Do-Youn Oh – Professor, Division of Medical Oncology, Department of Internal Medicine, Seoul National University Hospital

Seeing TOPAZ-1 succeed and genuinely change the standard of care for first-line biliary tract cancer showed me just how much impact this kind of work can have

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Professor Do-Youn Oh discusses advances in gastrointestinal oncology, reflecting on the practice-changing TOPAZ-1 trial, Korea's strengths in clinical research, and the importance of biomarker-driven therapies. She shares her approach to investigator-led drug development, industry collaboration, and translational research, while outlining emerging opportunities in ADCs, immunotherapy, AI, and multi-omics to improve outcomes for patients with gastric, pancreatic, and biliary tract cancers.

Could you introduce yourself to our international readers, along with the key milestones of your career?

I am based at Seoul National University Hospital, where my clinical focus includes gastric cancer, pancreatic cancer and biliary tract cancer, alongside new drug development, particularly Phase I studies. I also run my own laboratory, covering preclinical research, translational research and a broad range of clinical trials spanning first-in-human through to Phase III. My research purpose has always been simple: to deliver genuinely good outcomes for the patient in front of me. That patient’s situation is often urgent and dire, and as their treating physician, I feel that weight directly, alongside their families, in every conversation about the devastating nature of their

condition and the sheer scale of unmet need for new treatment options, delivered with the right approach at the right time.

That is why my preclinical work is never simply research for its own sake; it exists specifically to generate the evidence needed to advance a new compound or treatment strategy into clinical development. I collaborate with a number of large pharmaceutical companies and biotechs around promising new compounds and intellectual property, testing that IP within my own gastric, pancreatic and biliary tract cancer preclinical systems to generate new hypotheses. Where the data supports it, I propose an investigator-sponsored, hypothesis-generating clinical trial to the company, and in the best outcomes, those findings have gone on to inform a large pharmaceutical company's registration trial. So my research sits at the intersection of these two roles: actively engaging with industry to help guide drug development strategy and direction, while also testing new intellectual property directly in my own laboratory.

Korea has a notably high incidence of gastric cancer. From your clinical experience, what genetic or environmental factors help explain that prevalence?

Korea and Japan are well known as the countries with the highest incidence of gastric cancer, yet also among the countries with the lowest mortality from it. One reason is Korea's nationwide screening programme, which offers biennial endoscopic evaluation to everyone over the age of 40. That screening system enables early detection, which in turn drives generally good overall survival and prognosis. The high mortality-to-incidence gap is really a detection story, but the underlying incidence itself remains genuinely high. Historically, this was largely attributed to high rates of H. pylori infection, and while that infection rate has been declining, gastric cancer remains among the most common cancers worldwide.

Biliary tract cancer presents an interesting contrast. It is considered relatively rare from a US or European perspective, with an incidence of around two per 100,000 population in the US, whereas in Korea the incidence sits at around 10 to 12 per 100,000, making it a comparatively rare cancer globally but a far more prevalent one specifically within Korea. Pancreatic cancer, my other area of focus, shows a broadly similar incidence rate, though I recently came across an interesting summary showing a marked global rise in pancreatic cancer incidence and mortality over the past 30 years, with Asia specifically showing a rapid increase. There is also striking data showing notably high pancreatic cancer mortality among Korean women. Once you adjust for age, given that Korea and Japan are both relatively aged societies with a naturally higher underlying cancer

incidence, pancreatic cancer incidence remains genuinely high in both countries even after that adjustment.

From my own vantage point across these three cancers, gastric cancer incidence in Korea ranks among the highest globally, biliary tract cancer is unusually prevalent here specifically, and pancreatic cancer incidence is also notably high, all representing areas of genuinely high unmet medical need.

Given the success of the screening programme for early-stage gastric cancer, what do you see as the key bottlenecks in treating advanced or metastatic disease today?

That is precisely where the real challenge remains. Those patients are, for the most part, not curable, though recent progress in new therapeutic targets and drugs has genuinely extended median overall survival for metastatic gastric cancer patients, which is real and welcome progress. That said, unmet need clearly persists. The core bottleneck is that we still need to identify new therapeutic targets. We currently have several, including HER2, Claudin 18.2, MSI and PD-L1, but not many beyond that, so the priority is identifying further targets and then developing the right matching therapy for each one. Ultimately, our shared goal across the field is a genuinely biomarker-driven strategy, one precise enough to identify exactly which patients will truly benefit from a given drug.

You led the TOPAZ-1 trial, which helped establish a new standard of care in biliary tract cancer. What were the biggest hurdles, and why was the study so significant?

When discussing new drug development with pharmaceutical partners, most already have strong interest in gastric cancer generally, and Asian and Korean gastric cancer specifically, along with hepatocellular carcinoma linked to hepatitis B and C, given how well studied these high-incidence areas already are. Biliary tract cancer is different; most partners simply do not know a great deal about the disease itself, since it remains relatively under-recognised globally. That lack of awareness within the global pharmaceutical industry means biliary tract cancer patients have historically had far fewer opportunities for new drug development, since whenever a company has a promising new compound, it is typically tested first in major tumour types such as lung, breast and colorectal cancer, followed by gastric and urothelial cancers, leaving biliary tract cancer consistently underrepresented.

So my first real challenge was simply raising awareness of biliary tract cancer itself. The second was persuading a large pharmaceutical partner that rapid, well-designed drug development was genuinely achievable in this space. Both required a case built entirely on scientific rationale, not enthusiasm alone, which is exactly why I ran the relevant compound through my own preclinical laboratory first, generating evidence to make that case credibly.

Back in 2015, when I first approached AstraZeneca with the idea for an investigator-sponsored trial testing chemotherapy combined with a PD-L1 checkpoint inhibitor as first-line treatment for biliary tract cancer, my underlying idea was fairly simple. At that time, nearly a decade ago, researchers across lung, breast and melanoma were already assuming that combining cytotoxic chemotherapy with immune checkpoint inhibition made sense, on the basis that cytotoxic agents induce immunogenic cell death. Yet I noticed there was no solid evidence actually demonstrating that cytotoxic agents produced meaningful immunogenic cell death in this specific context; it was largely assumed rather than shown. So my proposal to AstraZeneca was to first generate the evidence that our chemotherapy regimen genuinely induced immunogenic cell death, and only then add the checkpoint inhibitor to boost that anti-tumour activity. They accepted that rationale and supported the trial with durvalumab and tremelimumab. We ran that investigator-sponsored Phase II trial with an originally very small single-arm cohort of around 30 patients, and as the data developed, I continued discussing it, ultimately ending with a total 128 patients of 3 cohorts.

How did your investigator-sponsored study evolve into the pivotal Phase III TOPAZ-1 trial, and what impact has it had?

I made the case to AstraZeneca on two fronts: that biliary tract cancer, while considered uncommon by global standards, actually represents a substantial patient population in Korea, and that there had been no exploration of immune agents in this disease at all, leaving patients and families genuinely eager for that option. On that basis, I completed my investigator-sponsored study, building in a rigorous translational research component throughout. Once we had efficacy and safety data in hand, we discussed with AstraZeneca the possibility of a registrational Phase III trial, the study that became TOPAZ-1, even before my own Phase II study had fully concluded, since the ongoing Phase II was itself already showing a meaningful response.

We built the Phase III protocol on the scientific rationale established through that earlier work, and my Phase II safety and efficacy data were directly incorporated into AstraZeneca’s discussions with the FDA, supporting the global launch of TOPAZ-1. I served as International Coordinating

Investigator for the study, and the results were strongly positive at the very first interim analysis, which ultimately served as the primary analysis. Since then, we have continued following patients long-term, and recently published four-year follow-up data, the longest available dataset for first-line chemo-immunotherapy combination treatment in biliary tract cancer, which today represents the global standard of care. Contributing to a genuine improvement in survival outcomes for biliary tract cancer patients worldwide has been one of the most meaningful moments of my career. I have received emails from complete strangers around the world telling me that a family member is being treated with durvalumab plus chemotherapy,with good outcomes, prolonging the meaningful lifetime of patients sharing with their families. Messages like that are a constant reminder of why we do this work for our patients and their families.

Investigator-led trials remain relatively uncommon in Korea. How have you built successful partnerships with pharma, and what advice would you give other physician-scientists?

Early in my career, building relationships with pharmaceutical partners meant constantly proving ourselves as investigators, demonstrating that we could run fast, high-quality trials backed by genuine scientific depth, essentially convincing companies to see us as trusted collaborators. That dynamic has shifted considerably over time. Global pharma and biotech today have far greater awareness of Korean investigators and of how efficient and well-developed Korea’s overall drug development ecosystem has become.

That said, building strong partnerships remains essential, both with companies and with fellow investigators internationally, since major trials are typically global Phase III efforts requiring close collaboration across US, European, Chinese and Singaporean investigators, among others. Maintaining transparent, genuine relationships, both with international colleagues and with industry partners, remains central to how this works well.

What makes Korea such an effective hub for clinical trials from a sponsor’s perspective?

Korea is a genuinely small country; even Jeju, our furthest region from Seoul, is just an hour’s flight away. In oncology specifically, the majority of cancer patients gravitate toward Seoul, where several major hospitals are concentrated, which means a single centre here can achieve patient volumes that would be far harder to replicate in a country like the US. Patients travel back and

forth to Seoul for both clinical trials and routine treatment, creating a genuinely concentrated, efficient environment for rapid trial recruitment. Beyond that, Korean investigators bring strong scientific training, and hospital infrastructure and institutional support for clinical research are genuinely excellent, which together explain why Korean trials are increasingly recognised globally for both quality and recruitment speed.

Cancer treatment is evolving rapidly, with ADCs and personalised immunotherapy at the forefront. Across gastric, pancreatic and biliary tract cancer, what developments excite you most right now?

From a mechanistic standpoint, ADCs are a genuinely exciting platform in gastric cancer already; HER2-targeted ADCs are now central to standard care, and a number of additional ADCs targeting Claudin 18.2 and other markers are in active development. Bispecific antibodies and T-cell engagers represent another genuinely compelling direction. In pancreatic cancer, we are now firmly in the era of RAS inhibition, and RAS inhibitors specifically are transforming both the treatment landscape and the broader drug development landscape in this disease, making small molecules an equally important platform to watch.

How are multi-omics and AI-driven biomarker discovery being incorporated into practice at Seoul National University Hospital today?

Next-generation sequencing is now genuinely routine across solid tumours in clinical practice. Broader multi-omic approaches, transcriptomics and beyond, remain more academic in nature at this stage rather than standard clinical practice, though we pursue that research actively. On AI specifically, from an operational standpoint, most major Korean hospitals are incorporating it directly into their electronic medical record systems to support physicians, though this remains very much an evolving process rather than a fully settled one. Pathology is a good example of a department where AI-driven and digital pathology methods are increasingly being adopted, a shift that is happening fairly universally worldwide. The real challenge now is how efficiently and accurately these modern techniques can actually be implemented in practice.

What advice would you give the next generation of Korean physician-scientists hoping to make a global impact?

You always have to persuade just one person: whoever is directly in front of you, and in turn, allow yourself to be persuaded by them. When a company or partner approaches me, I always ask them directly to persuade me, to explain why I should test their compound in my own patients. Equally, when I approach a company wanting to test a particular hypothesis using their intellectual property, I have to persuade them just as convincingly. It sounds simple, but I think this dynamic holds true broadly in life: focus on genuinely persuading the person right in front of you. That conviction has to be grounded in science, certainly, but it must be motivated, first and foremost, by your patients and their families.

As a final reflection, what continues to motivate you personally, and what ambitions are you working toward?

Seeing TOPAZ-1 succeed and genuinely change the standard of care for first-line biliary tract cancer showed me just how much impact this kind of work can have, benefiting patients regardless of where in the world they live. I want to help deliver another practice-changing study like that, and then another, continuing to genuinely change outcomes for patients wherever they are.

More broadly, I believe the Korean industry is developing in the right direction, and I am hopeful we will continue to see genuinely potent, homegrown intellectual property emerge. The nature of collaboration differs depending on the partner, whether global pharma, global biotech, large Korean pharmaceutical companies, or smaller domestic biotechs. Each brings its own strengths and limitations. Ultimately, I think success will come from combining those complementary capabilities to translate Korean innovation into globally competitive therapies.

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