



8th Annual Blueprint for Breakthrough Forum

Validating Real-World Endpoints for an Evolving Regulatory Landscape

September 18, 2019

Washington, DC

Introduction

Advances in data analytics and data capture through electronic health records (EHRs) and medical/pharmacy claims have brought the opportunities and challenges associated with using real-world evidence (RWE) to the forefront of the US healthcare industry. Increasingly, the promise of RWE to contribute to a more complete picture of the benefits and risks associated with therapies, when paired with results from randomized, controlled clinical trials, is being realized. RWE provides an opportunity to collect data rapidly on a broader patient population outside of a strict clinical trial protocol to help provide evidence for new indications or describe rare safety events, provide information that is more generalizable than clinical trial results, and confirm clinical benefit in the post-market setting.

Applications for RWE extend across the spectrum of therapeutics development from regulatory decision-making, to clinical use, to coverage and payment decisions. In the regulatory space, RWE has been utilized most frequently to evaluate drug safety through pharmacovigilance and adverse event monitoring in pre- and post-approval settings. However, RWE has increasingly been used to support effectiveness claims. Beyond regulatory decisions, RWE is frequently used to support clinical trial design, development of clinical practice guidelines, confirmation of population/subgroup size, and payment decisions including formulary placement.

Significant progress has been made in data collection efforts to support use of RWE in regulatory settings, however challenges remain, chiefly with developing methodologies and standard definitions when organizing and analyzing data from different sources that ensure appropriate translation of real-world data (RWD) into “fit-for-use” RWE. Friends of Cancer Research initially proposed a pilot project, comprised of six leading healthcare organizations with oncology data, to develop a data set curation process and framework to operationalize RWD collection and explore potential real-world endpoints that may be fit for regulatory purposes as well as assessing long-term benefits of a product. The results of this pilot were presented in July 2018¹.

A result of the initial RWE collaborative oncology research pilot showed that several different data sets were able to extract real-world time to treatment discontinuation (rwTTD) in a relatively consistent manner. In addition, rwTTD correlated well to real-world overall survival (rwOS) in the context of anti-PD-(L)1 use for treating advanced non-small cell lung cancer (aNSCLC).

¹ Friends of Cancer Research. The Future Use of Real-World Evidence Meeting. July 10, 2018. Washington D.C.

Establishing a New Pilot Project

Informed by the recent release of FDA's Real-world Evidence Program framework², and building off the successes from our 2018 RWE pilot project, "Establishing a Framework to Evaluate Real-World Endpoints", *Friends* initiated a new pilot project to further characterize how RWD can fill evidence gaps about the performance of approved agents used in a real-world setting. Additional insights can also be gained about populations that may not have been included in clinical trials for various reasons, such as feasibility or ethical concerns, rarity of the cancer, etc.

The RWE Pilot Project 2.0, which is ongoing, has been designed to provide insight into the opportunities and limitations of real-world endpoints and the ability to compare differences in effectiveness between therapies in terms of patient characteristics and observed effectiveness. The pilot will also allow us to understand the extent to which similar conclusions may be observed in real-world patient populations using established clinical trial patient populations (defined by applying agreed upon inclusion and exclusion criteria) as a relative benchmark. In addition to evaluating real-world endpoints in a case study, this pilot project will also provide an opportunity to start to a) align on how to evaluate data quality, b) define data standards, and c) determine essential elements of a potential analytic framework to evaluate real world endpoints.

This pilot project was initiated to help determine whether RWD can be used to develop an early perspective on real-world outcomes, as defined by real-world endpoints from EHR and claims data. Additionally, we sought insight into the generalizability of clinical trial results to patients treated in real-world settings. The pilot project evaluates the performance of real-world endpoints across multiple data sets by focusing on a common question: ***What are the real-world outcomes for aNSCLC patients treated with frontline therapies in usual care settings?***

Participating organizations began by agreeing upon necessary data elements to define demographic and clinical characteristics and internal processes to define real-world endpoints in the context of clinical trial definitions, taking into account the FDA regulatory framework and the variation of available data within EHR and claims-based datasets. While the project is in the preliminary stages, later phases of the pilot project will ultimately help evaluate whether the various data sets included in this study can reach similar conclusions upon application of uniform critical inclusion/exclusion criteria and appropriate analytic methodologies.

Pilot Project Study Design and Objectives

The on-going RWE Pilot Project 2.0 leverages parallel analyses from common data elements across multiple data sources to assess three frontline treatment approaches in real-world patients with aNSCLC. It is a retrospective observational analysis derived from EHR and claims data. The data sets generated for the study include all relevant, retrospective patient-level HIPAA-compliant de-identified data available for eligible individuals up to a single specific data cutoff date of March 31, 2018.

² US Food and Drug Administration. FRAMEWORK FOR FDA'S REAL-WORLD EVIDENCE PROGRAM. December 2018. Retrieved from <https://www.fda.gov/media/120060/download>.

It is important to note that this pilot is not intended to replicate results observed in RCTs nor draw formal conclusions regarding the performance of any product in real-world settings.

The study design includes two objectives that are being carried out in a phased manner:

Objective 1: Description of demographic and clinical characteristics of patients with aNSCLC receiving frontline chemotherapy doublet, PD-(L)1 monotherapy, or PD-(L)1 + doublet chemotherapy.

Purpose: Provide baseline understanding of the similarities/differences among the datasets to better understand what confounding factors may need to be considered when interpreting the data.

Objective 2: Evaluate treatment effect size in frontline therapy regimens using real-world endpoints.

Purpose: Agree on data source specific definitions and measurement of endpoints assessed through real-world data, in order to ensure reliability, consistency, and conservation of clinical meaning.

Methods

PROJECT DETAILS

BROAD COHORT AND INCLUSION / EXCLUSION CRITERIA

Inclusion:

- EHR-based data sets: Physically present at a practice or having an encounter (defined as a physician visit, intravenous medication administration, or vitals documentation) in the real-world database on at least two separate occasions on or after January 1, 2011 until data cutoff date (March 31, 2018).
- Claims-based data sets: Continuous enrollment in the health plan beginning on or after January 1, 2011 and before data cutoff date (March 31, 2018).

All Data Sets

- Diagnosis of (identified by ICD-9 code of 162.x or ICD-10 code of C33.x or C34.x) or pathology consistent with NSCLC
- Evidence of advanced disease on or after January 1, 2011 with advanced disease defined as either stage IIIB, IIIC or IV NSCLC at initial diagnosis or early -stage (stages I, II, and IIIA) NSCLC with a recurrence or progression to advanced or metastatic status.
- Date of recurrence or progression defined based on physician assessment through curation or as last radiology date prior to use of chemotherapy agents of interest.
- Regimen given to NSCLC patients subsequent to the patient’s date of advanced diagnosis including all agents received within 30 days following the day of first infusion:

**EHR AND CLAIMS-
DERIVED
ENDPOINTS
DEFINITION AND
ANALYTICAL
GUIDANCE**

- Platinum doublet chemotherapy (cisplatin, carboplatin, oxaliplatin, or nedaplatin with pemetrexed, paclitaxel, nab-paclitaxel, gemcitabine)
- PD-(L)1 monotherapy (pembrolizumab, nivolumab, atezolizumab)
- Any PD-(L)1 + doublet chemotherapy combination (pembrolizumab, pemetrexed and platinum or pembrolizumab, platinum and paclitaxel or nab-paclitaxel)

Exclusion:

- EHR-based data sets: Greater than 120 days from time of advanced diagnosis to evidence of clinical encounter
- Claims-based data sets: Less than 180 days baseline before the date of diagnosis

All Data Sets

- Incomplete historical treatment data available within the real-world database
- Treatment at sites without consistent historical reporting such that confidence of identification of frontline therapy is diminished.
- Received other therapies during frontline.

Index Date

- *Definition*: Earliest drug episode (e.g., first administration or non-cancelled order) of the frontline therapy for advanced disease.

Real-world Overall Survival (rwOS)

- *Definition*: Length of time from the index date to the date of death, or disenrollment (need to define gap in enrollment). For claims data, health plan disenrollment date is incorporated if deaths are not captured among those who leave health plan coverage.
- *Censor date*: Last structured recorded clinical activity within the real-world database including prescription, office or institutional billing claims data, or end of follow-up period, whichever occurs earliest.

Real-world Time to Next Treatment (rwTTNT)

- *Definition*: Length of time from the index date to the date the patient received an administration of their next systemic treatment regimen or to their date of death if there is a death prior to having another systemic treatment regimen.
- *Censor date*: Last known activity or end of follow-up.

Real-world Time to Treatment Discontinuation (rwTTD)

- *Data*: Length of time from the index date to the date the patient discontinues frontline treatment (i.e., the last administration or non-cancelled order of a drug contained within the same frontline regimen).
 - Discontinuation is defined as:
 - having a subsequent systemic therapy regimen after the frontline treatment;

- having a gap of more than 120 days with no systemic therapy following the last administration;
 - or having a date of death while on the frontline regimen.
- *Censor date*: Last known usage (i.e., administration or non-cancelled order) of frontline treatment.

Real-world Progression Free Survival (rwPFS)

- *Definition*: Length of time from the index date to the date of a real-world progression (rwP) event (i.e., distinct episode in which the treating clinician concludes that there has been growth or worsening in the aNSCLC based on review of the patient chart) at least 14 days after frontline treatment initiation, or death.
- *Censor date*: Date of rwTTNT. For patients without a rwP event or a rwTTNT event and at least 180 days follow-up from last frontline treatment, censor date will be rwTTD event date.

ANALYSES

Graphs 1-13:

- Description of demographic and clinical characteristics of aNSCLC patients treated with one of the above frontline treatment categories, example characteristics include:
 - Demographic: age, gender, and race
 - Clinical: smoking status, histology, group stage at time of initial diagnosis, PD-L1 expression status and staining, performance (ECOG) status, and presence/absence of brain metastasis.
 - Treatment description of population by treatment category including time from advanced diagnosis to index date (not shown), year of index date, structured follow-up time from advanced diagnosis (not shown), and structured follow-up time from index date (not shown).

Graphs 14-21:

- Real-world endpoints (rwOS, rwPFS, rwTTNT, rwTTD) for aNSCLC patients treated with frontline therapies of interest in the advanced setting (Kaplan-Meier curves for each endpoint and median time to event estimates), stratified by treatment category.

Contributing Organizations for Pilot Project Study

Aetion

Aetion is a health care technology company that delivers real-world evidence for biopharma, payers, and regulatory agencies. The Aetion Evidence Platform™ analyzes data from the real world to produce transparent, rapid, and scientifically validated answers to guide treatment development, commercialization, and payment innovation. For this engagement, Aetion is supporting data aggregation and analysis across participant data sources.



ASCO CancerLinQ/Concerto HealthAI

CancerLinQ®, an initiative of the American Society of Clinical Oncology (ASCO), is a web-based platform that collects and analyzes structured and unstructured real-world cancer data from multiple electronic health record systems (EHRs) to improve care and drive new research. Concerto HealthAI, a technology leader in AI solutions for real-world oncology data, also aggregates structured and unstructured data from multiple EHRs, to revolutionize clinical and outcomes research that will enhance patient care and improve outcomes. Concerto HealthAI curates data from both sources, which together hold two million patient records from more than 100 practices, generating de-identified datasets that support high-quality research by non-profit organizations, academia, government agencies, and industry.

COTA

The COTA Real-World Evidence (RWE) database is a HIPAA-compliant, de-identified data source drawn from the electronic health records (EHR) of contributing academic, for-profit, and community oncologist provider sites and hospital systems. The database includes detailed demographic, diagnostic, molecular and genomic testing, treatment, and outcome data. As of 2018, COTA's RWE is comprised of rich longitudinal patient records collected from over 40 unique locations across North America.

Flatiron Health

The Flatiron Health database is a nationwide longitudinal, demographically and geographically diverse database derived from de-identified electronic health record (EHR) data from over 280 cancer clinics (~800 sites of care) representing more than 2.2 million US cancer patients available for analysis. The de-identified patient-level data in the EHRs includes structured data (e.g., laboratory values, and prescribed drugs) in addition to unstructured data collected via technology-enabled chart abstraction from physician's notes and other unstructured documents (e.g., biomarker reports).

IQVIA™

IQVIA™ is a leading global provider of information, innovative technology solutions and contract research services focused on using data and science to help healthcare clients find better solutions for their patients. For this engagement, IQVIA's Real World team analyzed data from structured Oncology Electronic Medical Records (EMR) fields, combined with medical and pharmacy claims, and supplemented where possible with NLP and chart abstraction. IQVIA's data is sourced through multiple partners, including Inteliquet and IntrinsicQ Specialty Solutions. IntrinsicQ's affiliate Xcenda supported the project through the use of both their NLP technology and their chart abstraction team. The data are comprised of all payer types, all practice sizes and both community practices and hospital centers across the United States. The IQVIA Integrated EMR platform includes linkage to medical and pharmacy claims to capture activity outside of the oncology site and to apply a mortality index algorithm.

Kaiser Permanente Analysis Using Cancer Research Network

The Cancer Research Network originated as an NCI-funded consortium of research groups affiliated with integrated health care systems across the US; the participating health systems are a subset of those participating in the Health Care Systems Research Network. In the early 2000's, the CRN created the Virtual Data Warehouse (VDW), a living common data model to facilitate collaborative research across these health care systems. Data in the VDW are extracted from multiple source databases, including, but

not limited to, electronic health records, legacy databases, and databases for specific applications such as prescription medication orders and fills. The VDW is maintained by each research group with the possibility of pooling data under IRB-approved research protocols. For most participating institutions, the VDW has essentially complete information on care dating back to 1996 or earlier for most data domains. Domains include health plan enrollment periods, cancer registries, encounters including diagnoses and procedures, prescription and infusion medications, laboratory results, and other areas. The data provided are results from one of the participating CRN organizations.

Mayo Clinic Analysis using OptumLabs® Data Warehouse

OptumLabs® is an open, collaborative research and innovation center founded in 2013 as a partnership between Optum and Mayo Clinic with its core linked data assets in the OptumLabs Data Warehouse (OLDW). The database contains de-identified, longitudinal health information on enrollees and patients, representing a diverse mixture of ages, ethnicities and geographical regions across the United States. The claims data in OLDW includes medical and pharmacy claims, laboratory results and enrollment records for commercial and Medicare Advantage enrollees. The EHR-derived data includes a subset of EHR data that has been normalized and standardized into a single database. For this pilot project, clinical information from the health plan's cancer registries and prior authorization systems were linked to the health plan's administrative claims data for privately insured enrollees and death records.

McKesson

McKesson Data, Evidence & Insights uses robust regulatory-grade data to deliver meaningful, timely insights so informed clinical, regulatory, commercial and payer strategy decisions can be made. McKesson leverages iKnowMedSM, its oncology practice electronic health record (EHR) system, as well as reimbursement data from integrated structured retrospective and prospective databases. Using this innovative model, biopharma and life sciences companies are able to bring life-saving drugs to market faster and support rapid label expansion, as well as create commercialization plans and outreach strategies to support appropriate utilization of commercial products.

SEER-Medicare

The SEER-Medicare data reflect the linkage of two large population-based sources of data that provide detailed information about Medicare beneficiaries with cancer. SEER is supported by the Surveillance Research Program (SRP) within the Division of Cancer Control and Population Sciences (DCCPS) at the National Cancer Institute, which provides national leadership in the science of cancer surveillance as well as analytical tools and methodological expertise in collecting, analyzing, interpreting, and disseminating population-based cancer statistics. SEER collects demographic, tumor characteristic, treatment, and survival data as a part of legally mandated reporting requirements for cancer surveillance from registries within 19 geographic areas representing 34% of the US population. The SEER data provide information on cancer statistics in an effort to reduce the cancer burden among the U.S. population. Medicare is a federally funded insurance program in the US administered by CMS, insuring beneficiaries over 65 years old or those meeting other requirements. The Medicare data include administrative claims for health services submitted for reimbursement across various care settings. The publicly available linked dataset provides the ability to study population-based epidemiologic questions related to screening, treatment, costs, and outcomes among elderly cancer patients.

Syapse

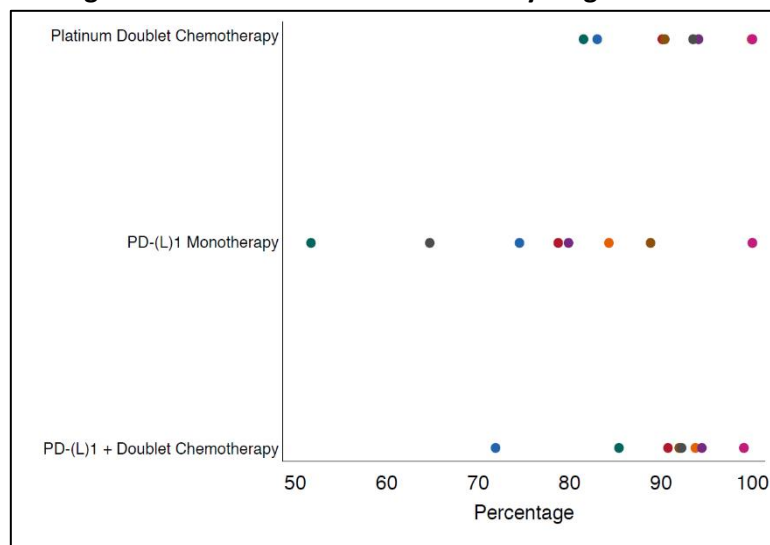
Syapse is on a mission to improve outcomes for every cancer patient through precision medicine. By bringing together leading healthcare providers into a unified ecosystem, we have built one of the world's largest Learning Health Networks of provider-driven precision medicine, comprising over 10% of cancer care at over 400 hospitals in the United States and South Korea. Our real-world evidence platform integrates clinical, molecular, treatment, and outcomes data from multiple structured and unstructured sources including EHRs, registries, radiology systems, and molecular testing labs, building a complete, longitudinal, and continuously updated picture of each cancer patient's journey, including non-oncology care. In collaboration with our partners — including Advocate Aurora Health, CommonSpirit Health, Henry Ford Health System, Providence St. Joseph Health, and Seoul National University Hospital — we are working toward a future in which all cancer patients have access to the best personalized care.

Tempus

The Tempus real-world oncology database comprises longitudinal oncology care data from a variety of stakeholders across the healthcare ecosystem (e.g. community practices, integrated delivery networks, and academic institutions) including more than 50 NCI cancer centers. Our data assets include structured patient-level data from various healthcare sources and formats (e.g. electronic medical records, enterprise data warehouses, tumor and death registries), integrated with abstracted clinical information from unstructured documents (e.g. physician notes, pathology, radiology, laboratory, and genomic sequencing/biomarker reports) and corresponding molecular data produced by our lab. This is acquired through purpose-built, semi-automated pipelines and harmonized to standard terminologies (eg. MedDRA, NCBI, NCI, NCI, RxNorm, SNOMED, etc.). Data captured include demographic, diagnostic, biomarker and genomic testing, laboratory values, treatment, outcome, and adverse event data.

Results^{3,4}

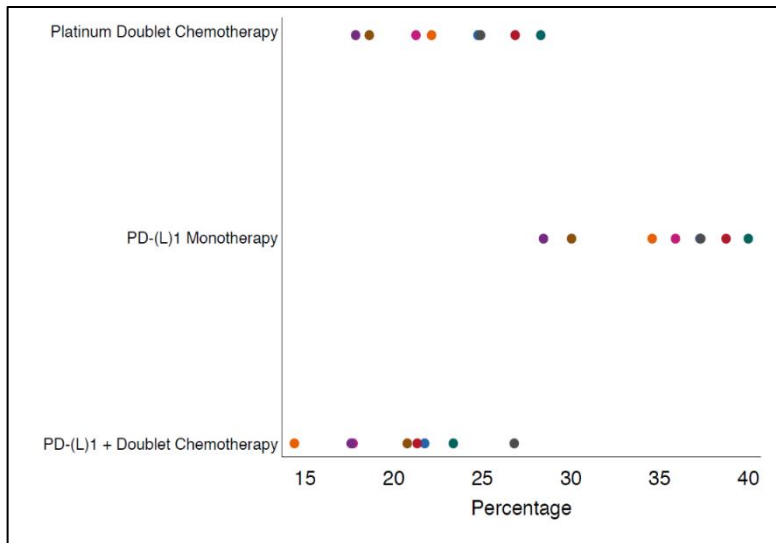
Graph 1. Percentage of Patients with Advanced vs Early Stage NSCLC at Initial Diagnosis



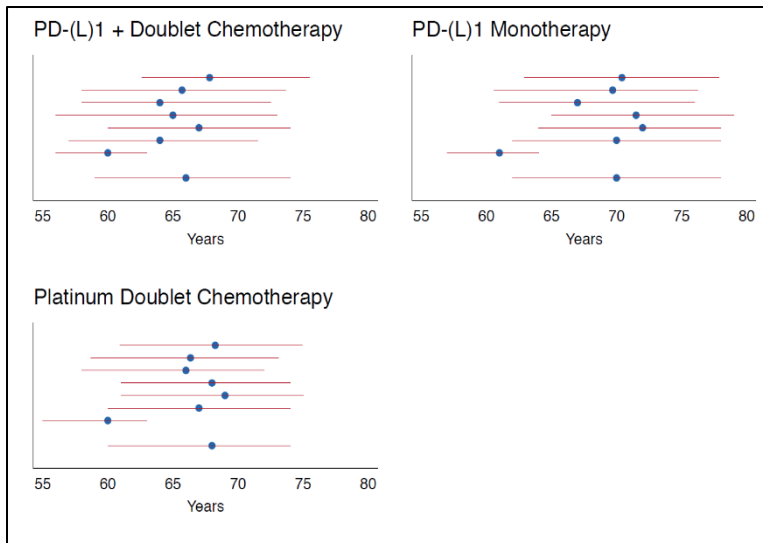
³ * Graphs are based on structured or unstructured information depending on the data source

⁴ Graphs represent data of patients with values reported. Missing/unknown data are not represented in these graphs. See Assumptions and Limitations section for more explanation.

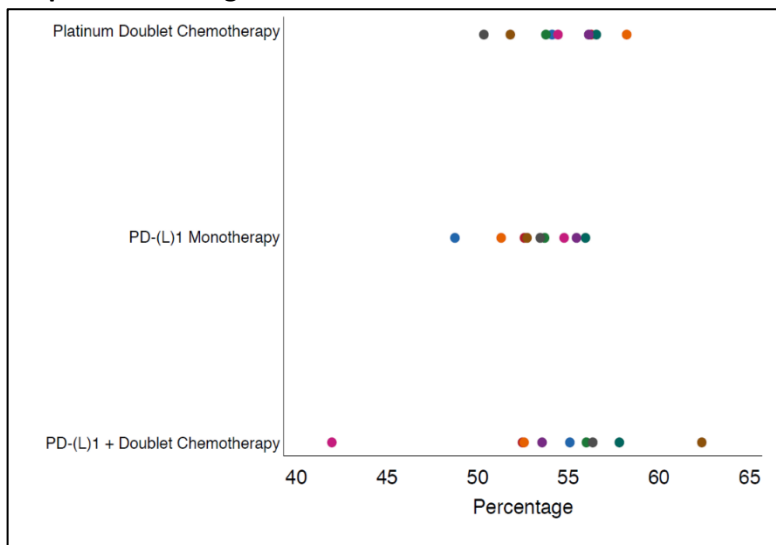
Graph 2. Percentage of aNSCLC Patients Age 75 or Older at Index



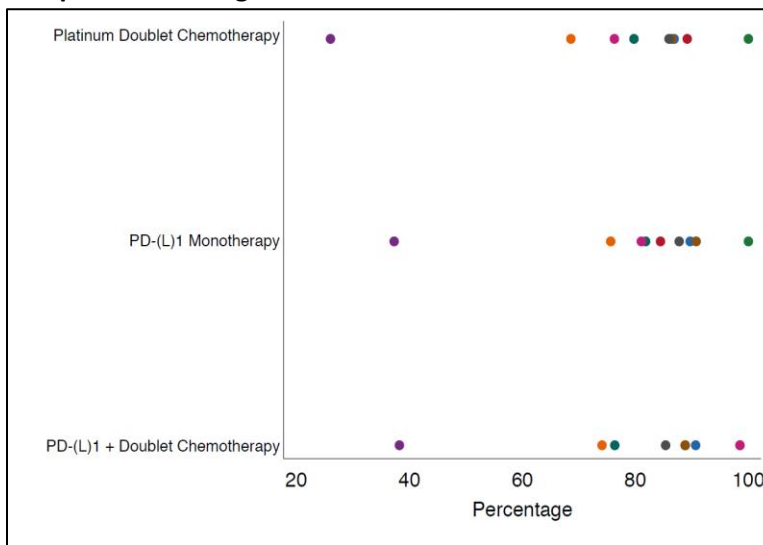
Graph 3. Median and Lower/Upper Quartiles of Age at Index



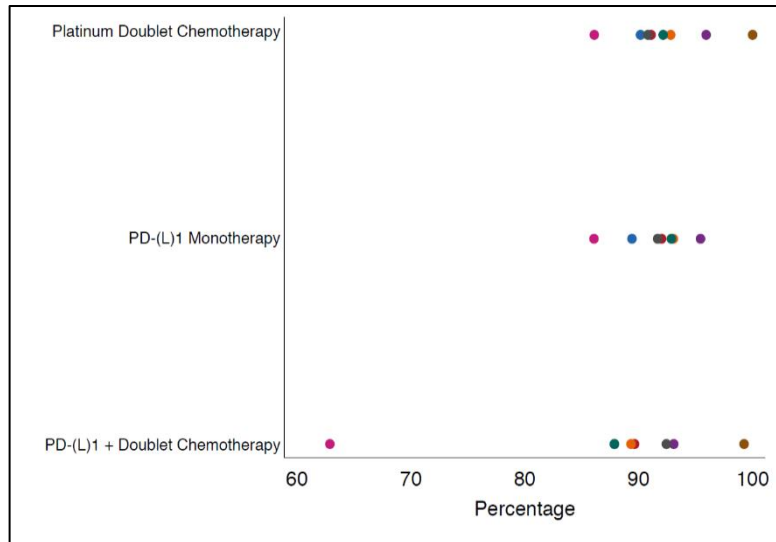
Graph 4. Percentage of Male aNSCLC Patients



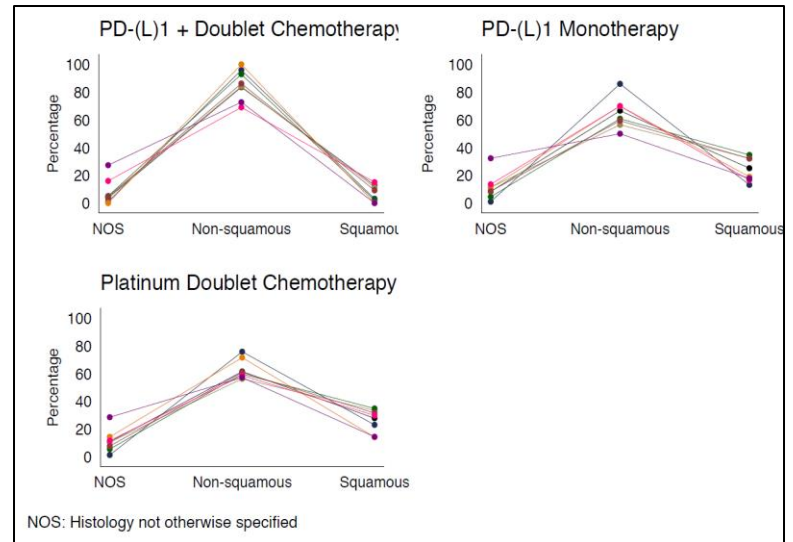
Graph 5. Percentage of aNSCLC Patients Whose Race is White



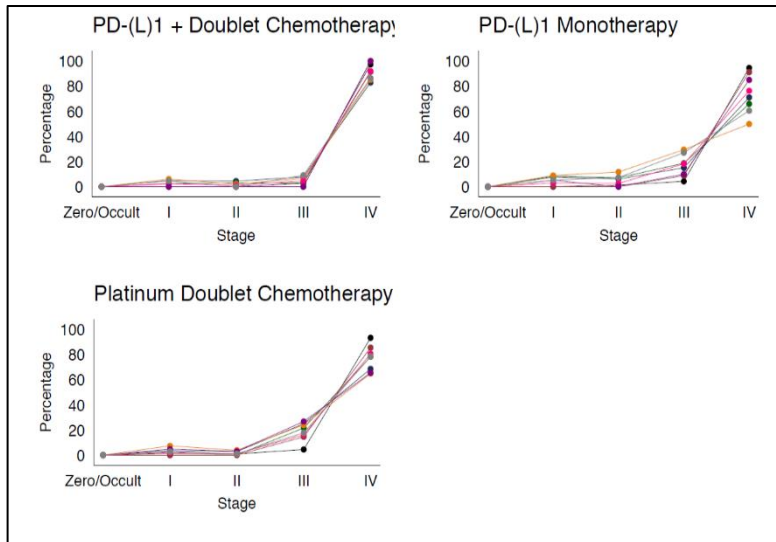
Graph 6. Percentage of aNSCLC Patients with a History of Smoking*



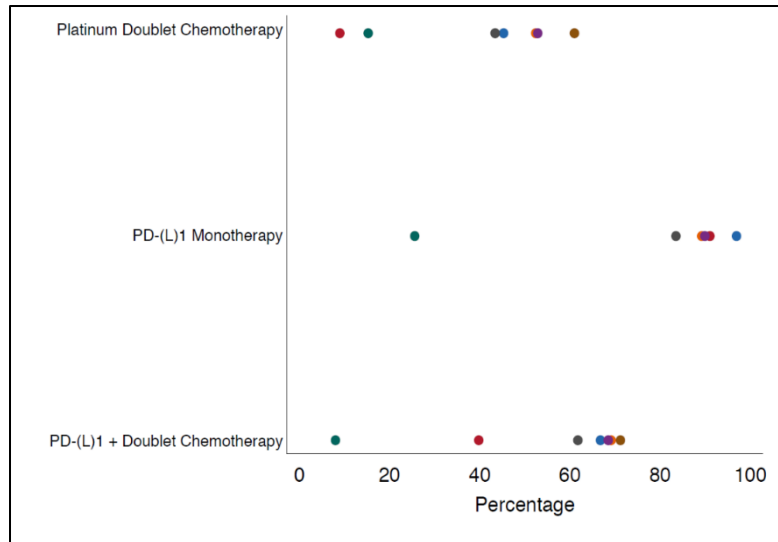
Graph 7. Histology of Patients with aNSCLC by Treatment Category



Graph 8. Group Stage of Patients with aNSCLC by Treatment Category⁵

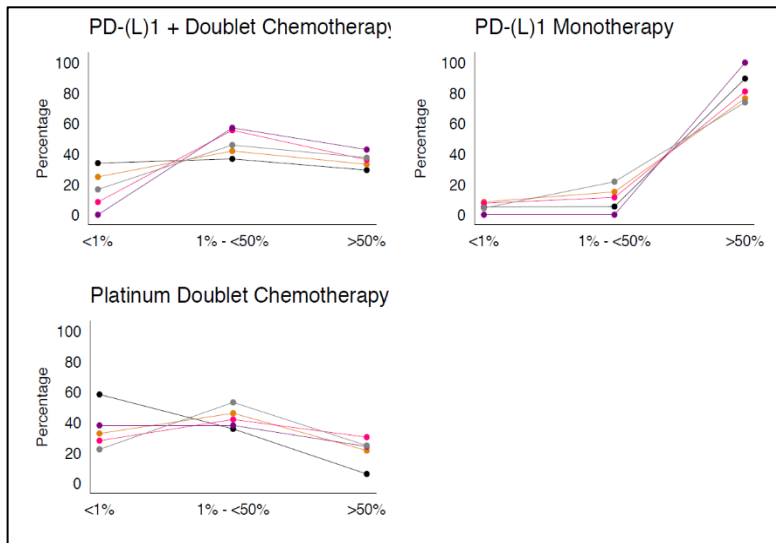


Graph 9. Percentage of PD-L1 Positive* aNSCLC Patients

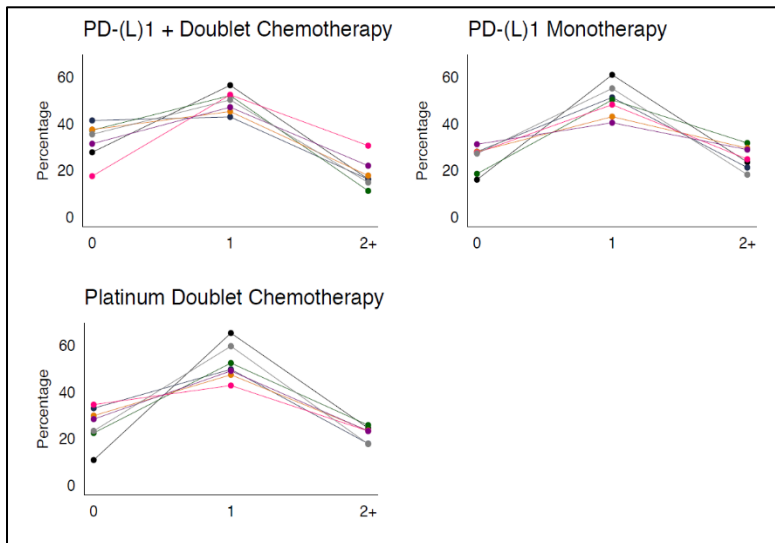


⁵ For patients where group stage was reported, patients with unknown group stage not included in percent calculations.

Graph 10. PD-(L)1 Staining of Patients with aNSCLC by Treatment Category^{6*}



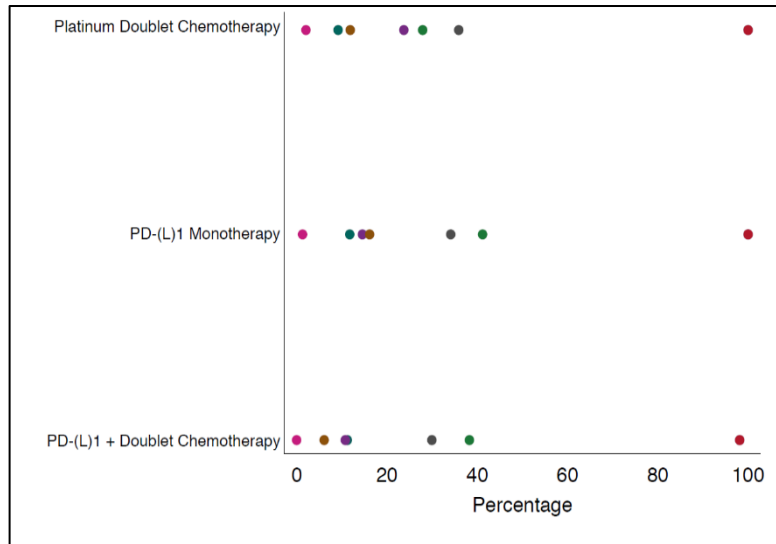
Graph 11. aNSCLC Patient Performance Status (ECOG) at Index⁷



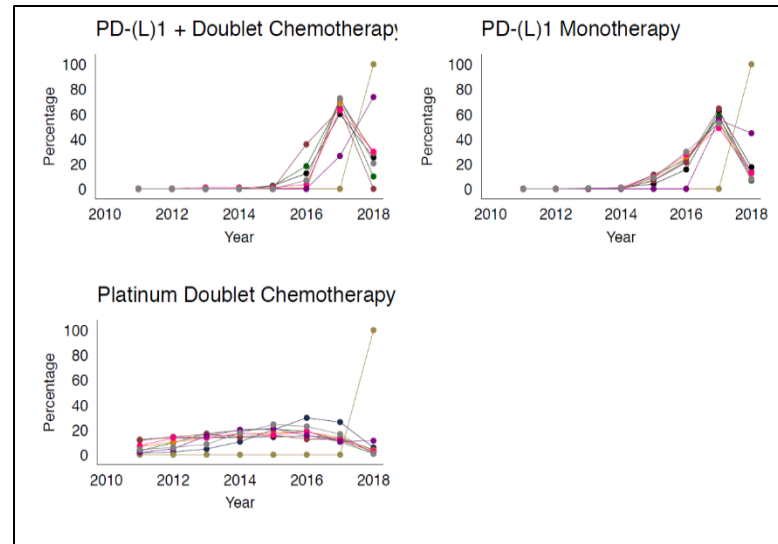
⁶ Among patients tested for PD-(L)1. Five (out of ten) data partners reported PD-(L)1 staining.

⁷ For patients where performance status was reported, patients with unknown performance status not included in percent calculation.

Graph 12. Percentage of aNSCLC Patients with Brain Metastasis at Index⁸



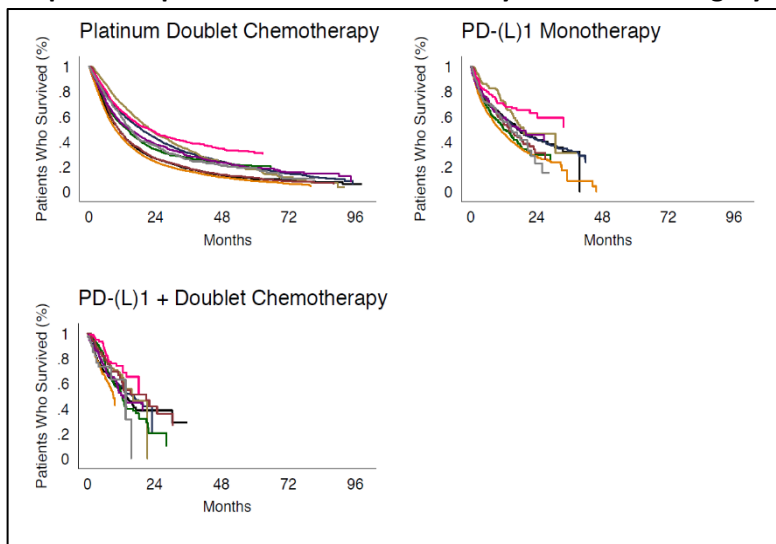
Graph 13. Year of Index Date by Treatment Category^{9*}



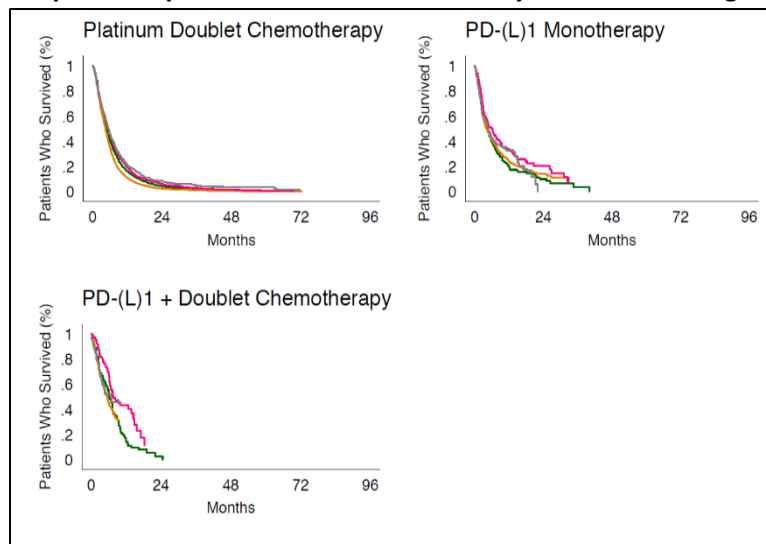
⁸ Based on structured ICD codes. For patients where brain metastasis was reported, patients with unknown group stage were not included in percent calculations except for one data set.

⁹ Study period of 2018 only included treatment and follow-up through March 31, 2018. Certain data reported in this document reflect this masking. See Assumptions and Limitations section for more explanation.

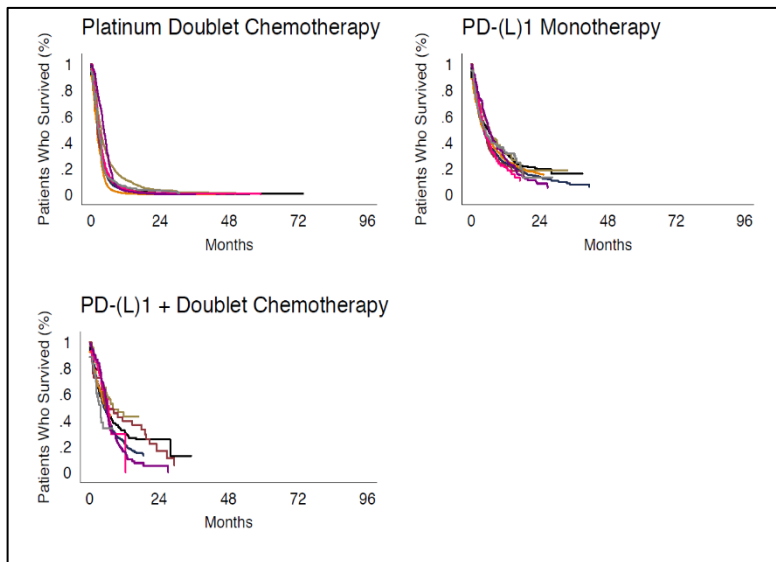
Graph 14. Kaplan-Meier Curve of rwOS by Treatment Category



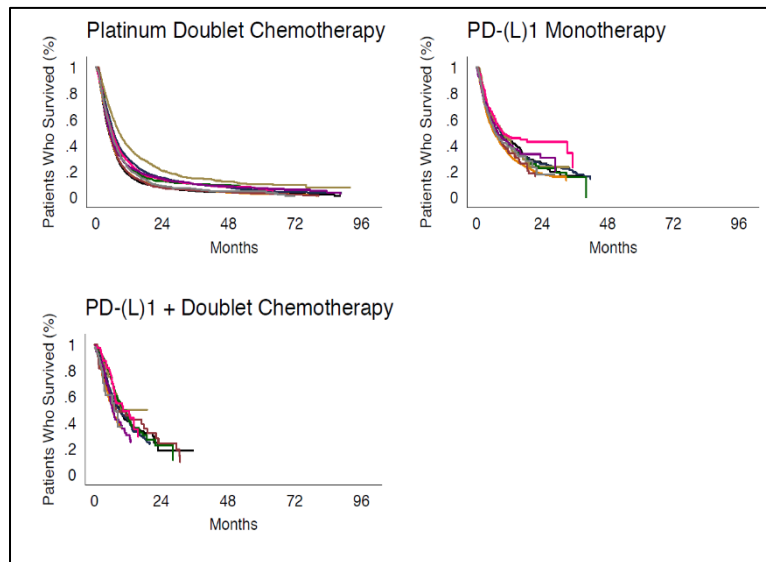
Graph 15. Kaplan-Meier Curve of rwPFS by Treatment Category



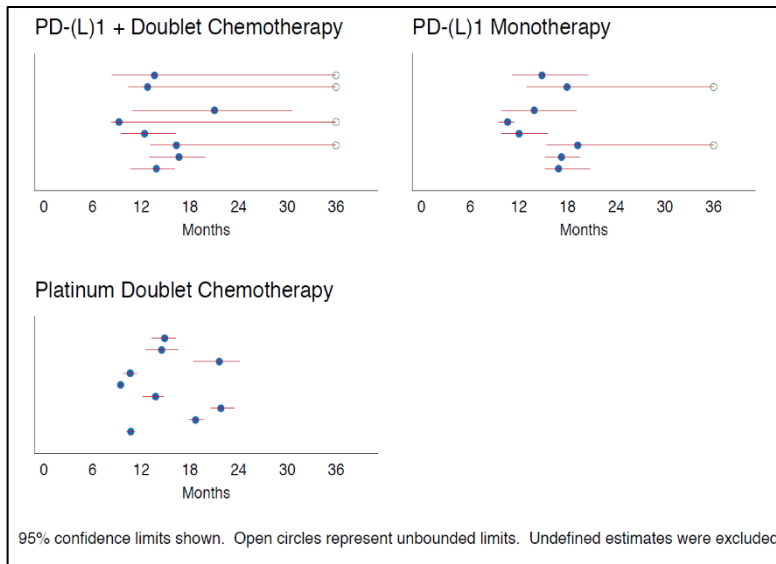
Graph 16. Kaplan-Meier Curve of rwTTD by Treatment Category



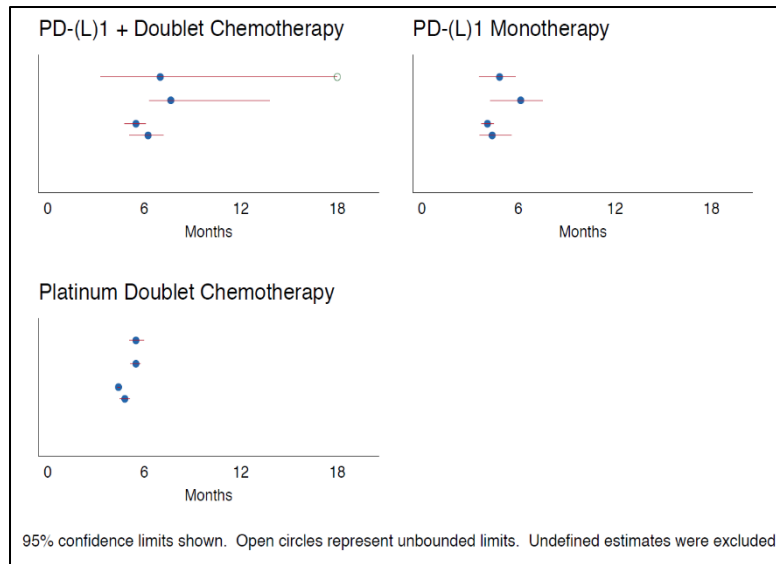
Graph 17. Kaplan-Meier Curve of rwTTNT by Treatment Category



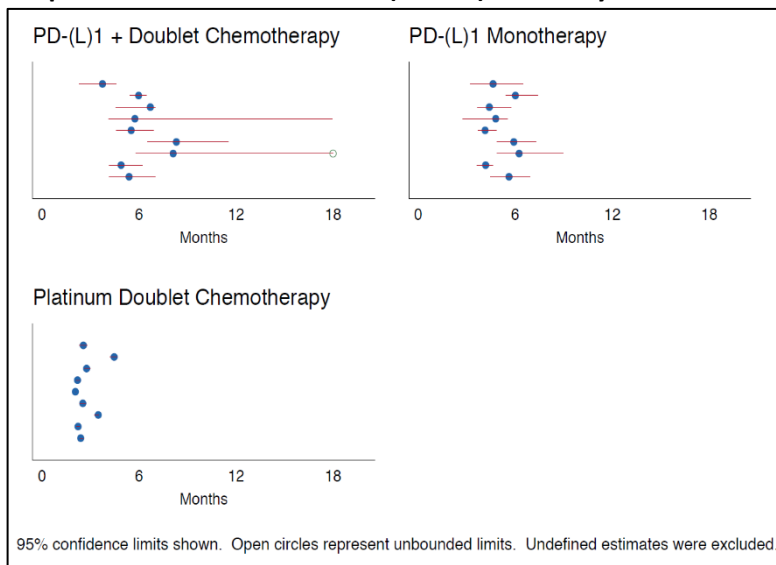
Graph 18. Estimates of Median (95% CI) rwOS by Treatment Category



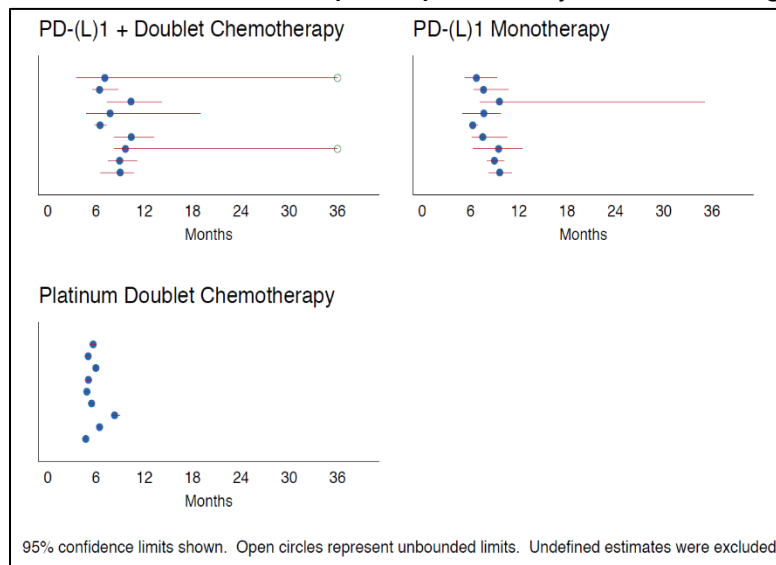
Graph 19. Estimates of Median (95% CI) rwPFS by Treatment Category



Graph 20. Estimates of Median (95% CI) rwTTD by Treatment Category



Graph 21. Estimates of Median (95% CI) rwTTNT by Treatment Category



Discussion

Conclusions from Pilot Project Study

1. It is possible to coordinate the efforts across numerous real-world oncology data organizations to reach high-level alignment on important data elements and definitions for real-world endpoints in the context of a focused research question. As part of this collaboration, there was a shared understanding of the important considerations to take into account when identifying aNSCLC patients treated with frontline therapy across diverse RWD sources.
2. The depth of data varied across data providers and distinct characteristics were identified among the cohorts provided by each organization, likely attributable to the characteristics of the data source and the underlying population it is capturing. These differences may influence the measurable outcomes observed.
3. The results of this phase of the pilot project highlighted the ability to show differences in important prognostic demographic as well as clinical characteristics between trial patients and heterogeneous real-world patient populations (e.g., median age, histology). It also demonstrated the ability to provide insight into recent trends in clinical care.

Assumptions and Limitations of Pilot Project Data Sets

- Preliminary findings are being presented today and subsequent analyses are planned.
- The observed unadjusted outcomes were evaluated in a broad set of patients with aNSCLC. In subsequent phases of the Pilot Project 2.0, it is important to apply relevant inclusion/exclusion criteria along with appropriate analytic methodologies to account for imbalances across critical prognostic variables.
- Discussions at the public meeting will also help identify additional action items.
- Interpretation of variable definitions may vary based on assumptions made in the conduct of analyses, even when using a common protocol and statistical analysis plan; a careful review and collaboration is needed to align on a consistent and reliable approach to be able to distinguish differences due to differences in the population characteristics, data source, and/or subtle differences in methodological assumptions made during the analyses.
- Granularity of certain variables within RWD may be limited because it is not always possible to distinguish between data that has not been captured in the data source versus data that is missing because the event never occurred.
- Cells with $\leq N$ patients (N ranges from 5 to 11 depending upon data source) were masked to maintain patient privacy in compliance with each data source internal policies. Certain data reported in this document reflect this masking (Graphs 5 and 13).
- Verifying and determining date of death may also prove challenging. Although discharge status and some diagnosis codes may be a source of mortality information, it is often incomplete. Some data partners rely on external linkages, such as to the public Social Security Administration death master file (DMF), but the public DMF has been shown to under identify deaths

highlighting the need to understand the underlying quality of specific data elements¹⁰. Other data partners linked to additional data sources (linking EMR with billing and pharmacy claims) to apply a mortality algorithm and reduce potential loss to follow-up and confirm mortality/survival status.

- For claims-based data, some patients with advanced disease may enroll in clinical trials and some or all the care received in a clinical trial setting may not generate insurance claims, thus, data for these patients may not be fully captured or captured at all.
- Provider data (EHR) may not identify all chemotherapy as patients may seek care inside and outside a provider group that contributes to the EHR data (e.g., chemotherapy at an academic center then move to a community setting). This may or may not be a source of missing information in the aNSCLC setting. Some data partners linked EHR data with billing data to minimize this risk and improve capture of care outside of the clinic setting.
- Ability to distinguish proportion of different therapies used within each treatment group will impact outcomes observed in RWD.

Discussion Questions

These questions may help guide the discussion during the meeting:

1. Are there processes to handle challenges associated with the availability and consistency of data across provider types and settings?
2. How to overcome difficulties associated with inherent biases within RWE?
3. What opportunities or incentives exist to help improve the format, quality, and validity of RWE?
4. Are there lessons from clinical trials, or registration trials, that need to be considered for RWD?
5. Can extractable endpoints from clinical trial “eligible” patients within EHR and claims databases be used to inform an internal assessment or sensitivity analysis of RWE?
6. What opportunities exist for FDA decision-making to be supported by RWE?
7. What opportunities exist to expand to other endpoints such as patient reported outcomes (PROs) and patient-generated health data?

¹⁰ Jones B, V. D. (2015, March). Measuring Mortality Information in Clinical Data Warehouses. AMIA Jt Summits Transl Sci Proc, 450-5