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SP411

\$2.1 BILLION IN VALUE. On April 20, TPG and AmerisourceBergen announced plans to acquire the OneOncology network from General Atlantic in a transaction valued at \$2.1 billion. It was one of a series of moves among oncology practice networks this spring, [SP411](#).



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FENDRICK

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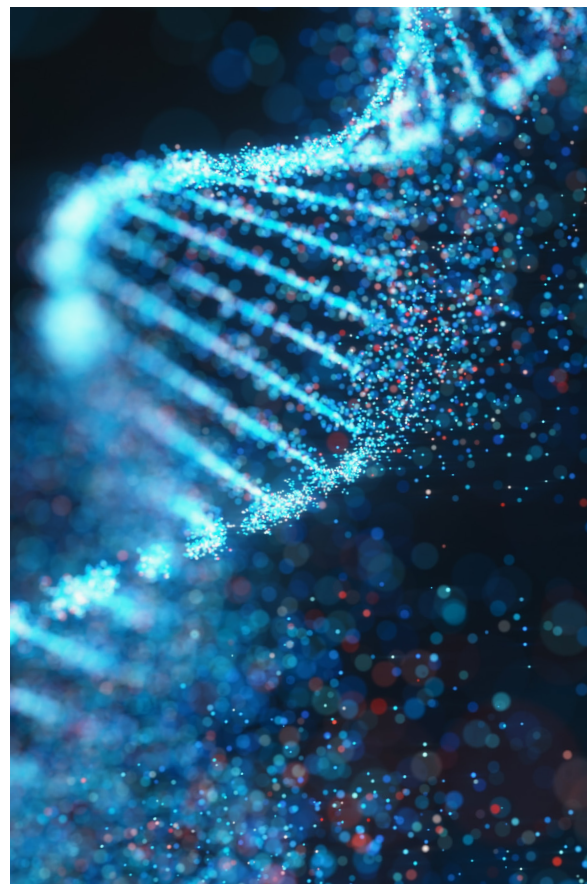
PRECISION MEDICINE

A Better Framework for Developing RWD to Support Tumor-Agnostic Targeted Therapies

Mary Caffrey

IN LATE MARCH, FDA converted its accelerated approval for pembrolizumab (Keytruda; Merck & Co) for certain patients with advanced microsatellite instability–high or mismatch repair–deficient solid tumors to a full approval, marking the latest advance for tumor-agnostic therapies.¹

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Treatments for therapies that target genetic mutations require studies involving patient groups that get smaller all the time. Real-world data offer investigators a solution.

PATIENT ACCESS

The Role of Automation in Meeting the Growing Demand for CAR T-Cell Therapies

John Tomtishen

WITH 6 APPROVED PRODUCTS currently on the market,¹ autologous chimeric antigen receptor (CAR) T-cell therapies have emerged as groundbreaking treatment options for patients with hematological malignancies. Once therapies of last resort, these treatments have demonstrated remarkable efficacy and durability compared with other options, and in some cases, have even been described as curative.² Although CAR T-cell therapies were initially approved for patients who had already undergone multiple lines of treatment, encouraging data that show cell therapies' sustained efficacy has led to a growing desire for them to be prescribed earlier in the treatment paradigm.³ In 2022, 2 such therapies were approved as second-line treatments.^{4,5} Considering the thousands of ongoing cell therapy clinical trials, it is likely that this trend will continue, with these therapies potentially becoming frontline treatments in the future.⁶ With many cancers the eligible patient population grows dramatically as treatments are approved for earlier lines of therapy—in some cases, an order-of-magnitude increase can be observed.^{7,8}

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THERAPEUTIC ADVANCES

Addressing Unmet Need: Could Children With Low-Grade Gliomas Have a New Treatment in Tovorafenib?

Mary Caffrey

BREATHKING ADVANCES IN CANCER CARE over the past 20 years have nonetheless left gaps, and a notable one is the need for more options for children with brain tumors. These young patients face hurdles at every turn. Even for adults, brain cancer is notoriously hard to treat; the blood-brain barrier that spares the brain and spinal cord injury from harmful agents also blocks most types of therapy. Depending on where the tumor sits, surgery can be a challenge, and radiation can damage surrounding tissue.¹

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The Role of Automation in Meeting the Growing Demand for CAR T-Cell Therapies

JOHN TOMTISHEN

CONTINUED FROM COVER

This increase in eligible patients runs counter to one of the biggest access challenges for these lifesaving treatments: current cell therapy manufacturing paradigms cannot meet patient demand. Patients with multiple myeloma are one of the hardest hit populations, due to viral vector shortages and limited production slots. These challenges can have deadly repercussions: data from a 2022 study showed that approximately 40% of patients with multiple myeloma had to wait a year to receive CAR T-cell therapy, and more than one-fourth of patients died while waiting for the treatment.⁹ It is estimated that 450,000 patients with cancer were eligible for CAR T-cell therapy treatment in 2019, and this number is only expected to rise, with an estimated 2 million eligible patients by 2029.¹⁰ In contrast, Cellares estimates that only 4,000 doses of CAR T-cell therapy were manufactured in 2021.¹¹

Currently, cell therapy manufacturing requires on the order of 50 manual processing steps per dose, totaling 80 or more hours of total “touch time.” Each step represents an opportunity for operator error or contamination, either of which can result in a failed batch.

Achieving the manufacturing throughput necessary to satisfy expected patient demand is dependent on several factors, including decreasing reliance on large, expensive manufacturing facilities; innovating parallel processing technologies; alleviating bottlenecks due to worker shortages and turnover; and reducing human-introduced errors. Addressing these factors holistically will allow the biopharmaceutical industry to ramp up cell therapy production while reducing the cost to manufacture these life-saving therapies. One emerging solution to tackle these roadblocks simultaneously is the implementation of automated cell therapy manufacturing technologies. Fully automated and closed, end-to-end cell therapy manufacturing solutions are poised to drastically reduce the size of manufacturing facilities, reduce the number of manufacturing operators, and enable organizations to scale up as manufacturing needs increase.

The reliance on very large cell therapy manufacturing facilities is one of the current bottlenecks restricting patient access to these life-saving therapies. Today, cell therapies are manufactured using manual processes accomplished by stringing together multiple instruments, each not originally conceived to support commercial scale manufacturing. The variety of required instruments, and the generally open nature of many of the cell therapy manufacturing processes, results in the need for massive facilities housing numerous expensive classified cleanrooms. For example, to manufacture only 4,500 doses per year, a cell therapy

manufacturer will require a facility of at least 200,000 sq ft in size, with upfront build-out costs greater than \$160 million for facilities and equipment.¹² Beyond construction, equipment, and lease expenses, there are additional, substantial costs associated with operating the classified cleanrooms required to accommodate the manual manufacturing of these therapies.¹³ These massive facility footprints and costs make it impossible to scale capacity to meet demand.

Decreasing space requirements while simultaneously devising techniques for parallel manufacturing represents a major opportunity for increasing patient access to these therapies. Several emerging technologies have the potential to disrupt current cell therapy manufacturing paradigms. These solutions are fully closed, end-to-end manufacturing platforms that support the manufacture of 10 or more cell therapies in parallel and have a footprint smaller than the space currently needed to manufacture a single dose. These technologies can increase manufacturing capacity by an order of magnitude or greater.

Complex manufacturing processes are another bottleneck to manufacturing cell therapy at scale. Currently, cell therapy manufacturing requires on the order of 50 manual processing steps per dose, totaling 80 or more hours of total “touch time”.^{14,15} Each step represents an opportunity for operator error or contamination, either of which can result in a failed batch. For the very sick patients awaiting these therapies, every day is critical. Physicians are often fighting to keep these patients alive until the therapy arrives. A failed batch means the patient will need to undergo another blood draw, but many patients won't live long enough for that. Implementation of a fully automated, closed manufacturing platform holds the potential for a 4-fold reduction in process failure rates by eliminating open transfer steps and limiting the number of steps requiring human intervention. This approach significantly reduces opportunities for operator error and improves the likelihood that the therapy will reach the patient in time.

Another contributing factor to the difficulty in scaling up manufacturing is an ongoing shortage of talent in the biopharmaceutical industry. It is estimated that in some regions of the United States, the demand for cell therapy manufacturing workers could grow by as much as 136% within the next decade.¹⁶ Commercial scale cell therapy manufacturing organizations are already struggling to staff the large teams of highly trained operators required for manufacturing today. Moreover, manufacturing operator roles have challenging work conditions, with operators working 12-hour shifts in full cleanroom suits. The difficult working conditions are contributing to high operator turnover rates of approximately 70% within 18 months. Restaffing these roles requires significant resource allocation toward recruiting and training, and may result in manufacturing downtime. Automation again holds the solution to help alleviate these challenges. It is estimated that by adopting a fully automated, closed cell therapy manufacturing solution, manufacturers can realize a reduction greater than 70% in required manufacturing headcount per drug product.¹⁴ An additional benefit with automation is the potential reallocation of the operator workforce to other value-added activities where their talents and skills can be better utilized. A valuable side effect of this redeployment of human resources may be the development of even more novel, life-saving treatments.



TOMTISHEN

John Tomtishen, vice president of operations, Cellares.

With the success of the first 6 approved cell therapies, the thousands of ongoing cell therapy clinical trials in progress, and the potential to cure intractable cancers and other diseases, it is no surprise that demand for CAR T-cell therapy has outpaced the supply of scalable manufacturing technologies.¹⁷ However, with the deployment of a fully automated, end-to-end manufacturing platform, it is likely that cell therapy manufacturing scales can be exponentially increased. The benefits of automated manufacturing also have the potential to significantly shrink the cost of production.¹⁸ By eliminating the need for cleanrooms, minimizing manufacturing footprints, decreasing the cost of wasted materials due to process errors, and reducing workforce requirements, cell therapy manufacturing costs can be reduced by more than 60%, increasing the availability of these therapeutics to patients in need.¹⁴ By shrinking the physical manufacturing footprint and eliminating manual manufacturing steps, enclosed automated systems can be distributed closer to apheresis sites, reducing the time and complexity of getting a dose to a patient, while also improving reproducibility and reducing process failure rates. This can be crucial for immunocompromised patients, who often struggle to produce enough healthy T cells as starting material for a dose.

In addition to these benefits, as automation technology continues to evolve and become an integral part of cell therapy development and manufacturing, the future potential benefits are wide reaching: improved patient outcomes, flexible manufacturing models, and adaptable technologies that can be applied to a variety of modalities are just a few examples. Automation is a net benefit to the industry, reducing the need for highly trained

personnel to spend long hours on the cleanroom floor in full personal protective equipment. Instead, it enables biopharmaceutical companies to leverage their ingenuity to keep the industry innovating and moving forward, rather than struggling to scale up manufacturing to meet patient demand. ♦

AUTHOR INFORMATION

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A Better Framework for Developing RWD to Support Tumor-Agnostic Targeted Therapies

MARY CAFFREY

CONTINUED FROM COVER

FDA broke new ground in 2017 when pembrolizumab, an immune checkpoint inhibitor, received the accelerated tumor-agnostic approval,² and it seemed the time had come for regulators to evaluate treatments based on their ability to target a given mutation, not just a specific tumor type. Since then, the number of tumor-agnostic approvals has increased (see **Table**).³ The first targeted therapy to receive a tumor-agnostic approval from FDA

was larotrectinib (Vitrakvi; Bayer), in 2018, to treat patients with solid tumors with *NTRK* gene fusions.⁴

Nonetheless, the path to approving targeted therapies in cancer based on changes they cause to a certain gene or protein has proved to be less than straightforward, and developing pathways and evidence to support this new concept remains a work in progress. In December 2018, FDA released its broad framework for the use of real-world evidence,⁵ but nearly 4 years passed between that

guidance and FDA's October 2022 draft guidance, "Tissue Agnostic Drug Development in Oncology."⁶

Regulatory approval is only one step—payer reimbursement is a different story. In a white paper published shortly before FDA's tissue-agnostic guidance,⁷ the research and data analytics organization IQVIA discussed the "assessment challenges" this new paradigm presents. "The factors that cause uncertainty in evidence packages for decision makers in these cases, primarily small

heterogeneous populations, are not typically an issue with tumor-specific drugs,” the authors state. “The situation requires a different framework for generating and evaluating evidence.”

A case study involving the targeted therapy entrectinib (Rozlytrek; Genentech), which, like larotrectinib, also disables proteins of mutated *NTRK* genes, served as a case study for the IQVIA authors, who examined challenges the drug faced with the European Medicines Agency. Entrectinib received FDA approval in 2019.⁸ Although the IQVIA paper was formally directed to a European audience, many of the same issues apply in the United States. The authors review lessons learned, which could inform regulators in the United States and Europe as they evaluate therapies for increasingly small populations.⁷

Use of real-world data (RWD) and development of real-world evidence (RWE), they argue, could significantly reduce the time and cost of such approvals, based on recommendations drawn from a panel IQVIA convened of oncologists, epidemiologists, RWD leaders, statisticians, and representatives from industry. The group identified several issues and challenges, including those that affect reimbursement⁷:

- If understanding of the natural history of the cancer is lacking, there may be uncertainty over a biomarker’s value.
- A typical trial would compare the study drug with standard of care (SOC); however, when looking across multiple tumor types, SOC may differ.
- When seeking reimbursement, more than one RWD source may be required “to understand the natural history as well as the prognostic value of these genomic alterations.”
- Investigators may need to develop new techniques to adjust for differences in patients evaluated based on RWD vs those enrolled in intent-to-treat trials, due to differences in access to care and timing of next-generation sequencing (NGS).
- Not every patient has access to NGS, yet its availability is critical to finding patients who should be studied and to making RWD generalizable for target populations.

The IQVIA authors foresee a need for flexibility from all stakeholders: from those designing real-world studies to reimbursement decision-makers evaluating evidence. A “paradigm shift” will be required, they write, that calls for academia, pharmaceutical companies, payers, and others to “collaborate more closely to develop a common framework for evidence generation.”⁷

To better understand these challenges, *Evidence-Based Oncology (EBO)* spoke with Emma Brinkley, innovation director of scientific services, IQVIA, and Laura Perez, principal real-world data scientist, Roche, who were among the coauthors of the IQVIA white paper. Brinkley, based in Raleigh, North Carolina, has worked on developing external comparators, using claims data, electronic health record data, and data generated by individuals. Perez, based in Basel, Switzerland, trained as an epidemiologist in the public health arena before coming to Roche. She, too, works on issues involving external controls, with a recent focus on targeted therapies.

This interview has been lightly edited for clarity.

EBO: Can each of you discuss the rise of tumor-agnostic therapies and why the use of RWE will be important in making these treatments available to diverse patient populations?

BRINKLEY: As a starting point, RWE can help you better understand the natural history of disease,

which is really critical to understanding who your true underlying population is. That’s where historically clinical trials have been focused on these large academic medical centers, and you’re often missing a large segment of the population. Once you understand what the true underlying population is, that’s where RWE can help you. You’re able to better come up with a plan to increase access to those patients—whether it’s going to different sites in your clinical trials, whether it’s using real world data—just to study them in an observational way.

That’s where, especially in clinical trials, there’s been a big push by IQVIA, Roche, and others to increase diversity and representativeness in clinical trials. But I think that’s where, starting at that top level, if you can understand who the population is,...the key [lies to] increasing access moving forward.

PEREZ: I agree with everything Emma said. But just to add [to] that, now that we are in the sphere of more targeted therapies, what we see is that the population available for trials gets smaller and smaller and smaller. And so, what we are facing when we design a trial, [and look at] the timelines and the reality of being able to enroll the patients, if you want to go into the trial in different tumors, [is that] it becomes almost unrealistic. Real-world data is needed to reach representativity in the trial.... It is linked absolutely with the natural history [of the disease], because if there are underlying characteristics of this population, you cannot grasp them anymore. You need to rely on these external sources.

EBO: As we understand who the population is, we know that the FDA came out several years ago with its framework for the use of RWE. There has been a lot of discussion about that framework and subsequent guidance from FDA. I’d like to hear from each of you how you see the term “framework” and what that involves. Is the use of the word framework around RWE broader than what was described by FDA?

PEREZ: The FDA framework [involves] everything. I will almost say that when we talk about the tumor-agnostic [therapies], it’s a bit of a subset; broadly, we talk about the FDA framework—of how it can help early design, it can help in postmarketing, with safety events. But in the tumor-agnostic area, what I see is the framework accompanying the whole trajectory of the drug, from very early [on] in the process to the discussions with the health authorities. »



BRINKLEY

Emma Brinkley,
innovation director of
scientific services, IQVIA.



PEREZ

Laura Perez, principal
real-world data scientist,
Roche.

TABLE. Tumor-Agnostic Cancer Therapies Approved by FDA³

PEMBROLIZUMAB, sold as Keytruda (Merck & Co). This immune checkpoint inhibitor has multiple tumor-specific approvals, but it has a tumor-agnostic approval—now final—for certain patients with advanced microsatellite instability–high or mismatch repair–deficient (dMMR) solid tumors.

LAROTRECTINIB, sold as Vitakvi (Bayer). This targeted therapy is used to treat certain tumors that are driven by mutations in the *NTRK* gene. The drug works by disabling proteins made by the abnormal genes; it is given when cancer has progressed despite other treatments or spread to distant parts of the body.

ENTRECTINIB, sold as Rozlytrek (Genentech). This targeted therapy also targets proteins in abnormal *NTRK* genes and is used in indications similar to those for larotrectinib; in addition, it can be used to treat patients with non–small cell lung cancer who have an abnormal *ROS1* gene.

DOSTARLIMAB, an immunotherapy sold as Jemperli (GlaxoSmithKline). A checkpoint inhibitor that targets PD-1 and might be an option for those patients with advanced or recurrent cancer if the cancer cells have a defect in a dMMR gene. It is used to treat patients whose cancer has progressed on all other options. It is also approved for advanced or recurrent endometrial cancer with dMMR.

DABRAFENIB, sold as Tafinlar, and **TRAMETINIB**, sold as Mekinist (Novartis). This combination hits a pair of targets: dabrafenib targets the BRAF protein, whereas trametinib targets the related MEK protein. Patients considered for this combination have a specific mutation, *BRAF* V600E, and their cancer has spread, cannot be treated with surgery, and has progressed on other therapies.

SELPERCATINIB, sold as Retevmo (Eli Lilly and Company). Useful in rare cancers with changes in the *RET* gene that cause formation of the RET protein. This targeted therapy can be used for patients with advanced cancer if they have a *RET* gene fusion.

Source: American Cancer Society

BRINKLEY: I completely agree. That was actually my perspective as well. The FDA guidance—and a lot of the guidance we’re seeing coming out—is, by design, quite broad; but they needed to apply [it] across these different-use cases, across therapeutic areas. And so I think what this paper has done, and what the working group did, was take the high-level guidelines, the high-level framework we’re seeing from FDA, and say, “OK, how do we apply this in the context of tumor-agnostic therapeutics?” How do you do that? There are specific considerations, right? If you’re going to group patients based on line of therapy, given the small sample sizes we see here, how do you do that? So I think this [paper] takes the more general guidance we’ve seen from FDA and others and focuses it and makes it specific to this area.

EBO: Who are the stakeholders that are most important to have at the table when we are thinking of RWE and developing it? Emma, would you like to start with this one?

BRINKLEY: Sure. In this context, certainly the sponsors and the payers are really key. Other stakeholders include academia; [for the IQVIA white paper] we spoke with different therapeutic area experts, other pharmaceutical companies, and the stakeholders themselves, and then specialties within each area. There’s epidemiology, biostatistics, and having clinicians at the table; that’s really important so you get those diverse perspectives. And that’s what I thought was so wonderful about this working group, [that] we brought a lot of those different voices together. There was a really rigorous debate, and I think that’s important.

The other piece that’s important is bringing in the voice of the patient. It’s something I’m really passionate about. I advocate with both my IQVIA hat and in my outside involvement with different rare disease organizations, and I think we are seeing increasing acceptance but also a push to incorporate patient-reported outcomes into research. What is the patient experience living with these conditions? What outcomes would be meaningful to them? How do they perceive benefit vs risk? I think that’s something that benefits the whole process.

PEREZ: From the methodological pathway, I would say “the usual suspects” that Emma mentioned, but the focus is different. We must include the different data owners and a way to consistently collect what is necessary—not each one collecting what they feel like but collecting data for the purpose of one’s own research or insurance. So there must be a common understanding that unless we collect in the same way, using the same variables, and that we need to answer the same questions, we will never be able to put this together. And so we cannot reach a level of representativeness in any source to really be meaningful. The data owners need to generate ICT [information and communication technology].... The payers need to participate because we should aim for changes in how we evaluate these drugs to get reimbursed.

As an example, it was very difficult with entrectinib to get reimbursement because there was no mechanism where we could say, “Let’s understand

the uncertainties now. And let’s plan some sort of data collection together with a trial. And in one year, let’s reevaluate if...this uncertainty [has diminished].” There was no pathway into that, to do pay for performance. So the payer is the other key stakeholder for me.

And in between, linking that, are the clinicians; they have knowledge of how these patients are treated. What are the important variables to look at? What is important for patients that can guide both the data collection path [and] also [that] of the reimbursement? And when we were working on our paper, the clinicians in the group were absolutely essential to bring us together, to define that it’s line of therapy and tumor types that are essential to know when we want to know something about patients.

EBO: What are the emerging issues in the tumor-agnostic therapy discussion, where the data being discussed will be especially important in speaking to payers—similar to the example mentioned that is highlighted in the paper?

PEREZ: The starting point is to know...when we start with a drug, are we starting [something] completely new or do we already know something on some tumors? That should define you differentially on your pathway. For entrectinib, it was a very new alteration. Nobody knew anything about the drug. So the bar must be really high, which is totally understandable. But when you talk maybe 2 years from now, when you have not 3 tumors but...7 in your data set, you will know more.

If drugs have already worked in 1 or 2 data sets, the path toward a tumor-agnostic approval should be a bit easier. And here what we face is, there was always a fear—from both the health authorities and the industry—for us to deviate from saying we want to have a tumor-agnostic level, instead of thinking stage by stage. So it can be, we want 1 tumor, we clear 1 tumor; and then we clear another, and then we clear another one. And when you have 3 you can start thinking about a tumor-agnostic approval.

EBO: Emma, did you want to add anything?

BRINKLEY: I’ll just reiterate what Laura said: You mentioned this balance between deciding whether to try to go after the tumor-agnostic approval upfront or go tumor by tumor. Then, when there’s this larger totality of evidence, it might tip you into a tumor-agnostic label or approval.

EBO: Are there other unresolved regulatory questions, either at FDA or elsewhere, that you would like to discuss?

BRINKLEY: There is one piece related to this, which Laura spoke to, that involves the data source and the people who own the data. I think data governance and interoperability is a really key area. Building off what Laura mentioned, it’s one thing to have the data in the same format, but how do you get access to the data? How do you maintain patient privacy and data security while also maximizing the usability of the data? And that’s something we saw in the United States with the evidence accelerator,

which was led by the Reagan-Udall Foundation that was focused more on COVID-19.⁸ One of the phrases they used was, “How do you connect the pipes?” In addition to thinking about how do we spend our standardized data at the source, how do we better connect those pipes in a way that maintains patient privacy, maintains really high standards and data security, but also allows us to use these data in really meaningful ways that impact patient lives?

The other piece would be, there [are] certainly no perfect real-world data. There’s no perfect world evidence. And so I think the more examples we can get from FDA or from payers on what they will accept, the more it will give industry confidence in terms of how to move forward with these guidelines that they put in place.

EBO: Laura, do you have anything to add?

PEREZ: Yes, the interoperability of data sources in this area for safety will be super important. My understanding is that it’s probably in a way easier to do in the United States than in Europe, where we are different countries, with different regulations, compliance, et cetera. This is going to be very challenging in Europe. The other thing is, in working together from very early [on] with FDA or with other health authorities, to define a pathway early [on], instead of being reactive to what we are asked. We can’t bring in a single-arm trial, and have them say, “Oh, do you have all the data?” and *then* we look for the data.

In this field, there are so few patients around, I don’t think it can work like that. It has to be planned beforehand. And all the efficacy measures—all the measures that will make the drug be OK or not OK—...should be predefined. My wish is more new thinking about how we are going to come to that place in this field, to preemptively prepare everything, and not being reactive to what we see in a single-arm trial. ♦

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