NTX measurements but not actually collected, an imputed NTXSS record is created using LOCF method (DTYPE='LOCF'). ANL01FL and ANL03FL are populated only when ANL02FL='Y'.
ADAELB	Combined AE and Lab events of interest	ADAELB combines Adverse Events and Lab events of interest. ADAELB is compliant with occurrence data structure of ADaMIG. ADAELB contains Adverse Events that occurred within Safety analysis period, defined as Day 1 up to 30 days after the last dose of any component of the regimen. Also, ADAELB contains lab events with lab test codes 'Hemoglobin (g/dL)', 'Absolute Neutrophil Count (x10 ³ /uL)' and 'Platelets (x10 ³ /uL)' which translate into Preferred terms of 'Anaemia', 'Neutropenia' and 'Thrombocytopenia'. Filter condition (PARAMCD in ('HGB', 'ANC', 'PLAT') and ANRIND='LOW' and MCRT1ML ne 'Not Treatment Emergent' and AVISIT ne 'Baseline' and ADY > 1) is used for considering records from ADLB.
ADQLQC30	QLQ-C30 Health Questionnaire Analysis Dataset	[Jinit] ADQLQC30 is special purpose Basic data structure dataset based on Patient reported outcomes data. It follows One record per parameter per analysis visit per subject. ADQLQC30 subset of SDTM QS dataset based on QS.QSCAT=QLQ-C30 HEALTH QUESTIONNAIRE. ADQLQC30 contains subject level analysis variables, additional derived PARAMCDs based on EORTC QLQ-C30 Scoring manual and to support CSR analysis needs. Please refer to additional definitions for more details on derivations.
ADFN	Febrile Neutropenia Analysis Dataset	ADFN is special purpose of occurrence data structure class based on ADaM guidelines. Dataset have one Febrile Neutropenia event record per subject. It is basically subset of ADAE with Preferred term is equal to 'Febrile neutropenia'. There are additional variables derived which will be utilized in the development of ADFNSUM to support CSR analysis needs. The treatment emergent FN only includes the events that started within the safety analysis period. The detail definition of FN resolution/improvement is included in ADaM_Additional_definitions
ADSTROID	Steroid Medications Analysis Dataset	ADSTROID is special purpose of Occurrence data structure class based on ADaM guidelines. Dataset have one Steroid Medication record per subject. ADSTROID is basically subset of ADCONMED with 'Steroid' medications identified based on lookup file. ADSTROID is implemented to support late imputation need of hyperglycemia analysis.

Table 3: Sample Tracker

- Maintain an SDTM-annotated CRF (blank, i.e., without raw data variable annotations) or at least annotate a raw data CRF (with raw data variable names) will help prepare a submission-ready aCRF in a short time. For accuracy and efficiency, this should be done before or during the assembly of the initial SDTM mapping specification and prior to starting SDTM dataset programming.
- Keep all programs (ADaM and TLF) clean during development and QC, prior to, and after database lock to help ensure programs are submission-ready at any time with minimal modification (if applicable):
 - Headers are up-to-date
 - Programs are well-commented
 - Prepare simplified or executable programs (without external dependencies) for submission which may help reduce IRs
- Maintain a pre-submission checklist for all ongoing submission related activities to help add efficiencies
- Follow eCTD file name requirements early on (use only hyphens, lowercase letters, and numeric)
- Apart from data validation checks, P21 Enterprise has several functionalities to help expedite submission data package activities:
 - Auto-populate annotated CRF page numbers in define.xml
 - Auto-populate several sections of reviewer's guides based on pre-fed information for data validation:
 - Acronyms list
 - Study data standards and dictionary versions
 - Trial design domains list and details
 - Core variables
 - Some study data overview information, such as whether submission datasets include screen failures and a dataset list with SUPP-- and QNAM
 - Data conformance summary
 - P21 validation issues summary and explanation

LEARNING FDA EXPECTATIONS AND OTHER PLANNING

- Regulatory Affairs may arrange an early FDA meeting right after top-line pivotal trials results are generated to learn the expectations.
- FDA may share specifics on data set expectations, which may help prepare for RTOR submission with a focused approach. Study teams developing potential submission studies must consider incorporating these guidelines, as applicable.
Example: [Pilot OOD Standard Safety Data Requests v1.1](#)
- Preparedness and willingness to submit the complete package (CDISC-compliant SDTM and ADaM data sets, define.xml, cSDRG and ADRG, aCRF, supporting documents, and ADaM/TLF programs) may enhance the RTOR review, help reduce IRs, and in turn help with early decision-making.
- Plan for frequent check-ins post submission to address IRs.
- Create dedicated groups and plan resources efficiently. Create a team of core functional leads, and a dedicated team within each function, for example, 2 biostatisticians and 4 programmers. This team can be the first defense for incoming IRs and should be available to work on any urgent request at very short notice.
- A core team empowered to make expedited and informed decisions, while at the same time critical decision-makers and executive-level approvers are available for any meeting at short notice.

Support by Biometrics for an RTOR Submission

- Help educate the team and work with them to better understand priorities from a data perspective. For example, components in the data package contributed by Statistical Programming must follow structural compliance standards and regulatory guidance such as conformance guides and technical rejection criteria, even if other functions may not fully understand such considerations. Also, last-minute updates by the team may impact the overall timelines, quality, and efficiency of RTOR e-submission activities by Statistical Programming, thus the team should be advised that early and sustainable decisions are required to avoid any late changes
- Be prepared for the intensity of IRs and understand FDA reviewers also work very hard throughout this process
- Be flexible on schedules (could be outside regular business hours)
- Early engagement with senior management on IRs is critical to ensure early alignment on the interpretation of questions and the proposed response strategy:
 - Biostatistics can help determine which components need Statistical Programming support immediately upon IR receipt
 - For IRs needing Statistical Programming support it's immensely helpful when Biostats sketches out shells even if they are in a simple (plain-text) format
 - Close collaboration with short-turnaround iterations of draft output production and review between Statistical Programming and Biostats before sharing for review by the wider IR team
- Work as one Biometrics team and help each other where possible: sometimes it may be helpful to share the responsibilities between Biostatistics and Statistical Programming as we are often heavily involved in many IRs
- Carefully review response documents before they are finalized to ensure proper interpretation of analysis results

CONCLUSION

There are no clear guidelines for RTOR submission by FDA yet. Project teams may need to think proactively and plan creatively to meet the RTOR expectation. A successful RTOR submission requires extensive planning, collaboration, partnership and teamwork, not just within the project teams but also with the FDA review team.

The success of the program can help reduce review time enormously which in turn will help get effective treatment options out to cancer patients faster.

ACKNOWLEDGMENTS

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RESOURCES

FDA Real-Time Oncology Review Pilot Program:

<https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program>

CONTACT INFORMATION

Your comments and questions are valued and encouraged.

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