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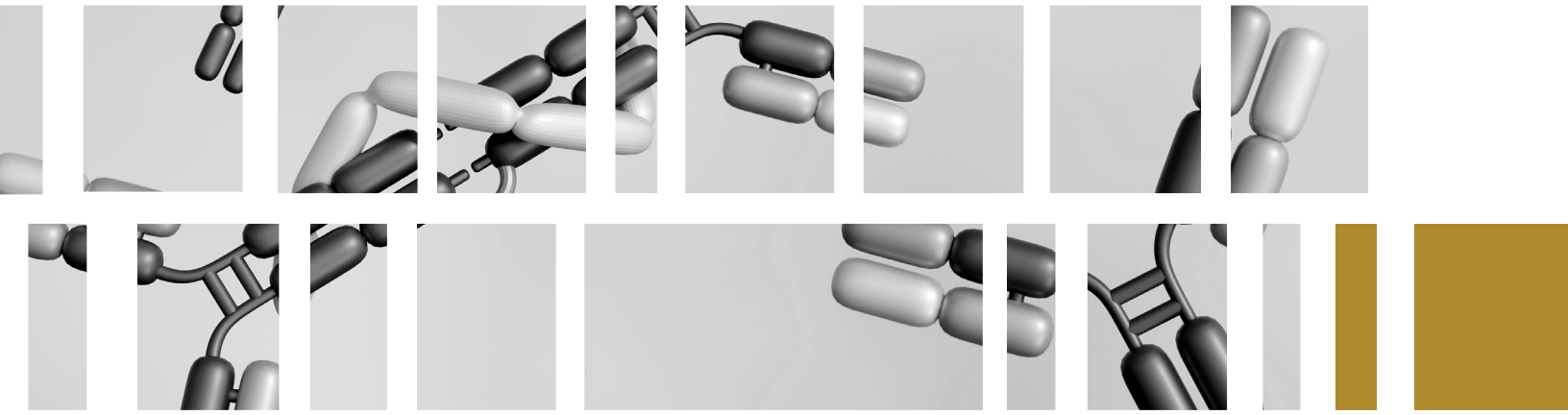

A WHITEPAPER FROM INSTITUTE@PRECISION

Moving ADCs to the Front Line

Perspectives from FDA Oncology Experts

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Executive Summary

Antibody–drug conjugates have emerged as a transformative class of therapies for both solid tumors and hematologic malignancies, with multiple trials delivering practice-changing results in the front-line setting. Along the way, the field has also seen several setbacks, with a number of clinical trials being discontinued due to toxicity superseding efficacy.

Three practice-changing clinical trials, evaluating trastuzumab deruxtecan (Enhertu), enfortumab vedotin-ejfv (Padcev), and brentuximab vedotin (Adcetris), highlight key aspects of the assets' development which enabled successful front-line strategies. Lessons learned can help inform current and future clinical development plans for stakeholders, who are aiming for high probability of regulatory and technical success.

The Promise of ADCs in Oncology

Antibody drug conjugates (ADCs) comprise monoclonal antibodies (mAbs) covalently linked to cytotoxic agents via chemical linkers[1].

Unlike traditional chemotherapies, these agents are designed to provide highly specific tumor targeting, enabling improved efficacy and reduced off-target effects[2].

While ADCs are a relatively novel class of biotherapeutics[3], they find their conceptual origin in the 'magic bullets' postulated by Paul Ehrlich more than 100 years ago[4].

Early success stories in ADC development engendered great enthusiasm around an elegant and targeted approach. However, this turned to cautious realism, as numerous ADC development programs were stalled or challenged by toxicities and failed trials, some even leading to withdrawn indications[5–7].

More recently, the field has seen high-impact results from several registrational, Phase III trials[8–10]. Given the transformative nature of such assets in both solid tumors and hematologic malignancies, FDA has leveraged regulatory programs and review processes to foster their development and approval. These include efforts led by the Oncology Center of Excellence, such as Project Optimus to drive earlier dose optimization, and Project Orbis and Real-Time Oncology Review to enable concurrent international review and enhanced access[11–13]. In addition, FDA has issued clinical pharmacology guidance specific to ADCs, clarifying expectations around bioanalytical methods, exposure–response modeling, and immunogenicity evaluation, standardizing requirements that once slowed progress[14].

Enhertu, Padcev, and Adcetris: Moving to the Front Line, Lessons Learned

Moving a novel asset to the front-line setting is often considered the gold standard for drug developers; an FDA-approved indication for previously untreated patients provides earlier access to efficacious therapies, leading to broad impact across a larger population and fulfilling high unmet medical needs.

The clinical development programs of Enhertu, Padcev, and Adcetris have had notable success in moving into front-line settings. These development programs provide critical insights that may facilitate more efficient and successful development of this therapeutic class.

Enhertu: A New Era for HER2+ Metastatic Breast Cancer

Enhertu (fam-trastuzumab deruxtecan-nxki) comprises a HER2-directed monocloncal antibody (mAb) connected to a topoisomerase-1 inhibitor, deruxtecan – a highly potent cytotoxic agent – via a tumor-selective cleavable linker[15].

Enhertu has a high and homogenous drug-to-antibody ratio (DAR) of approximately eight, one of the highest DARs of any ADC[16].

Early Promise

Enhertu was developed by Daiichi Sankyo and AstraZeneca for the treatment of a variety of solid tumors[17]. FDA-approved indications are summarized in Table 1.

Indication	Approval Type	Approval Date
Adult patients with unresectable or metastatic HER2+ (IHC 3+ or ISH positive) breast cancer who have received a prior anti-HER2-based regimen either in the metastatic setting, or in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy.	Regular approval	May 2022
Adult patients with unresectable or metastatic: • HR+/HER2-low (IHC 1+ or IHC 2+/ISH–) or HER2-ultralow (IHC 0 with membrane staining) metastatic breast cancer who have received at least 1 line of endocrine therapy in the metastatic setting. • HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received prior chemotherapy in the metastatic setting or have disease recurrence during or within 6 months of completing adjuvant chemotherapy.	Regular approval	January 2025
Adult patients with locally advanced or metastatic HER2+ (IHC 3+ or IHC 2+/ISH positive) gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.	Regular approval	January 2021
Adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 mutations and who have received a prior systemic therapy.	Accelerated approval	August 2022
Adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options.	Accelerated approval	April 2024

Table 1. Enhertu has FDA approval for 5 indications to date[18].

The FDA's Accelerated Approval Pathway allows for approvals which provide improvements over available therapies, supported by early or intermediate endpoints. In solid tumors and some hematologic malignancies, this traditionally has equated to objective response rate (ORR) and duration of response (DOR)[19].

Enhertu was granted an Accelerated Approval in 2019, based on DESTINY-Breast01, a single-arm, multicenter trial[20]. Treatment with single agent Enhertu (N=184) in adults who had received two or more anti-HER2-based therapies in a metastatic setting garnered an ORR of 60.3% (95% CI: 52.9, 67.4), with a median duration of response (DOR) of 14.8 months (95% CI: 13.8, 16.9)[21].

During the early stages of development, FDA expressed concerns about the identification and management of interstitial lung disease (ILD), which occurred in 9.4% of patients and was fatal in 2.6% of patients according to the final labeling from the first approval[22]. While the therapy showed great promise, ILD was then a relatively uncommon toxicity for drugs utilized by oncologists specializing in breast cancer, with Everolimus as one of the only other drugs which caused this toxicity[23].

Throughout early development of Enhertu, FDA highlighted concerns regarding the rates and severity of ILD, and the need to identify strategies to mitigate risk and reduce the class of safety events. In collaboration with their medical teams and investigators, the sponsor pursued a robust and actionable global awareness campaign for safe use of Enhertu, directed at trial investigators and patients, to reduce the risk of severe and fatal ILD[22].

Recommendations included close monitoring for early signs of ILD, and proactive management through dose modification and steroids[22]. Subsequent confirmatory trial results demonstrated a reduction in grade 4 and 5 ILD events, reflecting the impact of earlier identification and intervention[24].

Confirmatory Trials and Moving to the Front Line

DESTINY-Breast03 served as the confirmatory randomized trial for the 2019 accelerated approval, enrolling more than 500 patients with HER2-positive metastatic breast cancer previously treated with trastuzumab and a taxane. Patients were randomized to receive trastuzumab deruxtecan or trastuzumab emtansine[24].

The trial met its primary endpoint of progression free survival (PFS) demonstrating a statistically significant PFS hazard ratio (HR) of 0.28 (95% CI: 0.22, 0.37). Median PFS was not reached in the Enhertu arm (95% CI: 18.5, not estimable) versus a median of 6.8 months (95% CI: 5.6, 8.2) in the ado-trastuzumab emtansine arm[17]. The incidence of adjudicated interstitial lung disease or pneumonitis was 10.5% and 1.9%, respectively, with no grade 4 or 5 events. These results confirmed the substantial improvement in clinical outcomes and supported conversion from accelerated to traditional approval in May 2022[24, 25].

With additional follow-up, the DESTINY-Breast03 trial demonstrated a statistically significant advantage in overall survival (OS) with an OS HR of 0.64 (95% CI: 0.47, 0.87) with an approximate 10-month improvement in OS[26, 17]. The OS data solidified the benefit first observed in 2019 and moving Enhertu to an earlier line of treatment[24, 25].

As Enhertu reshaped the treatment paradigm for HER2+ metastatic breast cancer, advancing this asset to the front-line setting was paramount.

To this end, a front-line trial, DESTINY-Breast09, initiated in 2021[27], was designed to evaluate Enhertu in combination with pertuzumab compared with taxane, trastuzumab and pertuzumab (THP).

Topline results from an interim analysis were presented at ASCO 2025 and were widely discussed as potentially practice-changing, based on a median progression-free survival (PFS) of 40.7 months vs. 26.9 months with the long-standing CLEOPATRA regimen (pertuzumab plus trastuzumab plus docetaxel), the current front-line standard of care[28].

Given that the CLEOPATRA regimen was approved in 2012, the results of DESTINY-Breast-09 mark the first significant development in first-line treatment for patients with HER2+ metastatic breast cancer in more than a decade[29, 30].

Sponsors Daiichi Sankyo and AstraZeneca are currently in discussion with global regulators and have filed an application to FDA for an indication in front-line metastatic HER2+ breast cancer. FDA's Division of Oncology 1 has granted them Priority Review, with a PDUFA goal date of January 23, 2026[31].

Key Takeaways

Enhertu is a blockbuster ADC with multiple indications spanning solid tumors, as well as a highly coveted tissue-agnostic FDA approval[32]. While the asset showed early signs of high efficacy in part attributed to its high DAR, early and aggressive toxicity management was key to its global success and integration into clinical practice.

"The early response rates for Enhertu in late stage HER2+ breast cancer were a clear breakthrough. But ILD toxicity warranted early consultation with regulators, as well as a robust awareness campaign to thoroughly manage ILD risk and severity. Both were critical to Enhertu's success."

– Harpreet Singh, CMO, Precision for Medicine

Padcev: A Breakthrough Front-line Therapy for Advanced Urothelial Cancer

Padcev (enfortumab vedotin-ejfv, Astellas Pharma and Pfizer) comprises a nectin-4-directed antibody conjugated to monomethyl aurostatin E, a small molecule microtubule disruptor[33]. The asset has been developed for the treatment of adult patients with locally advanced or metastatic urothelial cancer. Padcev has two FDA-approved indications[34,35].

- **Monotherapy** for previously treated locally advanced or metastatic urothelial cancer (la/mUC)
  - December 2019 – Accelerated approval: Granted for adult patients with locally advanced or metastatic urothelial cancer (la/mUC) who had previously received a PD-1/PD-L1 inhibitor, and platinum-containing chemotherapy in the neoadjuvant/adjuvant setting or in the locally advanced or metastatic setting.
  - July 2021 – Regular approval: Converted from accelerated to full approval and expanded to include patients who were ineligible for cisplatin-containing chemotherapy and had received one or more prior lines of therapy.
- **Combination therapy** with pembrolizumab (Keytruda) for first-line treatment of la/mUC
  - April 2023 – Accelerated approval: Granted for cisplatin-ineligible adult patients with la/mUC.
  - December 2023 – Regular approval: Expanded to all adult patients with la/mUC, making it the first and only ADC plus PD-1 inhibitor combination approved as an alternative to platinum-based chemotherapy in the first-line setting.

Early Promise

Padcev was granted FDA accelerated approval in December 2019, based on the EV-201 trial[36]. The study enrolled approximately 125 patients with metastatic urothelial cancer who had previously received both a programmed death receptor-1 (PD-1) or programmed death ligand-1 (PD-L1) inhibitor and a platinum-containing chemotherapy[37].

The ORR of 44% (95% CI: 35.1, 53.2), including a CR rate of 12%, and a median DOR of 7.6 months (95% CI: 6.3, not estimable)[37], was considered a clear breakthrough relative to standard of care single-agent chemotherapy.

Moving to the Front Line

In 2017, Astellas Pharma collaborated with Merck to evaluate the combination of enfortumab-vedotin and Merck's Keytruda (pembrolizumab) for patients who were considered cisplatin-ineligible, a subset of patients with urothelial cancer with high unmet need[38].

This collaboration garnered an accelerated approval in April 2023 based on the EV-103/KEYNOTE-869 trial, which demonstrated a durable ORR of 68% (95% CI: 59, 76), with 12% of patients achieving complete response[34].

Benefit was confirmed in the front-line setting in EV-302/KN-A39, an open-label randomized trial enrolling 886 patients with untreated la/mUC to receive either enfortumab-vedotin plus pembrolizumab or platinum-based chemotherapy with OS and PFS as the primary endpoints[9]. EV-302 demonstrated a highly statistically significant and clinically meaningful improvement in OS with a HR of 0.47 (95% CI: 0.38, 0.58) representing an approximately 15-month improvement in median OS with a median OS of 31.5 months (95% CI: 25, not estimable) with enfortumab-vedotin plus pembrolizumab versus median OS of 16.1 months (95% CI: 14, 18) in the control. A statistically significant PFS advantage was also demonstrated with a PFS HR of 0.45 (95% CI: 0.38, 0.54) with a 6-month improvement in median PFS[34].

Impact

Until EV-302/KN-A39, no treatment had surpassed platinum-based chemotherapy in improving OS for the front-line metastatic urothelial setting.

These breakthrough results led to FDA approval of enfortumab-vedotin plus pembrolizumab in December 2023[40], transforming the landscape and establishing a new standard of care.

Key Takeaways: What Secured Padcev's Success?

The collaboration between Astellas and Merck allowed early and deep exploration of enfortumab-vedotin in combination with pembrolizumab—well before its accelerated approval as a monotherapy. The EV-302 trial, initiated in 2020, built directly on the early-phase EV-103 study, which demonstrated that combining an ADC with a PD-1 inhibitor was both feasible and safe, paving the way for a front-line trial designed to replace chemotherapy as the standard of care[9].

Early-phase studies informed the front-line strategy. Preclinical and clinical data showed that enfortumab vedotin could be safely and effectively combined with pembrolizumab, supporting initiation of a pivotal front-line trial.

- **Chemotherapy replacement with a targeted ADC.** The combination offered the cytotoxic impact of chemotherapy with the precision of targeted delivery, eliminating the need for platinum-based regimens.
- **Effective management of predictable toxicities.** The development program incorporated robust toxicity monitoring and mitigation strategies for known adverse events including ILD, skin reactions, fatigue, peripheral neuropathy, and hyperglycemia—the latter being a unique class effect related to the MMAE payload[34].
- **Trial design aligned with FDA expectations.** The EV-302/KEYNOTE-A39 study addressed a clear unmet medical need, with clinically meaningful OS and PFS endpoints that demonstrated a compelling advantage over the control arm.
- **Early regulatory engagement paid off.** Continuous dialogue with the FDA helped refine trial endpoints, patient selection, and safety monitoring, accelerating both development and review timelines.

"Enfortumab-vedotin plus pembrolizumab was the first regimen to demonstrate an overall survival benefit over platinum-based chemotherapy in previously untreated urothelial cancer. Early and successful combination work was a critical milestone."

– Harpreet Singh, CMO, Precision for Medicine

Adcetris: A Transformative Front-line Option for CD30+ PTCL

Adcetris (brentuximab vedotin, Takeda and Pfizer) is an ADC composed of an anti-CD30 antibody linked to monomethyl auristatin E, a microtubule inhibitor[41]. Adcetris is FDA-approved for the treatment of multiple lymphoma indications within classical Hodgkin lymphoma and B and T cell lymphoma[42].

- **2011:** classical Hodgkin lymphoma (cHL) after failure of autologous hematopoietic stem cell transplantation (auto-HSCT) or at least two prior chemotherapy regimen in patients who ineligible for auto-HSCT.
- **2011:** systemic anaplastic large cell lymphoma (ALCL) after failure of at least one prior chemotherapy regimen.
- **2015:** cHL at high risk of relapse or progression as post auto-HSCT consolidation.
- **2017:** primary cutaneous ALCL or CD30-expression mycosis fungoides who have received prior systemic therapy
- **2018:** previously untreated stage III or IV cHL, in combination with chemotherapy
- **2018:** previously untreated systemic ALCL or other CD30-expression peripheral T-cell lymphoma (PTCL) in combination with chemotherapy
- **2022:** pediatric patients 2 years and older with previously untreated high risk cHL in combination with chemotherapy
- **2025:** relapsed or refractory large B-cell lymphoma (LBCL) after two or more lines of systemic therapy who are not eligible for auto-HSCT or chimeric antigen receptor (CAR) T cell therapy in combination with lenalidomide and rituximab.

Early Promise

The FDA granted Adcetris accelerated approval in 2011 for the treatment of cHL and systemic ALCL) based on two single-arm trials in the relapsed/refractory setting[43].

The sALCL trial demonstrated an ORR of 86% (95% CI: 77, 95), with a CR rate of 57% (95% CI: 44, 70). The median DOR was 12.6 months (95% CI: 5.7, not estimable)[44].

This was the first new FDA-approved treatment for cHL since 1977, and the first approved specifically for the treatment of ALCL[45].

Moving to the Front Line

Multi-agent chemotherapy has been the cornerstone of the standard of care in cHL, systemic ALCL, and LBCL for decades. With encouraging monotherapy data, the sponsor quickly evaluated Adcetris in multiple combinations across lymphoma subtypes early in development[46,47]. For systemic ALCL and PTCL, this included combining Adcetris with CHP (cyclophosphamide, doxorubicin, and prednisone), replacing vincristine (Oncovin) in the standard CHOP regimen given the related mechanism of microtubule inhibition between both products[48].

The early combination data led to ECHELON-2, a phase 3, double blind, multicenter trial that enrolled 452 patients with previously untreated CD30-expressing PTCL, randomized to either Adcetris plus CHP or CHOP[49]. The trial demonstrated a statistically significant improvement in PFS with a HR of 0.71 (95% CI: 0.54, 0.93) representing a 28-month improvement in median PFS (48.2 vs 20.8 months). A statistically significant OS advantage was shown with an OS HR of 0.66 (95% CI: 0.46, 0.95) and at the 5-year follow-up analysis, the median OS was noted reach in either arm with the 5-year rate 70% (95% CI: 63, 76) in the Adcetris arm versus 61% (95% CI: 54. 67) in the CHOP control arm[42, 50].

Impact

The ECHELON-2 trial results were unprecedented with a PFS and OS advantage over CHOP chemotherapy, the standard of care for decades. Given the practice-changing results, the FDA approval of Adcetris plus CHP was completed in less than two weeks after official biological license application (BLA) submission through the Real-Time Oncology Review pilot program, the fastest approval of an oncology agent[51].

The magnitude of the improvement in PFS and OS instantly made A+CHP the new front-line standard of care for CD30+ PTCL and was the first FDA approval for patients with newly diagnosed PTCL[52].

"The results of the ECHELON-2 trial represented a true paradigm shift. Because of the magnitude of benefit in the front-line setting of a disease with known poor outcomes, facilitating access to this regimen was paramount. This need underpinned the regulatory effort to perform such an expeditious review."

– Nicholas Richardson, VP Clinical Development, Precision for Medicine

Key Takeaways:

Adcetris is a practice-changing ADC across multiple lymphoma indications, with several trials demonstrating an advantage in overall survival.

- **Early phase studies prioritized combination therapy.** The Adcetris development program executed multiple cohorts in early phase studies exploring Adcetris in combination across lymphoma histologies, generating the necessary data to inform subsequent trials in the relapsed or refractory setting and ultimately the front-line setting.
- **Use of substitution design.** The replacement of Adcetris, a targeted delivery of a microtubule inhibitor, for vincristine in the CHOP regimen and for bleomycin in cHL multi-agent chemotherapy regimens, allowed for enhanced efficacy with the ADC and manageable toxicity.
- **Effective toxicity management.** The Adcetris program readily characterized the toxicity profile and mitigated the identified risks of peripheral neuropathy, neutropenia and infections, pneumonitis, skin reactions, hepatotoxicity, and hyperglycemia.
- **The FDA leveraged expedited programs.**
  - The FDA used the Real-Time Oncology Review Pilot Program to accelerate application review[51].
  - For drugs that are likely to demonstrate substantial improvements over currently available therapies, the program facilitates submission of early efficacy and safety data to enable an earlier start to the FDA's review of an application[13].

Moving ADCs to Front-line Indications: Key Takeaways for Developers

1. Commit to early combination and toxicity work

Exploring how your asset combines with other therapies and modalities – understanding synergistic effects and managing and mitigating overlapping toxicities – is critical for program success.

Gilead's TRODELVY (sacituzumab govitecan), for example, faced challenges on their path to a front-line bladder indication. Following accelerated approval for third-line metastatic urothelial cancer[54], TRODELVY failed to show a significant improvement in PFS and OS in TROPICS-04, a single-agent confirmatory trial in the third-line setting[55]. Without combination data to enable a front-line exploration, Gilead, in consultation with FDA, voluntarily withdrew the urothelial cancer indication from the market[54].

"If your asset can be safely combined with other therapies and modalities, that's a promising first step that it may advance to a front-line setting, improving the potential for a truly blockbuster therapy."

– Harpreet Singh, CMO, Precision for Medicine

2. Collaborate early and closely with the FDA

FDA oncologists are classically trained at some of the most highly respected institutions in the world, with a large percentage maintaining a clinical practice while also regulating drug development. Moreover, FDA has visibility into data across classes of drugs that are not publicly available. The FDA's regulatory advice is informed by a totality of evidence across drug classes and should be considered by sponsors throughout the life cycle of a program.

> "We advise drug developers, whatever their level of experience with regulatory agencies such as the FDA, to seek support from competent and knowledgeable individuals who can help them get the most out of FDA collaboration throughout the development cycle."
>
> – Harpreet Singh, CMO, Precision for Medicine

AT A GLANCE: ACTIONS FOR ADC DEVELOPERS

- ✓ Aggressively manage the toxicity profile of your asset in monotherapy and in combination with other agents early in development
- ✓ Plan and initiate trials early based on combination safety data and viable treatment paths
- ✓ Engage with the FDA early and often, and deeply consider their regulatory advice, particularly with respect to overall risk-benefit profile throughout development
- ✓ Early in development, seek the support of experts who can enhance your FDA collaboration

Continuing ADC Success

ADCs are a therapeutic modality with significant promise that has now been realized in several practice-changing front-line indications across solid tumors and hematologic malignancies.

These case studies bring to light clear lessons for ADC developers: bringing a practice-changing therapy to market relies on aggressive toxicity management, the ability to safely combine with other agents, and close collaboration with regulatory agencies and other key stakeholders. For the best PTRS, developers should also seek input from experts with extensive experience in oncology drug development and sponsor-FDA interactions.

Authors

Dr. Harpreet Singh

Dr. Harpreet Singh is the chief medical officer of Precision for Medicine, and former Director of FDA's Division of Oncology 2. At the FDA, Dr. Singh oversaw development and approval of more than 40 therapies, with ADC approval oversight in breast, lung, urothelial, and other cancers. While at the FDA, Dr. Singh also spearheaded Project Pragmatica, a program to streamline clinical trials and enhance patient centricity.

In addition, Dr. Singh was Associate Director for Cancer in Older Adults and Special Populations at the FDA Oncology Center of Excellence (OCE), and was a Fellow at the National Cancer Institute. Dr Singh is a world-renowned expert in oncology.

Dr. Nicholas Richardson

Dr. Nicholas Richardson is Vice President of Clinical Development at Precision for Medicine and former FDA Deputy Director of the Division of Hematologic Malignancies 2. At the FDA, Dr. Richardson led regulatory oversight for development of therapies for lymphoma, chronic lymphocytic leukemia (CLL), and multiple myeloma (MM), including oversight of multiple ADC approvals in lymphoma and multiple myeloma.

Dr. Richardson also spearheaded initiatives to develop novel endpoints in blood cancer, such as minimal residual disease (MRD) in lymphoma and CLL, helping accelerate drug development. Dr. Richardson is a leading expert in hematology and oncology.

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