



U.S. Food and Drug Administration  
and Project Data Sphere  
Symposium VI



Small Cell Lung Cancer (SCLC) “External Control Arm”:  
A Paradigm Shift in Cancer Drug Evaluation/Registration

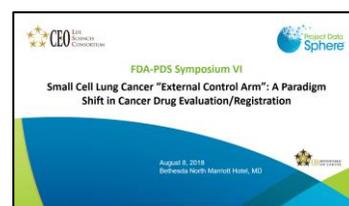
Summary Report

More than 60 oncologists, data scientists, pharma/biotech industry leaders, patient advocates, health science research investigators, and regulators representing myriad esteemed institutions convened in Bethesda, Md., on August 8 for *Project Data Sphere, LLC's (PDS)* sixth symposium co-sponsored with the U.S. Food and Drug Administration (FDA). With the goal of accelerating new options for small cell lung cancer patients (SCLC) in a stagnant treatment landscape, *PDS* is collaborating with the FDA on the development of an external control arm for SCLC clinical trials. This would enable patients to be enrolled directly into a trial's new drug investigational arm, which ultimately would reduce the number of patients per trial as well as the cost and time of discovery for new treatment options. The daylong event featured a combination of individual and panel presentations and lively discussions that are summarized below.

Represented institutions included:

- Amgen
- Asana BioSciences
- AstraZeneca
- Bristol-Myers Squibb
- Center for Medicare Services
- CEO Roundtable on Cancer
- Columbia University Medical Center
- Cota Healthcare
- Dana-Farber Cancer Institute
- Eli Lilly and Co.
- EMD Serono
- Genentech
- Hogan Lovells US LLP
- In-Q-Tel
- IQVIA
- Janssen Research & Development LLC
- Life Sciences Consortium
- Loxo Oncology
- LUNGeVity Foundation
- Massachusetts General Hospital
- MD Anderson Cancer Center
- Merck & Co., Inc.
- National Cancer Institute, NIH
- Novartis
- Pfizer, Inc.
- R Simon Consulting
- The Leukemia & Lymphoma Society

**SESSION 1:** Leading off the day, Mace Rothenberg, MD (Pfizer, Inc. and co-chair of the *Life Sciences Consortium*) provided an overview of the previous five symposia. These events are a collaboration between *Project Data Sphere, LLC* and the FDA's Oncology Center of Excellence; this “special elixir” allows FDA and *PDS* to collaborate toward shared goals. Dr. Rothenberg outlined two major categories of *PDS'* focus: establishment/growth of its data platform (which now hosts data from 130,000 patients; is used by more than 1,900 researchers; and has had more than 12,000 downloads of data) and convergence science programs – using big data analytics to address key areas in cancer treatment and care. He talked about *PDS'* four research programs: Immuno-Related Adverse Events; Rare Cancer Tumor Registries; Imaging and Algorithms; and the External Control Arm, which is being developed in concert with the FDA and for which SCLC is serving as a testing ground.



[Presentation link](#)

**SESSION 2:** In a morning keynote address, Paul Howard, PhD (FDA) prefaced his talk by stating that the forthcoming represented his opinions and not necessarily those of the FDA. A primary challenge for oncology research today, he said, is to find ways to make evidence generation nimbler while keeping the cost of it sustainable. “Everyone thinks of data as the new gold,” he argued, “but I disagree.” Instead, Howard suggested that

oil is a more appropriate metaphor for patient data, because it comes to us in crude form and must be processed before we can use it. The means by which it is processed determines its value and suitability for use. He went on to champion the benefits of building federated systems to collect, curate, and share data by aligning them with historically successful scaled infrastructures such as the interstate highway system and the internet, both designed for the public good.

Dr. Howard said that trust is paramount in a system in which the cost of cancer care creates financial toxicity for many patients. Clinical trials are the most powerful tool for determining the safety and efficacy of new products, but we need nimbler, more efficient trials, he said. Patients expect that their experiences will help the patients who follow them, but too much of that data is shelved or siloed. *PDS* encourages data sharing to support the development of pre-competitive science tools to reduce death and suffering from cancer, modernize clinical trial designs, and expand trial access to more patients who may not be able or eligible to participate in trials today.

**SESSION 3:** During introductory remarks on behalf of *PDS*, President Bill Louv, PhD, noted a historically unique moment of alignment between the FDA, pharmaceutical industry, and academia around the innovative use of data to improve outcomes for cancer patients. He summarized his vision for the near term, which includes continuous investment in the *PDS* platform, federation with other data-sharing platforms, and the in-development external control arm featuring in the approval of cancer therapies. With regard to the present, Louv cautioned against drowning in a “sea of opportunity.” During the next 12 months, he said, *PDS* will focus on “4 plus 2”: four program areas, crowdsource challenges, and improving the usability of the data sharing platform.

**SESSION 4:** During introductory remarks on behalf of the FDA, Sean Khozin, MD, MPH, warned that we are nearing the limits of biomedical reductionism and that we need a more holistic approach to oncology regulatory science. We are dealing with a certain level of complexity in drug development, and it is no longer sufficient to have a reductionist view of disease and patient health status. We need to shift from a linear view of drug development to a more systems-based view; this includes losing the arbitrary separation between research and clinical care. Dr. Khozin also talked about the importance of perspective; it is everything when looking at data, he said. At the end of the day, it’s about enhancing our perspective and bringing data to supplement/guide clinical judgement.



[Presentation link](#)

**SESSION 5:** Brian Alexander, MD (Harvard/Dana-Farber) moderated a panel discussion on **Best Methods for Developing an External Control Arm**. Individual presentations during this session included:

*Yuan-Li Shen, PhD, Biostatistician with the FDA (No slides provided)*

Key points:

- Trials involved historical controls only reserved for special circumstances:
  - Disease with high and predictable mortality
  - The effect of the drug is self-evident and /or large
  - Rare disease
- If a historical control arm is used to support a submission, adequate data based on pre-determined patient selection criteria and pre-specified statistical analysis plans are required.

Kathryn Lang, MBBS, MRCP, Global Medical Strategy Head of Data Science, Pfizer (No slides provided)

Key points:

- External control arms constructed from previous studies will be possible up to a point, but the rapidity of change in standard of care means that new sources must be identified.
- Real-world evidence, collated and standardized in a controlled manner, could form the basis of external control data for areas of high unmet need, where populations are small and where standard of care is difficult to standardize globally.
- Data standards for real-world evidence submissions need to be formally communicated, and a growing industry around these initiatives needs regulatory oversight.
- We cannot forget data ownership and the interest of the citizen-scientist in being an active participant in the use of external control data.

Richard Simon, DSc, former director of the Biometric Research Program, National Cancer Institute (NCI)

Key points:

- When the treatment effect is small to moderate, you need a control arm that excludes small to moderate amounts of bias. This excludes use of registry or literature or electronic medical record (EMR) controls.
- There are many sophisticated methods for creating a matched control group for a study using a database of possible controls. The degree of sophistication of the method is no guarantee that the controls are valid. You need a database of clinical trial control groups to validate the method of creating an external control group. *PDS* could serve as a valuable resource for validating control group methods.
- Validation of a method for constructing an external control group means establishing that the inter-study variability in outcome for that group is small.
- The melanoma meta-analysis by Korn et al. is an excellent example of constructing and validating an external control group model.



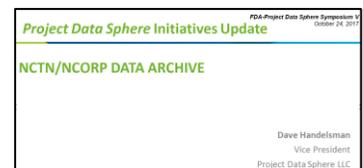
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**SESSION 6:** Dr. Alexander moderated a second panel discussion on **Key Considerations for Small Cell Lung Cancer.**

Ariel Lopez-Chavez, MD, Global Head, Oncology Strategic Innovations, Roche

Key points:

- The IMpower 133 phase I/III trial of Atezolizumab in combination with standard of care chemotherapy in the front-line treatment of extensive stage small cell lung cancer (ES-SCLC) met its co-primary endpoints of progression free and overall survival.
- These results will potentially translate into a new standard of care regimen in the treatment of the patient population under study.
- The possibility of a new standard of care should be considered in the design of an external control arm in front line ES-SCLC.
- Additional challenges such as data recency, quality and completeness of data, differences in the underlying populations, and validation should be considered.



[Presentation Link](#)

Andrea Ferris, MBA, Chief Executive Officer, LUNgevity (No slides provided)

Key points:

- Up to 25,000 people die annually from SCLC. We must improve the effectiveness of clinical trials to help these patients.
- How many datasets are required to accurately represent the underlying disease state?
- How do we structure an EMR) database so we're capturing the appropriate data to be used for an external control arm?
- What do we do when the standard of care changes over time? Can the external control arm model be adaptive?
- What needs to happen to make an external control arm a standard of care globally?

Jennifer Christian, PharmD, MPH, PhD, FISPE, Vice President Clinical Evidence, Center for Advanced Evidence Generation, IQVIA

Key points:

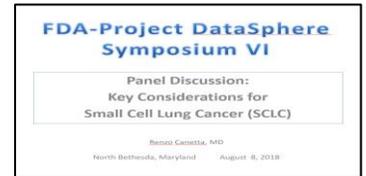
- Consider using the term external “comparator” rather than “control” given that many of the comparators are not placebos but rather active controls, on treatment or standard of care, from a randomized control trial (RCT, real world data, or patient registry. And there is far less ‘control’ than what would be assumed from an RCT.
- Separate external comparator methods from other approaches that provide benchmarks so that we can distinguish when a method is being used to control for differences between the retrospective clinical single-arm trial and the external comparator arm from other approaches that do not do any adjustments.
- Having comparator arms from RCT data and real-world data is likely to help answer important and possibly different questions.
- External comparators using RCT data may be considered under the following circumstances: an RCT is not possible because of very poor prognosis & unethical to randomize to a ‘no-treatment or placebo’ group; condition is low or rare; significant challenges in recruitment; and there is available, relevant trial data that is accessible to use.
- External comparators using real-world data may be used under those same circumstances but also considered when data from RCTs is limited or not accessible to re-use; RCT populations are not comparable or not appropriate for the scientific question under study; or standard of care has changed since the RCT was completed and there is a need for contemporaneous comparators.
- Consider a mosaic approach of data generation that allows one to answer a range of important patient-centric questions.
- The pilot project by Friends of Cancer Research in collaboration with several data partners is one example demonstrating how real-world endpoints correlate with RCT endpoints and could be a framework for future evaluations in other cancers and therapeutic areas.
- Further work is needed to determine which endpoints may need to be validated when used for regulatory decision-making.
- Early engagement with regulators is needed in a timely manner for agreement on evidence needs.



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Key points:

- Diseases with a long-established standard of care lend themselves to optimal utilization of large retrospective databases.
- Due to the rapidly evolving body of knowledge, it would still be necessary in most cases to adopt (even if small) a concomitant control group.
- It would be very important to link clinical databases to molecular databases.
- For SCLC, both Phase II and III could be amenable to utilize historical controls (with the above caveats), and lines of therapy (first, maintenance, second or more) could be studied.



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**SESSION 7:** “If not now, when?” was a question recalled by Martin J. Murphy, DMedSc, PhD, FASCO (*Project Data Sphere, LLC/CEO Roundtable on Cancer (CEORT)*) during a “fireside chat” between him and Dr. Howard. The appropriate time to share clinical trial data was an oft-asked question with the CEORT prior to the birth of *PDS*. Corporate lawyers told *CEORT* that the risks associated with data sharing were too great, that companies hold on to data as non-sharable, proprietary property. “We went to the FDA and said, ‘We know you have all the data and know, by law, you can’t share it. But would it be possible for us to research that data with you?’” Dr. Murphy also said it is prudent to keep at the forefront of our minds that smarter, more efficient trials will lead to lower costs.

Dr. Howard talked about the FDA’s mandate to “protect, preserve, and promote health,” with research being at the heart of that. With thanks to the patient community, he said, the relationship between patients and regulatory agencies has improved. The FDA is becoming more efficient in how it analyzes data. He delved into FDA Commissioner Scott Gottlieb’s vision for where the agency is with oncology, which has been echoed by Richard Pazdur, MD, Director of the FDA’s Oncology Center of Excellence. “Cancer is a rapidly fatal disease, with few options,” Howard said, adding that we need to find tools that don’t compromise standards, and we need to take advantage of new tools.

**SESSION 8:** In his afternoon keynote address, Jeff Abrams, MD (NCI) discussed key focus areas at NCI, including basic science, big data, workforce development, and clinical trials. Two recent big data projects that NCI has launched in the clinical arena are NCI Navigator and the National Clinical Trials Network (NCTN)/NCI Community Oncology Research Program (NCORP) Data Archive. NCI Navigator is an online site where qualified investigators can search for and access specimen collections from clinical treatment/prevention/cancer control trials with associated demographic and outcome data. The NCTN/NCORP Data Archive, meanwhile, is an online data repository of patient-level data from completed NCI treatment/prevention/cancer control Phase III trials. This controlled-access database is publicly available to qualified investigators, and it has partnered with *PDS* to make NCI’s publicly funded trials also available on the *PDS* site.



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**SESSION 9:** Dr. Murphy delivered a rousing call to action around *PDS*’ desire for data. “We need your datasets,” he urged attendees, “and we need your voice to get them.” He noted that skeptics had suggested that new SCLC treatments would obviate the need for the external control arm program, but the external comparator has value, he said – now and in the future. Dr. Murphy described *PDS*’ role as a “convener, collaborator, and catalyst.” Finally, he lauded all in attendance for what they were collectively accomplishing: “Cancer patients have a right to expect the very best from us,” he said. “Today, that’s what you have given. This has been a good day for patients.”

**SESSION 10:** Dr. Khozin led an open session in which attendees delved into discussion around what an external control arm will look like. “What is the outcome we are trying to achieve?” he asked. “What data do we need to achieve it? We can work our way backward from there.” There are opportunities to create new processes as we work our way backward, he noted, such as going straight to the mosaic of evidence. That would be bold and venturesome, he said, which is just what we need at this juncture to address challenges we have.

Select points of discussion:

- The standard of care may change. Is this a barrier to developing an external control arm? Would the external control arm need to be a “living, breathing repository” that is continually updated?
- Prognostic models are “a dime a dozen,” and don’t have a lot of impact. They are easy to develop but difficult to validate. Could validation of models be a unique role for *PDS*? Can the external control arm serve as a control and a mechanism for validation?
- Since most breakthroughs happen with a new biomarker, how do you use historical controls as a comparator arm if many breakthroughs are related to biomarkers not previously measured?
- Question on whether *PDS* SCLC trials are already curated. Most datasets are so fresh they are not curated. Dr. Murphy replied before asking Dr. Lopez-Chavez (Roche) if he could join in advising *PDS* on curation.
- Dynamic use of an external control arm during the early stage of drug development could be very successful. Can we, with 2,000 patients, be more precise and split patient groups in a finer fashion with a 3:1 or 4:1 ratio of patients, so if you do enroll a disproportionate number of patients not likely to respond, you can still salvage the results of the trial?
- Skepticism over an external control arm being used in Phase III. Can we prove this capability in Phase II? Patients would accept 2:1 or 3:1 in Phase III. If you have an equal chance of getting the control, why even be in the trial?
- Comment about the US-centric nature of the “standard of care.” Does a standard of care even exist? With precision medicine, most patients aren’t actually getting the same treatment for the same disease.
- You need an accurate control group if you’re expecting a small to moderate treatment effect.
- A first step may be to conduct an RCT with a traditional control arm and compare the results of the external control arm/comparator arm to the traditional. When the external control arm is validated in that way, the next RCT could use only the external control arm.
- Interesting crowdsourcing challenge: Look at prognostic indications of assays that normally wouldn’t be considered.