Student Oncological Advocates in Pharmacy (SOAP) is committed to elevating awareness for all different types of cancer. As a part of the University of Georgia, College of Pharmacy, we deepen our understanding through education and involvement to continue to provide support to our community, focusing on those affected by cancer.

**Acknowledgements**

Thank you to everyone who contributed to the creation of this newsletter. I want to express my gratitude, especially to Dr. Clemmons and NCODA, for their invaluable editing assistance. It has been an honor to serve as the newsletter editor, and I look forward to future editions!
Semester Recap

The Spring semester has come to end! Throughout the semester, we have continued learning, growing, and spreading awareness in oncology pharmacy. Our roster of guest speakers, including representatives from HOPA, Pharmacy Times, and NCODA, illuminated the diverse avenues through which pharmacists can impact patient care and education. Additionally, for continuous education, our members engaged in journal club presentations, delving into the latest clinical trials across various cancer types, from cervical to colorectal.

Other fun events included participating in UGA’s Miracle Dance Marathon to support Children’s Healthcare of Atlanta. We then hosted our annual Spring Pillympics filled with fun events like pharmacy trivia and relay events. Proceeds from the Pillympics went to Emory Winship Cancer Institute.

Lastly, congratulations to our outstanding members, Jamie Le and Monica Ngo, for receiving 2nd place in NCODA’s PQI Competition! We are so proud of your achievement!
Human epidermal growth factor receptor type 2 (HER2) is a tyrosine kinase receptor that mediates cellular proliferation and survival via intracellular signaling pathways.¹ These pathways include phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) and mitogen-activated protein kinase (MAPK), all of which are normally activated by dimerization.¹ HER2 overexpression is the primary biomarker in aggressive, metastatic breast cancer with poor prognosis, promoting uncontrolled cell proliferation and tumor growth progression via ligand-independent dimerization and unregulated activation of PI3K/AKT/mTOR and MAPK.²,³ The rise of HER2-targeted therapies for patients with HER2 positive (HER2+) advanced-stage breast cancer consisting of monoclonal antibodies (mAbs), tyrosine kinase inhibitors (TK-is), and antibody drug conjugates (ADCs) has transformed progression-free survival outcomes in an otherwise, primarily incurable disease state.²

The Rise of Anti-HER2
Trastuzumab stands at the forefront of HER2 inhibitors as the pioneering monoclonal antibody and breakthrough in the treatment paradigm of HER2+ breast cancer. In 2001, the addition of trastuzumab to first-line standard-of-care (SOC) therapy, paclitaxel, demonstrated not only an overall survival (OS) benefit but also a favorable cardiac safety profile, solidifying its status as the preferred first-line treatment for metastatic HER2+ breast cancer.²

After a decade, the 2012 Phase 3 CLEOPATRA study introduced a novel therapy combining trastuzumab and docetaxel with pertuzumab (THP), demonstrating significant clinical benefit.²,³ The combination presents a dual HER2 blockade.² While trastuzumab targets the extracellular domain IV of HER2, pertuzumab’s inhibition of downstream signaling by binding to extracellular domain II and disrupting HER2 heterodimerization, proved to be more significant.² Notably, the trial revealed that 16% of patients remained free from disease progression after eight years.²

Currently, the first-line regimen for metastatic HER2+ breast cancer is coadministration of docetaxel for 6–8 cycles with trastuzumab and pertuzumab, followed by trastuzumab and pertuzumab alone until disease progression.² Combination therapies using alternative taxanes such as paclitaxel or nab-paclitaxel to replace docetaxel have shown comparable safety and efficacy outcomes based on the PERUSE phase III trial.² The phase II VELVET trial exhibited vinorelbine as a suitable alternative for patients who cannot tolerate taxanes due to an improved adverse effect profile.² The ongoing phase 3 heredERA trial marks the first randomized study that evaluates the clinical benefit of the addition of giredestrant, an oral selective estrogen degrader, into the maintenance regimen of trastuzumab and pertuzumab in patients with hormone-receptor positive, HER2+ disease.² The results of this trial hold promise for advancing limited, multidisciplinary treatment approaches in triple-positive breast cancer.

Anti-HER2 Resistance
While HER2–targeted therapies have spearheaded the revolution in the management of HER2-positive breast cancer, pathways of resistance, in the forms of intratumoral heterogeneity in HER2 expression and dysregulated intracellular signaling, continue to pose a significant challenge.²,³ Intratumoral heterogeneity refers to the variation of HER2 expression levels within a tumor and dependence of HER2 as an oncogenic driver, resulting in a poorer response to HER2 inhibitors compared to homogenous HER2 expression.²,³
Its existence complicates the accurate categorization of tumor HER2 status and the implementation of optimal treatment regimens; however, new-generation ADCs such as fam-trastuzumab deruxtecan (T-DXd) have demonstrated promising efficacy.³ In addition, mutational activation of intracellular pathways, particularly PI3K–AKT, the dominant downstream signaling cascade of activated HER2, is also subject to resistance and poorer clinical outcomes.³ Ongoing trials are addressing these mutations by investigating combination therapies targeting the PI3K/AKT/mTOR pathways including PI3K inhibitors such as ipatasertib and apitolisib.³ As collaborative research efforts persist in understanding and addressing these challenges in clinical practice, there continues to be hope for advancing the treatment landscape and improving the outlook for patients diagnosed with advanced HER2+ breast cancer.

References
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ANTIBODY-DRUG CONJUGATES:
A TARGETED APPROACH TO CANCER THERAPY
By Monica Ngo, Pharm.D Candidate, 2026

Antibody–drug conjugates (ADCs) combine the targeted specificity of monoclonal antibodies with potent chemotherapeutic payloads. This molecular design enhances antitumor efficacy while minimizing systemic toxicity, leading to improved clinical outcomes. ADCs are characterized by optimized structural components, including the antibody, cytotoxic payload, and chemical linker. Humanized and fully human IgGs, particularly of the IgG1 subclass, serve as the backbone for most ADCs due to their stability and engagement of innate immune cells.³ Target selection is critical for achieving tumor-specific delivery of cytotoxic payloads, with strategies aimed at enhancing tumor specificity and optimizing ADC internalization rates. Payloads used in ADCs are highly potent and include antimitotic agents, DNA-damaging agents, and topoisomerase inhibitors, with fine-tuning necessary to balance efficacy and toxicity.² Cleavable linkers enable efficient payload release within cancer cells while minimizing systemic toxicities.³ Kadcyla (ado-trastuzumab emtansine) exemplifies this optimized structure. The antibody component of Kadcyla, trastuzumab, is a humanized IgG1 monoclonal antibody. This humanized structure minimizes immunogenicity, reducing the risk of allergic reactions in patients.⁴ Trastuzumab specifically binds to the HER2 protein, a well-characterized target overexpressed on HER2-positive breast cancer cells.
This targeted binding allows Kadcyla to deliver its cytotoxic payload, emtansine, directly to cancer cells.⁵ The linker connecting the antibody and payload is designed to be stable in circulation but cleavable within the tumor microenvironment, ensuring the release of emtansine where it can effectively kill cancer cells through microtubular inhibition.⁵ Kadcyla's targeted approach highlights the potential of ADCs to minimize side effects associated with traditional chemotherapy drugs that can harm healthy cells throughout the body.

The development of targeted therapies using antibody-directed protein degraders, such as degradation antibody conjugates (DACs), represents significant advancements to ADCs. DACs work by targeting specific proteins within cancer cells for degradation, thereby inhibiting tumor growth or inducing cell death.⁶ These conjugates consist of an antibody component that recognizes a surface protein on cancer cells and a payload that induces protein degradation.⁶ By selectively targeting proteins essential for cancer cell survival or proliferation, DACs offer a highly targeted approach to cancer therapy with potentially fewer side effects compared to traditional chemotherapy.⁶ An example of a DAC in development is ORM-5029, targeting the GSPT1 protein specifically in HER2-positive cancers.⁷ HER2 overexpression is a well-established driver of aggressive tumor growth, and GSPT1 plays a crucial role in this process.⁷ By tagging GSPT1 for degradation with ORM-5029, researchers hope to achieve a more precise and effective therapy for HER2-positive cancers. This approach highlights the potential of DACs to target vulnerabilities within specific cancer subtypes, paving the way for personalized medicine with improved patient outcomes.

Dual-drug antibody-drug conjugates have the potential to elicit additive or synergistic effects while simplifying dosing regimens.¹ These improved ADCs combine two different cytotoxic payloads within a single antibody construct, allowing for synergistic or additive effects against tumor cells. By delivering multiple drugs simultaneously, dual-drug ADCs have the potential to overcome drug resistance and improve treatment outcomes.⁸ However, optimizing the selection and ratio of payloads, as well as ensuring homogeneous conjugation to the antibody, are crucial challenges that must be addressed for these therapies to reach their full potential.

In conclusion, antibody-drug conjugates (ADCs) have revolutionized cancer treatment by delivering targeted therapies with reduced side effects. However, challenges like tumor heterogeneity necessitate further development.
Advancements in bispecific ADCs, degradation antibody conjugates (DACs), and dual–drug ADCs offer promising avenues for overcoming these hurdles. Continued research focused on optimizing payload and linker design, identifying tumor–specific antigens, and developing effective biomarkers is crucial to maximize ADC efficacy and improve patient outcomes. Despite the significant progress with numerous approved ADC formulations and a robust clinical pipeline, future efforts must address tumor heterogeneity and treatment resistance to ensure a future where ADCs deliver on their full potential for cancer patients.

References


ANOTHER ONE BITES THE DUST: ASSESSING THE ROLE OF BISPECIFIC T-CELL ENGAGERS IN THE TREATMENT OF RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMAS

By Alexander Durant, Pharm.D Candidate, 2024

Diffuse large B-cell lymphoma (DLBCL) is the most diagnosed lymphoid neoplasm in adults, with an estimated incidence of 4.68 cases per 100,000 people as of 2021.¹ Diffuse large B-cell lymphoma (DLBCL) is the most diagnosed lymphoid neoplasm in adults, with an estimated incidence of 4.68 cases per 100,000 people as of 2021. Around 65% of patients exhibit complete response (CR) after first-line treatment, which commonly is the rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) regimen, though other regimens exist for patients with poor left ventricular function and for frail patients unable to tolerate chemotherapy. Despite advances in the treatment of DLBCL, around 20-40% of patients will develop relapsed or refractory (R/R) disease.² Second-line treatment may involve further chemotherapy with a separate regimen, followed by high dose therapy and autologous stem cell rescue (HDT/ASCR) or chimeric antigen receptor T-cell (CAR-T) therapy. Patients with R/R disease have a 1-year overall survival (OS) rate of around 59%, necessitating the development of novel agents for this patient subset.

Bispecific T-cell engaging (BiTE) antibodies are fusion proteins that work by binding to both B-cells and cytotoxic T-cells. BiTE therapies have previously demonstrated efficacy in other B-cell derived cancers, such as R/R precursor acute lymphoblastic leukemia (ALL), and work by directing a cytotoxic T-cell response to the associated B-cell, resulting in targeted B-cell destruction.³ For the management of DLBCL specifically, these agents are bispecific CD20-directed CD3 T-cell engagers.
Glofitamab-gxbm (Columvi) and epcoritamab-bysp (Epkinly) are BiTE antibodies recently approved by the FDA for the treatment of relapsed refractory (R/R) DLBCL after two or more lines of systemic therapy. In a phase I/II open-label trial⁴, glofitamab was administered with ramp-up dosing during cycle 1 followed by a fixed 30 mg dose on day 1 of each 28-day cycle for a maximum of 12 cycles to patients with R/R DLBCL who had received ≥2 lines of prior systemic therapy. Notably, patients received one dose of the CD20-directed antibody obinutuzumab as pretreatment to deplete peripheral B-cells and reduce the risk of cytokine release syndrome (CRS). In addition, 40 of the 154 patients included also received pretreatment dexamethasone. The primary endpoint was CR rate as assessed by an independent review committee using the Lugano criteria⁵, defined as a reduced metabolic response (score of 1, 2, or 3) with or without a residual mass on a 5-point scale and no evidence of FDG-avid disease in the bone marrow, where FDG is the standard method used to visually detect disease on scans. The CR rate was 39% (95% CI, 32 to 48) after a median of 13 months of treatment with glofitamab. No difference existed in CR rates between those who had previously received CAR-T therapy and those who had not (35% vs. 42%, respectively). The most common adverse reaction was CRS, occurring in 63% of patients enrolled. Grade 3 or higher CRS occurred in 4% of these patients. Grades 1 and 2 immune effector cell-associated neurotoxicity syndrome (ICANS) occurred in 8% of patients, and all events resolved. Infections occurred in 38% of patients while febrile neutropenia and tumor lysis syndrome (TLS) occurred in less than 5% of patients each. The authors concluded that glofitamab appears to be as effective as other standard of care therapies for R/R DLBCL while exhibiting comparatively fewer neurologic side effects.

In a separate phase I/II open-label trial⁶, epcoritamab was administered until disease progression in 157 patients with R/R DLBCL unresponsive after ≥2 lines of prior systemic therapy. Epcoritamab was given in 28-day cycles with ramp-up dosing during cycle 1, followed by day 1, 8, 15, and 22 dosing in cycles 2–3, day 1 and 15 dosing in cycles 4–9, then day 1 dosing for subsequent cycles until disease progression or unacceptable toxicity. All patients received acetaminophen, diphenhydramine, and prednisolone for CRS prophylaxis. The primary endpoint was overall response (OR) rate as assessed by an independent review committee and defined using the Lugano criteria, where OR represents the sum of CR and partial response (PR). PR is defined by the Lugano criteria as a score of 4 or 5 on a 5-point scale with no new progressive lesions and reduced bone marrow uptake higher than that in normal marrow but lower than that observed at baseline. The OR rate was 63.1% (95% CI, 55.0 to 70.6) and the CR rate was 38.9% (95% CI, 31.2 to 46.9) at a median follow-up of 11 months with a 6-month PFS of 44%. Those who had not received prior CAR–T therapy had a numerically greater OR rate than patients who received prior CAR–T therapy (69% vs. 42%, respectively). CRS occurred in 49.7% of patients, with CRS of grade 3 or higher present in 2.5% of patients. Infections, neutropenia, and ICANS occurred in ≥10% of patients (40.2, 21.7, and 10%, respectively), while TLS occurred in 1.3% of patients. The authors concluded that epcoritamab may offer a more convenient, subcutaneous alternative to intravenous therapies for R/R DLBCL while maintaining a similar efficacy.

Limitations of these studies include the lack of an active comparator and relatively low rates of patients who had a prior HDT/ASCR despite its common use.

BiTE therapy shows promise in patients with R/R DLBCL who have unsuccessfully received ≥2 lines of prior systemic therapy. BiTE therapy may also be useful in patients requiring third-line treatment who cannot receive cellular therapy and require an alternative treatment. An ongoing trial in the recruitment phase plans to compare the efficacy of glofitamab plus obinutuzumab to glofitamab monotherapy for R/R DLBCL.⁷
Additionally, an ongoing trial will assess the efficacy of epcoritamab and venetoclax in patients with R/R chronic or small lymphocytic leukemia. Future research will need to include more patients who received prior cellular therapy, as well as specify the optimal duration of BiTE therapy for achieving a CR while minimizing adverse events.

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WHAT’S THE BUZZ ON THE KRAS DRUGS? A FOCUS ON ADAGRASIB

By Grace Zeineddine, Pharm.D Candidate, 2026

Taking the cancer industry by storm are a new class of cancer drugs known as the KRAS G12C inhibitors. With the first one, known as Sotorasib, being approved in 2021, Adagrasib followed soon after on 12/12/2022 under accelerated approval for patients with locally advanced or metastatic G12C mutated non-small cell lung cancer (NSCLC), who have received at least one prior systemic therapy.

KRAS, also known as kirsten rat sarcoma, is an oncogene that’s most frequently mutated in human cancer. The translated KRAS protein is a signaling G protein involved in cell growth and differentiation of the MAPK pathway. It switches between a GDP bound inactive state and GTP bound active state which facilitates a downstream signaling cascade to lead to changes in gene transcription and activation. KRAS G12C is the most common KRAS mutant in human cancer (40%). A single point mutation on codon 12 is replaced from a Glycine to a Cysteine which locks KRAS in the active state (GTP form) favoring proliferation, differentiation, oncogenic signaling, and tumorgenesis. Adagrasib, brand name Krazati, works by binding to this mutated cysteine residue and locks it in the GDP bound inactive state thus stopping uncontrolled growth and signaling.

In NSCLC, 10–13% show this KRAS G12C mutation for which adagrasib is approved for. Continued approval for this indication may be contingent upon confirmatory clinical trials that verify its clinical benefit.
It was approved based on objective response rate (ORR) and duration of response (DOR). ORR (including complete and partial responses) was 43% (n=112; 95% CI: 34-53). DOR was a median of 8.5 months (n=112; 95% CI: 6.2-13.8) with 58% having a response duration of ≥6 months.¹ Note that 6.9% of patients had to discontinue the drug due to toxicity.⁴

Adagrasib, comes in 200mg tablets. It’s recommended to take 600mg twice daily with or without food. The most common adverse reactions to the drug (≥25%) includes nausea (70%), diarrhea (60%), vomiting (57%), fatigue (55%), musculoskeletal pain (38%), hepatotoxicity (37%), renal impairment (33%), edema (30%), dyspnea (26%), and decreased appetite (20%). Nausea, diarrhea, or vomiting led to dosage interruption or dose reduction in 29% of patients and permanent discontinuation of adagrasib in 0.3%. Additionally, “the most common Grade 3 or 4 (≥ 2%) laboratory abnormalities were decreased lymphocytes (20%), decreased hemoglobin (7%), increased alanine aminotransferase (4.5%), increased aspartate aminotransferase (4.2%), hypokalemia (3.6%), hyponatremia (3.4%), increased lipase (2.5%), decreased leukocytes (2.5%), decreased neutrophils (2.3%), and increased alkaline phosphatase (2.0%).”¹

Some warnings and precautions include gastrointestinal adverse reactions. In addition to the nausea, vomiting, diarrhea mentioned above, GI bleeding occurred in 3.8%.¹ Another warning/precaution is QTc interval prolongation. Out of the pooled safety population of 366 patients, 6% had at least one post-baseline electrocardiogram (ECG) assessment had an average QTc ≥ 501 msec and 11% of patients had an increase from baseline of QTc > 60 msec.¹ For this reason, it is important to avoid taking adagrasib with other drugs that cause QTc prolongation. A third warning was hepatotoxicity. Drug-induced liver injury was reported in 0.3% of patients and 32% of patients had increased ALT/AST enzymes.¹ Monitor liver laboratory tests monthly for 3 months after starting the dose.¹ The final warning/precaution is interstitial lung disease/pneumonitis (monitor for new or worsening respiratory symptoms indicative of this such as dyspnea, cough, fever). ILD/pneumonitis occurred in 4.1% of patients.¹

Adagrasib is a CYP3A4, 2C9, 2D6, and Pgp inhibitor; thus, avoid joint use with drugs that are sensitive to these substrates because it can lead to increased exposure of other drugs. Additionally avoid strong CYP3A4 inducers and inhibitors with Adagrasib because it is a CYP3A4 enzyme.¹

It will be interesting to see recent data that emerges as this drug stays on the market, but for now, that’s the buzz on this KRAS drug.

References