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In This Issue

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Improving Quality Management: What's Needed to Make Actual Progress?

By James Miessler

Drastic changes in drug development mean quality management approaches are more critical than ever, with meaningful advancement hinging on cultural shifts, crossfunctional alignment and top-down approaches within organizations, as well as thoughtful, stakeholder-informed trial designs.

To cope with new methods ranging from decentralized/hybrid trials and real-world data (RWD) elements to larger IT infrastructures and data streaming directly from sites, clinical trials need to employ quality management tools, such as quality by design (QbD), risk-based monitoring (RBM) and risk-based quality management (RBQM), says Peter Stein, director of the FDA's Office of New Drugs.

"We aren't dealing with common chronic diseases to the same extent that we were; we're dealing more with rare diseases for which there's limited precedent," Stein said during a public meeting led jointly by the agency and the Duke Margolis Institute for Health Policy. "There's not a protocol that you can take off the shelf and say, 'this is how we're going to design this trial for this rare disease.'"

"We're looking at disease subtypes and other new platforms, different kinds of endpoints, different ways that patients interact with program development and the design of studies," he continued. "The environment has dramatically changed, and on top of that, the tools that we have to do work in developing the designs of studies and to implement studies have also changed."

In Stein's eyes, site feedback on trial protocols is absolutely essential to properly practicing QbD as part of quality management today. While it's also important to gather the patient point of view on trial designs, ensuring trials are actually feasible for sites and investigators is critical from a risk management perspective.

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The Patient Voice: How Boehringer Ingelheim Went All in on Using Patient Input

By James Miessler

Boehringer Ingelheim (BI) has done a full 180-degree turn on patient involvement in trial design in recent years, moving from virtually no patient input to incorporating patient feedback in nearly all of its protocols today. The German pharma giant elaborated on how it accomplished this during a session at the 2024 Summit for Clinical Ops Executives (SCOPE).

Prior to 2021, BI had incorporated patient feedback in only two trials, according to Kimberley Kallsen, head of global clinical development and operations, patient and site engagement. Since then, BI has transitioned to leveraging patient input in nearly two-thirds of its trials (64 percent) in 2022 and 88 percent in the first half of 2023.

How did the company achieve such a turnaround? It was a conscious, concerted effort to turn the utilization of patient feedback into a systematic process that brought hundreds of hands on deck, Kallsen explained. Many of its employees were eagerly waiting for such an initiative to take place across the company, she said.

"You would think there needs to be a lot of convincing [internally], but actually not. I think lots of the people working in clinops are really intrinsically motivated to be patient-centric. Most of them were just waiting for these processes," she said.

Looking back at their journey to prioritize patient centricity, Kallsen and her team identified nine essential developments that BI engaged in to boost its patient centricity efforts:

- Strong, ongoing support and communication from senior leadership. BI's human pharmaceutical business unit placed patient centricity

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Cracking the Talent Shortfall: Strategies for Delivering the Right Talent With an FSP Model

__Jason Tate__, talent strategy lead for PPD Functional Service Provider (FSP) Solutions, lays out multiple approaches to weathering clinical research workforce constraints through the use of FSPs.

The demand for clinical development professionals continues to outpace supply. To meet this challenge, organizations are increasingly turning to FSP models to outsource specific functions of clinical trials (e.g., clinical operations, pharmacovigilance, etc.). In a recent survey by the PPD clinical research business of Thermo Fisher Scientific, 41 percent of respondents reported increased use of FSP models compared to the full-service outsourcing (FSO) model's 29 percent growth. This demand surge for FSP professionals calls for bespoke recruitment strategies that combine the agility of an FSP with the deep internal talent pool that is the hallmark of an FSO arrangement.

When evaluating an FSP partner, look for these five characteristics.

1. **Take an internal-first approach, staffing client projects using existing staff.** Because staff sourced from an FSP partner's internal talent pool is already vetted and trained, they can be mobilized quickly to fill gaps. FSP partners with a large internal talent pool spanning functional areas and the globe — including emerging markets — are especially well-positioned to rapidly deploy swaths of qualified employees to new FSP engagements when and where you need them.
2. **Deploy ahead-of-the-curve recruitment strategies.** At times, your needs for expertise may be extremely specialized. Or they may be broad, involving different roles in multiple regions that could involve hundreds, perhaps thousands, of professionals. An FSP needs a mature global recruitment engine to continually identify and engage top-tier candidates.

   Finding top talent, including passive candidates not actively job searching, often takes a combination of recruitment methods centered around active recruiter-to-candidate outreach, from searching traditional platforms like LinkedIn and Indeed to leveraging data-driven programmatic solutions to streamline candidate targeting, ad distribution and screening. The effort also might involve, for example, the creation of proprietary searchable databases using a range of sources, combing job board historical data to identify experienced professionals who entered their profession years ago, and using employee referral programs to reveal high-caliber candidates who aren't on the open job market.
3. **Ensure skilled and experienced recruiters** are at the core of the FSP's recruitment strategy. Armed with the latest recruitment methodologies, technologies, databases and tools, they have clear messaging, bespoke approaches that fit unique requirements and a deep network. They know how to find those professionals with the expertise and insights that will move the needle for clients.
4. **Secure the right fit.** Success is about more than the quality of the person; it's about the quality of the match. The ideal FSP partner will collaborate with you to understand your needs and culture and the talent profile that will succeed within your team.
5. **Confirm rebadging expertise.** Some companies decide to transition groups of existing employees to an FSP partner to reduce headcount while retaining the same experienced, valued colleagues on their projects. Your FSP partner should have the rebadging knowledge and processes to ensure business continuity without negatively impacting programs. It takes a skilled, empathetic, crossfunctional team to assist with onboarding and role changes.

   The ongoing talent shortage demands innovative approaches to attract and retain skilled professionals. By prioritizing internal staff allocations, leveraging dedicated recruiters, applying sophisticated recruitment strategies and focusing on identifying the right fit for the client, FSP partners can help their clients achieve success.

Key Questions to Ask a Potential FSP Partner

1. Will you primarily staff my engagement with internal staff or rely on external hires?
2. Can you meet my timelines?

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Why Haven't We Solved Patient Recruitment?

***Tyler Bye**, director of site solutions and product strategy for WCG's Clinical Research Solutions, provides a high-level look at the perpetual struggle of recruiting participants and opportunities that are emerging as trials grow increasingly more complex.*

Patient recruitment costs were estimated at $9.4 billion and rising in 2022, according to a report by Roots Analysis, a pharma and biotech market research company. Although recruitment is often perceived as a challenge due in part to the associated costs, it is not itself a problem that needs solving, but rather a critical component at the heart of reaching a study's end goals. By the time a study reaches the active recruitment of participants, significant R&D investments and countless hours of researchers' valuable time have been made. Patient recruitment is a crucial step in clinical research that determines the success of a study and can often be the rate limiter.

Through study startup, thoughtful plans are laid out and assumptions are made about every aspect of the future course of the study. When it is time for first patient first visit (FPFV), real-world factors play into the overall study progress. Patient recruitment represents the results of all prior assumptions and actuality of the study. In the eyes of a patient, everything that comes before them may not be apparent. To industry professionals, reaching FPFV can be a daunting task with substantial work still to come.

In terms of broad strokes, we tend to think about participants falling into two buckets: internal (already patients of the site) and external (everyone else). Internal recruitment is truly working with the site's patients and converting them to participants. While these individuals can often be queried in an electronic medical record based on diagnosis, specific inclusion/exclusion criteria, biomarker and genetic requirements often require further evaluation. While sites have the benefit of established care, making the leap from patient to participant requires education and commitment from both the site and patient.

When thinking about recruiting from the external pool, this is where many different "top of the funnel" tactics come in to play. Study advertising can encompass numerous ways to bring a study opportunity to a participant: digital and social media; traditional broadcast mediums; outdoor and transportation (such as billboards and public transit ads); flyers and leaflets; patient advocacy groups; volunteer registries; and the list goes on.

Patient recruitment is the blend of logistics and operational execution, along with psychological and behavioral analysis to understand the participant profile(s). Sometimes we need a reminder that participants are not just an enrollment num-

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ICH E6(R3) Perceptions, Preparation to Be Discussed at AQC Summit

The upcoming Avoca Quality Consortium (AQC) Summit will play host to valuable insights on the most impactful changes clinical trials are going through today. Chief among those are survey findings about industry's awareness of ICH E6(R3) and the effect these revisions will have on trials.

Avoca's yearly industry survey began in January with a goal of gathering stakeholder thoughts on the changes put forward by ICH E6(R3), including preparedness for these changes. At the AQC Summit, attendees will see the results of this survey, learning more on how ready industry is for E6(R3) and where the biggest impacts are expected to be seen.

"The objective of the annual Avoca industry survey is to understand the awareness of the proposed E6(R3) changes and how these changes may impact clinical trial execution, including perceived challenges for sponsors, providers and sites," explains Karen Harvey, senior director of Avoca, a WCG company.

Following ICH E6(R3)'s release in May 2023, AQC gathered stakeholder feedback from its members and submitted comments to the FDA (*The CenterWatch Monthly*, Sept. 11, 2023).

Since then, the consortium has been busy guiding stakeholders on the proposed changes, walking through the draft guideline and explaining its considerable revisions, many of which are aimed at addressing growing trial complexity and digital elements (*The CenterWatch Monthly*, Aug. 1, 2023).

The AQC Summit will be held virtually on May 14-15. Learn more here.

Quality Management

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Trial risk assessment needs to begin on the ground floor, the site, Stein said, with sponsors thinking deeply at the protocol design stage about what is possible at the site level and what would clash with properly conducting the trial. Make it a standard practice to meet with investigators, ask them to review protocols and gather their feedback on what's expected of sites that take on your trials, he advised.

"If you don't understand what the site perspective is and also adjust the protocol where you can to ensure it is implementable, then I don't think you're really embracing QbD," Stein said.

Site networks can also help individual sites improve their quality efforts and augment sponsors' and CROs' initiatives, added Kelsie Pearson, supervisor of scientific and network partnerships at Seattle Children's Hospital. That network, established in 1998, started out by emphasizing standardization, quality and training at the site level beginning with patient care, made sure care was standardized amongst sites, then moved that approach into their trials.

"We collect metrics on our sites [and] we provide them back to them for quality improvement opportunities," Pearson said. "I think that really helps walk alongside the sponsor, so as they're doing their quality improvement and quality efforts and RBM efforts, that really can just translate right into a network that's also primed in those approaches as well."

From an organization perspective, it's essential to create a democratized process that brings everyone in an organization together across different functions and to define what "good" actually looks like for trial quality, said Michael Torok, vice president, global head of quality assurance programs at Roche/Genentech.

So is company leadership that drives the transition into a culture of quality, sets a tone and "give[s] permission that we're actually going to change the way we're working," he said" as employees begin using the right technology, thinking critically about quality and working crossfunctionally. Set that expectation and perhaps even incorporate aspects of quality management into performance goals, he advised.

> "There's an opportunity to just be very clear up front: here's what we're saying is worth protecting, here's how we've assessed the risk against that, here's our plan on how we're going to monitor and mitigate it. I think transparency is the mother of mitigation."
>
> -Michael Torok, vice president, global head of quality assurance programs, Roche/Genentech

Shifts to quality culture should aim for full internal alignment on language, vocabulary and basic learning, Torok believes, and there are tools to aid in this, such as risk assessment categorization tools, which Roche has found useful in reaching wide agreement on risks in clinical trials.

A centralized change management unit has also helped the company significantly in coordinating its quality management efforts and driving change across the enterprise.

"We don't want to just own it; we want to make sure we drive change across the functions so we have a group that actually drives that change," he said, "the learning, the training, the updating, pulling together the data so that we can mine it and actually trying to drive knowledge management towards continuous improvement."

"We want everyone to really own this and make it their way of working so that it's just natural," he continued. "Getting everyone around the table to agree on the risks and start to actually assess them and think about detectability, impact, likelihood — you start to see light bulbs ... come on in a crossfunctional way."

One day, Torok hopes that RBQM in clinical research can reach a point of full transparency that runs the gamut of quality management, including critical-to-quality elements, QbD, RBM, fast and effective issue management and the sharing of case studies, a point that industry may not fully be at yet. Openness on RBQM strategies could be achieved through inclusion in protocols or in other communications and could even support inspection readiness efforts, he says.

"I think there's an opportunity to just be very clear up front: here's what we're saying is worth protecting, here's how we've assessed the risk against that, here's our plan on how we're going to monitor and mitigate it," he said. "There's an opportunity to be more transparent about that. Pull that through to sites, to your CROs, your different development partners. I think transparency is the mother of mitigation."

Patient Input

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as its top guiding principle and made patient/site engagement on trial designs mandatory. In addition, BI developed a patient engagement playbook, clearly defined responsibilities and budget sources, and created two teams focused on driving implementation

- Setting an ambitious goal to be ranked number one by site staff/patient organizations and seen as a preferred sponsor by 2025
- Creating impact by forging early and long-term partnerships, truly listening and taking action. This effort included closely working with the company's patient engagement function; creating a panel of patients and physicians that spans the company's therapeutic areas and countries it works in to inform priorities and codevelop processes; identifying the main problems encountered by site staff and patients and prioritizing solutions; setting metrics to track if patient and site needs have been met; and creating experience surveys for all trials
- Spreading engagement responsibilities across 700-plus colleagues and adding these responsibilities to their job profiles and annual goals
- Increasing companywide visibility for the initiative by using empathy mapping, a team visualization tool, to tailor clear communication approaches by company role; raising awareness at key internal meetings and on BI's internal social media channels; designating patient engagement ambassadors and running internal campaigns; and focusing on patient engagement at large meetings with colleagues
- "Creating ownership" by motivating through direct patient interactions and patient testimonials, recognizing and rewarding early adopters, and understanding role-specific barriers to implementation, among other strategies
- Sharing case studies to dispel internal doubts and concerns about patient engagement
- Building knowledge and skills through continuous improvement of BI's patient engagement playbook, offering trial simulations for sites, conducting trainings and workshops, and other efforts
- Sharing the status of its patient engagement work through metrics, communications every six months and comparisons across therapeutic areas and products

There was some internal doubt about the value and practicality of consulting patients on trial designs before BI's patient engagement initiative got underway, Kallsen noted, a doubt she disagrees with.

"Before we started engaging with patients for trial design, one comment that I often heard [was], 'it's not realistic to discuss with patients a trial concept, we need to have the clinical trial protocol first,' or 'engaging with patients will always delay the trial.' It's not true," she said. "If you do it the right way, it's just not true."

So, what's next? With the lessons it has learned from these patient engagement efforts, Kallsen says BI is well-equipped to move forward on making meaningful impacts on clinical trial diversity, equity and inclusion (DE&I). As part of this, its DE&I strategy will center on working with communities and community leaders early in the clinical development process and building long-lasting partnerships founded in trust.

WCG Insights

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ber, but people. People are multifaceted, with varying values and motivations, and should not be defined only by their disease. Therefore, there is usually not just one modality or medium for recruitment that will be effective for any one study. Key planning requires thoughtful consideration of what method of outreach will most likely intersect with potential participants in their daily lives.

__Most patient recruitment tactics align to a U.S. audience, given that North America accounted for 51 percent of the global clinical trial market share in 2023, according to Vision Research Reports There is a need to realize that cultural and healthcare system differences require a thoughtful approach to recruitment. Where the U.S. is heavily conditioned to see direct-to-consumer pharmaceutical advertisements, the rest of the world may not respond to clinical trial advertisements (where allowed) the same way. A global media campaign will not yield the same performance in every country or region; the cultural perceptions of clinical research need to be taken into account when planning what efforts will be used to reach enrollment goals.

With so many different options to choose from, it can seem overwhelming to plan effective recruitment strategies. Keeping in mind that there is no singular cure-all for recruitment creates an opportunity for using various methods of recruitment. As the participant population becomes more specific, there will be an increased need to include multiple options to reach the desired audience. Setting expected benchmarks and variances for each method's return on investment allows for constant optimization of a campaign during its lifecycle. With recruitment representing real world study execu-

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tion, we also must acknowledge there are not unlimited resources. Whether financial, labor force, or ultimately time, whatever limitations are present need to be considered when preparing and executing a recruitment campaign.

In a traditional study, enrollment ultimately happens at the site. In cases where various tactics are in place, they need to be streamlined for sites to be able to process incoming participants effectively. Technology with central platforms can create a uniform process that can lead to efficiencies and consistent measurements across a study. With consistent advancements in tech and daily evolutions of AI-enabled solutions, it will be important to implement effective technology aligned to the recruitment strategies at hand.

The emphasis and need for successful patient recruitment is not going away anytime soon. As we drive into new areas of research, such as precision medicine, we will only see increased complexity. However, with new challenges, we also have new opportunities to find novel solutions and increase efficiency. Keeping in mind that patient recruitment isn't something that any one solution will solve allows us to focus on patient recruitment as a process of continuous improvement, ultimately refining efforts in to bring therapies to market more rapidly.

Viewpoint

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3. Can you provide examples of innovative recruitment methods you use to attract top talent?
4. What percentage of your hires comes from referrals?
5. Does your staff have the expertise/experience to apply the latest insights, approaches, and best practices to optimize my study?
6. Do you have the operational structure and footprint to scale resources when and where we need them?
7. How do you ensure FSP candidates will be a good cultural fit with my team?
8. When rebadging, what is your average transfer and retention success rate?

Access PPD's white paper on FSPs here.
Access the PPD survey here.

The opinions expressed here are those of the author and do not necessarily reflect the views of The CenterWatch Monthly.

Study Lead Opportunities

CenterWatch analyzes data in its drug intelligence database to provide advance notice of clinical trials expected to enter the next phase of clinical development soon. Contact information is provided for follow-up. **Sponsors/CROs:** to list an upcoming trial here, contact Leslie Ramsey, 703.538.7661, lramsey@wcgclinical.com.

Company name	Drug name	Indication
phase 1		
Ankyra Therapeutics	ANK-101	Solid tumors
Arvinas	ARV-102	Neurodegenerative diseases
Eilean Therapeutics	Balamenib	Relapsed/refractory acute myeloid leukemia
Kura Oncology	Ziftomenibplus gilteritinib	NPM1-mutant or KMT2A-rearranged acute myeloid leukemia
Kura Oncology	KO-2806 plus cabozantinib	Clear cell renal cell carcinoma
OnCusp Therapeutics	CUSP06	Platinum-refractory/resistant ovarian cancer and other advanced solid tumors
PassPort Technologies	Zolmitriptan PassPort	Migraine
Synnovation Therapeutics	SNV1521	Solid tumors
phase 1a/1b		
NextPoint Therapeutics	NPX887	Solid tumors expressing HHLA2/B7-H7
phase 1b		
atai Life Sciences	VLS-01	Treatment-resistant depression
phase 1b/2a		
Iterion Therapeutics	Tegavivint	Advanced hepatocellular carcinoma
phase 1/2		
Aleta Biotherapeutics	ALETA-001	Advanced B-cell malignancies
Innate Pharma	IPH6501	Relapse/refractory CD20-expressing B-cell non-Hodgkin's lymphoma
phase 1/2a		
Arrowhead Pharmaceuticals	ARO-DM1	Type 1 myotonic dystrophy

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Company name	Drug name	Indication
phase 1/2a continued		
Immuneering	IMM-1-104	First-line pancreatic ductal adenocarcinoma
phase 1/2/3		
Grace Science	GS-100	NGLY1 Deficiency
phase 2		
Asklepios BioPharmaceutical Bayer	AB-1002 gene therapy	Congestive heart failure
Bayer	BAY3018250	Deep vein thrombosis
Cardiff Oncology	CRDF-004	RAS-mutated metastatic colorectal cancer
Dianthus Therapeutics	DNTH103	Generalized Myasthenia Gravis
Halia Therapeutics	HT-6184	Inflammation and pain following tooth extraction
ReAlta Life Sciences	RLS-0071	Acute exacerbations of chronic obstructive pulmonary disease
Regor Therapeutics Group	RGT-075	Obese or overweight adults with weight-related comorbidities
Supernus Pharmaceuticals	SPN-820	Treatment-resistant depression
phase 2a		
NorthSea Therapeutics	Orziloben (NST-6179)	Intestinal failure-associated liver disease
phase 3		
89bio	Pegozafermin	Metabolic dysfunction-associated steatohepatitis
Akeso	Cadonilimab plus chemotherapy	First-line PD-L1 negative non-small cell lung cancer
AstraZeneca	Breztri Aerosphere (budesonide/ glycopyrronium/formoterol fumarate)	Chronic obstructive pulmonary disease
CG Oncology	Cretostimogene	Intermediate-risk Non-Muscle Invasive Bladder Cancer
NewAmsterdam Pharma	Obicetrapib and ezetimibe	Adults with Heterozygous Familial Hypercholesterolemia and/or Atherosclerotic Cardiovascular Disease
Nielsen BioSciences	CANDIN	Verruca vulgaris (common warts) in adolescents and adults

FDA Actions

The following is a sampling of FDA regulatory actions taken during the previous month, compiled from CenterWatch and third-party sources, including the FDA and company press releases. For more information on FDA approvals, visit centerwatch.com/fda-approved-drugs.

Company name	Drug name	Indication	FDA action
Aprea Therapeutics	APR-1051	Cyclin E overexpressing cancers	IND approved
ARTHEx Biotech	ATX-01	Myotonic dystrophy type 1	IND approved
Atara Biotherapeutics	ATA3219	Lupus nephritis	IND approved
Cantargia	Nadunolimab	First-line pancreatic cancer	IND approved
Cullinan Oncology	CLN-619	Relapsed/refractory multiple myeloma	IND approved
Immunofoco	IMC001	EpCAM-positive advanced gastrointestinal tumors	IND approved
Jacobio Pharma	JAB-30300	Advanced solid tumors	IND approved
Kurome Therapeutics	KME-0584	Advanced acute myeloid leukemia and high-risk myelodysplastic syndromes	IND approved
	IND approved	EGFR inhibitor-induced acneiform rash	IND approved
Lipella Pharmaceuticals	LP-410	Oral graft-versus-host disease	IND approved
PhotonPharma	Innocell	Stage III/IV ovarian cancer	IND approved
Allecra Therapeutics	Exblifep (cefepime/enmetazobactam)	Complicated urinary tract infections	Approved
Hugel America	Letybo (letibotulinumtoxinA-wlbg)	Moderate-to-severe frown lines	Approved
Iovance Therapeutics	Amtagvi (lifileucel)	Advanced melanoma	Approved
J&J	Rybrevant (amivantamab-vmjw)	First-line locally advanced or metastatic non-small cell lung cancer with EGFR exon 20 insertion mutations	Approved
AstraZeneca	Tagrisso (osimertinib) plus chemotherapy	EGFR-mutated non-small cell lung cancer	Approved for new regimen
J&J	Tecvayli (teclistamab-cqyv)	Advanced multiple myeloma	Approved for new regimen
Genentech	Xolair (omalizumab)	Reduction of allergic reactions following accidental exposure to one or more foods in people one and older	Approved for new indication
Mirum Pharmaceuticals	Livmarli (maralixibat) oral solution	Cholestatic pruritus in patients five and older with progressive familial intrahepatic cholestasis	Approved for new indication
Novo Nordisk	Wegovy (semaglutide)	Reducing risks of cardiovascular death, heart attack and stroke in obese/overweight adults with cardiovascular disease	Approved for new indication
Gilead Sciences	Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide)	HIV patients with suppressed viral loads and known or suspected M184V/I resistance	Approved for expanded indication
Regeneron Pharmaceuticals	Praluent (alirocumab)	Pediatric patients eight and older with heterozygous familial hypercholesterolemia	Approved for expanded indication
Bristol Myers Squibb	Opdivo (nivolumab) plus cisplatin and gemcitabine	First-line unresectable or metastatic urothelial carcinoma	Approved for expanded indication and regimen