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NON–SMALL CELL LUNG CANCER
FEBRUARY 3, 2023
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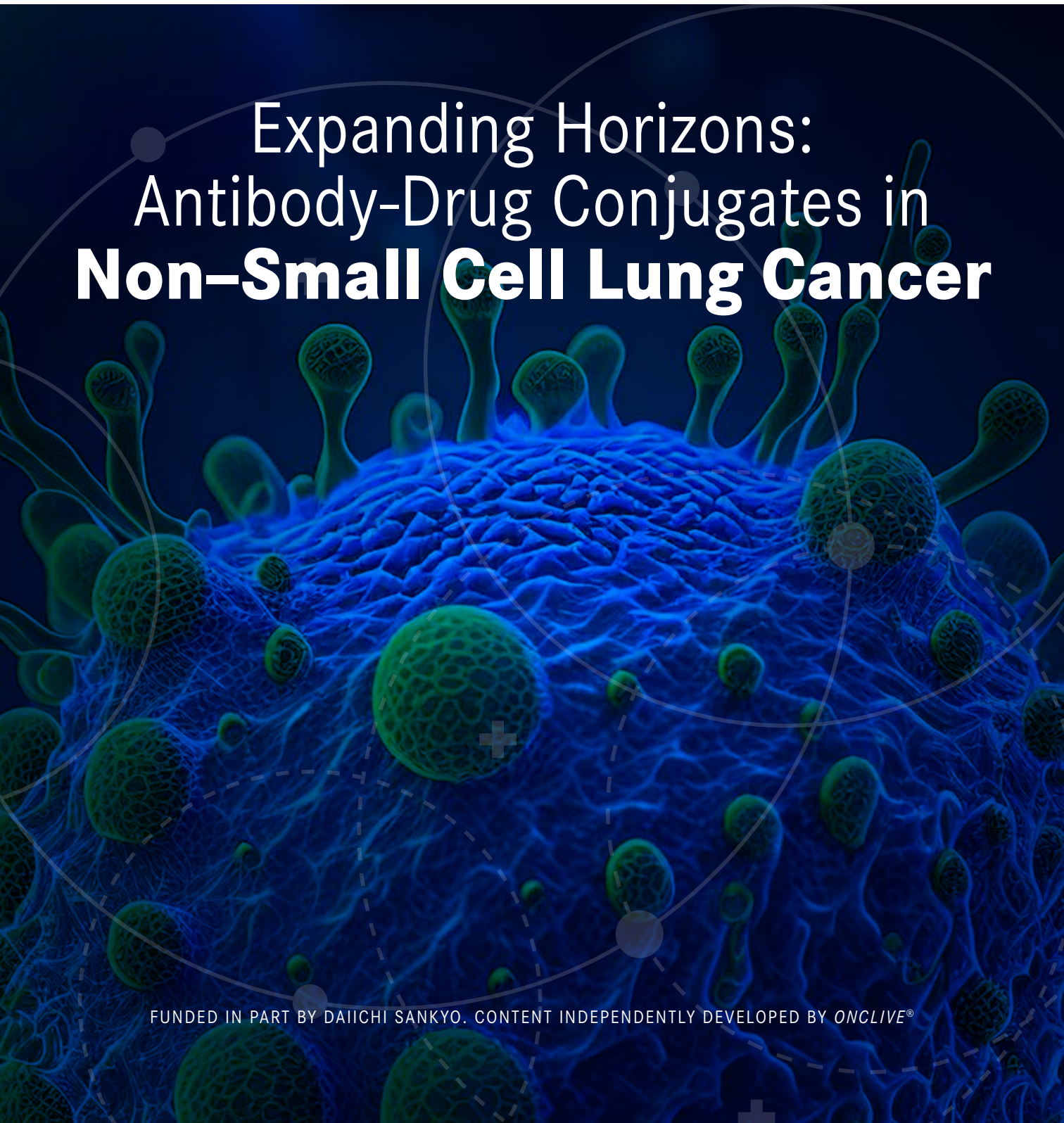
Expanding Horizons: Antibody-Drug Conjugates in **Non–Small Cell Lung Cancer**



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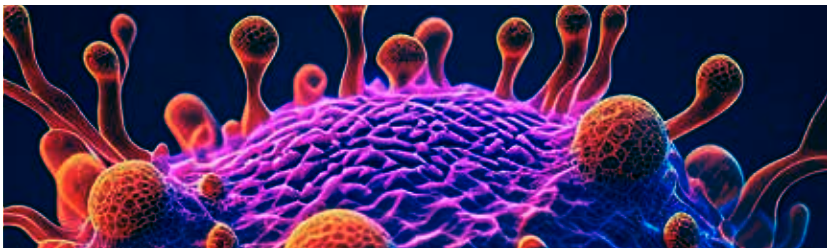

KEY TAKEAWAYS

- The advent of antibody-drug conjugates (ADCs) introduced an exciting potential option for treatment in non–small cell lung cancer (NSCLC), particularly for tumors harboring actionable mutations.
- Tusamitamab ravtansine, an ADC that selectively targets CEACAM5, could fit into the NSCLC treatment paradigm as a second-line treatment. Because keratopathy is a prominent treatment-emergent adverse event (TEAE), patients should be followed concurrently by an ophthalmologist.
- Trastuzumab deruxtecan is an effective second-line treatment in the HER2-mutant treatment space, with a safety profile similar to that of standard platinum-based chemotherapy. Future studies are expected to investigate its first-line use.
- Patritumab deruxtecan has clinical activity independent of resistance mechanisms in EGFR tyrosine kinase inhibitor (TKI)-resistant NSCLC, making the drug an appealing option for patients without on-target resistance.
- The TROP2-directed ADCs datopotamab deruxtecan and sacituzumab govitecan may have a place in the second-line treatment of NSCLC. Still, data do not yet support routine screening for TROP2 as an actionable biomarker.
- Any biomarkers, whether actionable or nonactionable, found in a tissue sample should be noted; their action status may change, and ADCs directed toward them may be on the horizon.

Expanding Horizons: Antibody-Drug Conjugates in **Non–Small Cell Lung Cancer**

INTRODUCTION

ON FEBRUARY 3, 2023, a select group of oncologists participated in a workshop to discuss the growing role of ADCs in the treatment of patients with NSCLC. The workshop, Expanding Horizons: Antibody-Drug Conjugates in Non–Small Cell Lung Cancer, was moderated by **Martin Dietrich, MD, PhD,** assistant professor of Internal Medicine at the University of Central Florida in Orange County and medical oncologist at Florida Cancer Specialists & Research Institute in Orlando. The panelists shared insights about the mechanistic rationale supporting the role of ADCs in treating NSCLC; current and emerging data on the application of novel ADCs in managing patients with NSCLC; and strategies to integrate novel ADCs into clinical practice, including the management of treatment-associated toxicities.

THE ROLE OF ANTIBODY-DRUG CONJUGATES IN NSCLC

ADCs are therapeutic agents combining monoclonal antibodies (mAbs) with cytotoxic drugs that specifically target markers on tumors and deliver potent antitumor agents.[1] Advances in ADC drug design have resulted in greater precision, stronger drug payloads, and lower overall toxicity. ADC biomarker targets under investigation in NSCLC include HER2, HER3, CEACAM5, TROP2, and other biomakers. A summary of some biomarker targets, ADCs targeting these markers, and clinical trials investigating the use of these ADCs in NSCLC can be found in the TABLE.[2-16]

STAKEHOLDER INSIGHTS

Regarding the impact of ADC development on clinical practice, **Jessica Lin, MD**, expressed that she uses the HER2-targeting ADC trastuzumab deruxtecan as a treatment option for patients who have advanced *HER2*-mutant lung cancer, and noted the evolving conversation about first-line use of ADCs in that setting. **Wade Thomas Iams, MD; Seth D. Cohen, MD**; and **Lin** agreed that toxicities, particularly interstitial lung disease (ILD), are a concern when using first-line chemoimmunotherapy and progressing to second-line ADC treatment. **Simi Rai, MD,** noted that most biomarkers are routinely tested upon diagnosis, so there is not much of a barrier if ADCs require biomarker testing to justify their use in treating NSCLC. Noting that benchmarks for safety and efficacy are low with standard second-line docetaxel, **Iams** believed that a progression-free survival (PFS) of 6 to 9 months with an ADC is good. **Cohen** and **Lin** agreed, but noted that while toxicity may be less than with docetaxel, dose reductions with ADCs are often needed, and toxicities such as ILD, cytopenias, and neuropathy are observed.

ADC TARGETS OF INTEREST IN NSCLC

ADCs Targeting HER2

HER2 is a member of the ERBB family of tyrosine kinase receptors; alterations of these receptors in cancer cells promote uncontrolled cell growth.[17] *HER2* alterations in NSCLC include gene amplification and mutation and protein overexpression. *HER2* amplification occurs in 2% to 5% of lung adenocarcinomas and is associated with women, never smokers, and patients having adenocarcinoma histology. *HER2* mutations, 83% of which occur in exon 20, are prevalent in 1% to 5% of patients with NSCLC; they are primarily found in nonsmokers. Additionally, HER2 overexpression is associated with papillary predominant histology, poor disease prognosis, and shorter OS; it has been reported in 10% to 15% of NSCLC cases.

Use of the HER2-directed ADCs trastuzumab emtansine and trastuzumab deruxtecan have been investigated in *HER2*-mutant or -overexpressing NSCLC.[12,15] Trastuzumab emtansine comprises trastuzumab bound to the potent antitubulin maytansine derivative emtansine via a noncleavable thioether linker; it is currently approved for the treatment of breast cancer.[15,18] Trastuzumab deruxtecan consists of the HER2-targeting mAb trastuzumab linked to deruxtecan, a potent

TABLE.
ADC TARGETS AND TRIALS RELATING TO NSCLC[2-16]

Target	ADC	Trial (Phase)	NCT	Phase/Status
CEACAM5	Tusamitamab ravtansine	SAR408701 in solid tumors	NCT02187848	Phase 1/2/Active, not recruiting
		CARMEN-LC03	NCT04154956	Phase 3/Recruiting
		CARMEN-LC05	NCT04524689	Phase 2/Recruiting
HER2	Trastuzumab deruxtecan	DESTINY-Lung01	NCT03505710	Phase 2/Active, not recruiting
		DESTINY-Lung02	NCT04644237	Phase 2/Active, not recruiting
		DESTINY-Lung04	NCT05048797	Phase 3/Recruiting
	Trastuzumab emtansine	Efficacy of T-DM1 HER2 NSCLC	NCT02289833	Phase 2/Completed
HER3	Patritumab deruxtecan	U31402-A-U102	NCT03260491	Phase 1/Active, not recruiting
		HERTHENA-Lung01	NCT04619004	Phase 2/Active, not recruiting
		HERTHENA-Lung02	NCT05338970	Phase 3/Recruiting
TROP2	Datopotamab deruxtecan	TROPION-PanTumor01	NCT03401385	Phase 1/Recruiting
		TROPION-Lung02	NCT04526691	Phase 1b/Recruiting
	Sacituzumab govitecan	IMMU-132-01	NCT01631552	Phase 1/Completed
		TROPiCS-03	NCT03964727	Phase 2/Recruiting
		EVOKE-01	NCT05089734	Phase 3/Recruiting

ADC, antibody drug-conjugate; NSCLC, non–small cell lung cancer; T-DM1, trastuzumab emtansine.

antitopoisomerase I payload, via a tetrapeptide-based cleavable linker.[12] Trastuzumab deruxtecan was granted accelerated FDA approval in August 2022 for the treatment of patients with unresectable or metastatic NSCLC and activating *HER2* mutations and who have received previous systemic therapy, based on results of the DESTINY-Lung02 study.[19]

DESTINY-LUNG01

Trastuzumab deruxtecan was evaluated in the multicenter, phase 2 DESTINY-Lung01 study (NCT03505710) in 91 patients with relapsed or refractory, metastatic, HER2-overexpressing or *HER2*-mutant NSCLC.[12] The primary end point was overall response rate (ORR), and secondary end points were duration of response (DOR), progression-free survival (PFS), overall survival (OS), disease control rate (DCR), and safety. With a median duration of follow-up of 13.1 months, ORR by blinded independent central review (BICR) occurred in 55% of patients. Median DOR (mDOR) was 9.3 months, median PFS (mPFS) was 8.2 months, and median OS (mOS) was 17.8 months.

Treatment-emergent adverse events (TEAEs) of grade 3 or greater occurred in 46% of patients, the most common event being neutropenia (19%); 25% of patients discontinued treatment due to TEAEs. In addition, adjudicated drug-related ILD/pneumonitis occurred in 26% of patients. Studies of tumor response revealed that of *HER2* mutations, 86% were in exon 20; HER2 proteins were expressed in 83% of patients, and *HER2* gene amplifications were seen in 4.4%. Responses were also observed in patients with no detectable HER2 expression or *HER2* amplification.

DESTINY-LUNG02

The blinded, randomized, non-comparative, phase 2 DESTINY-Lung02 trial (NCT04644237) assessed the benefit-risk profile of 2 doses of trastuzumab deruxtecan, 5.4 and 6.4-mg/kg, in patients with unresectable or metastatic, *HER2*-mutant, non-squamous NSCLC with disease progression after prior systemic therapy. The primary end point was confirmed ORR by BICR and secondary end points were DOR by BICR, confirmed DCR, and safety.[7] The prespecified early cohort (PEC; patients randomly assigned ≥ 4.5 months before data cutoff) included individuals with postbaseline tumor assessments, and the safety analysis set (SAS) included randomly assigned patients who received 1 or more doses of trastuzumab deruxtecan. In the PEC, ORR was 53.8% and 42.9% in patients receiving trastuzumab deruxtecan 5.4 or 6.4 mg/kg, respectively.

The lower dose also showed superior safety and tolerability, including a lower rate of ILD, leading to the approved recommended dose of 5.4 mg/kg every 3 weeks.[19] In the PEC and SAS, TEAEs were observed more frequently among patients receiving trastuzumab deruxtecan 6.4 mg/kg vs those given 5.4 mg/kg. In both cohorts, the median treatment duration in the higher-dose arm was shorter than noted in the lower-dose arm (PEC, 4.7 vs 5.5 months, respectively; safety population, 3.3 vs 3.7 months). Any-grade adjudicated drug-related ILD occurred in the SAS in 5.9% and 14.0% of patients receiving trastuzumab deruxtecan 5.4 or 6.4 mg/kg, respectively.

DESTINY-LUNG04

The open-label, multicenter, phase 3 DESTINY-Lung04 study (NCT05048797) will evaluate the efficacy and safety of first-line trastuzumab deruxtecan vs standard of care in systemic treatment–naive patients with unresectable, locally advanced or metastatic, nonsquamous NSCLC with *HER2* exon 19 or 20 mutations and no targetable oncogenic alterations.[13] Patients will be randomly assigned to receive trastuzumab deruxtecan or the standard of care regimen (platinum [investigator's choice of cisplatin or carboplatin], pemetrexed, and pembrolizumab). The primary study end point is PFS, defined by RECIST version 1.1 (RECIST v1.1) per BICR; secondary end points include OS, ORR, and DOR (by RECIST v1.1 per BICR and investigator), investigator-assessed PFS (by RECIST v1.1), and time to second progression or death (per local standard clinical practice), central nervous system PFS (by RECIST v1.1 per BICR), landmark PFS at 12 months (by RECIST v1.1 per BICR and investigator), and landmarkOS at 24 months.

NCT02289833

The efficacy and safety of trastuzumab emtansine in patients with previously treated, advanced, HER2-overexpressing NSCLC were investigated in a multicenter, single-arm, phase 2 study (NCT02289833) with 2 cohorts (49 patients total) based on an HER2 immunohistochemistry (IHC) of 2+ and 3+.[15] The primary end point was investigator-determined ORR according to RECIST v1.1, defined as complete response (CR) or partial response (PR) on 2 consecutive assessments at least 4 weeks apart; secondary end points were PFS, DOR, clinical benefit rate (CBR), OS, and safety.

There were no treatment responses in the IHC 2+ cohort (29 patients) and 4 PRs (25%) in the IHC 3+ cohort (20 patients), with an ORR of 20%. The CBR was 7% in the IHC 2+ cohort and 30% in IHC 3+ cohort. The DORs for the 4 IHC 3+ responders were 2.9, 7.3, 8.3, and 10.8 months; 3 of these responders had *HER2* amplification. The mPFS and mOS were similar between cohorts (IHC 2+ and IHC 3+, respectively: mPFS, 2.6 vs 2.7 months; mOS, 12.2 vs 15.3 months).

Any-grade AEs of interest occurring in patients with at least 1 AE were infusion reaction (6 patients [12%]); hemorrhage, peripheral neuropathy,

or thrombocytopenia (each, 7 patients [14%]); and hepatotoxicity (5 patients [10%]); the only grade 3 AE occurring in more than 1 patient was fatigue (2 patients [< 1%]), and there was 1 grade 4 AE (seizure).

STAKEHOLDER INSIGHTS

Participants agreed there is a place for trastuzumab deruxtecan as a second-line treatment for *HER2*-mutant disease based on available efficacy data. One participant indicated that the safety profile of trastuzumab deruxtecan is similar to that of standard chemotherapy in regard to neutropenia and gastrointestinal disturbances, but noted concern about ILD seen with use of trastuzumab deruxtecan and the lack of standardized monitoring for ILD in patients treated with ADCs. Further studies are needed to evaluate first-line trastuzumab deruxtecan with HER2 expression or *HER2* mutations as additional markers.

ADCs Targeting HER3

The proto-oncogene HER3, when aberrantly expressed in *EGFR*-mutated NSCLC, contributes to EGFR TKI resistance by blocking apoptosis through HER3/PI3K/AKT signaling.[20] HER3 expression is associated with poor prognosis, and it has been reported to be highly expressed in greater than 40% of lung adenocarcinomas.[21] Patritumab deruxtecan (U3-1402) is a novel anti-HER3 ADC composed of the mAb patritumab coupled with a potent topoisomerase I payload deruxtecan via a tetrapeptide-based cleavable linker.[9] Partitumab deruxtecan was granted breaktrhough therapy designation by the FDA in December 2021 for the treatment of patients with metastatic or locally advanced *EGFR*-mutated NSCLC with disease progression on or after treatment with a third-generation TKI and platinumb-based therapies.[22]

U31402-A-U102 TRIAL

The U31402-A-U102 phase 1, multicenter, open-label, multicohort, dose escalation and expansion study (NCT03260491) examined the safety and efficacy of patritumab deruxtecan in patients with EGFR inhibitor–resistant, *EGFR*-mutated NSCLC.[9] In all, 57 study participants received patritumab deruxtecan 5.6 mg/kg intravenously (IV) once every 3 weeks. At a median follow-up of 10.2 months, the confirmed ORR by BICR was 39%, and the mPFS was 8.2 months; responses were observed in patients with known and unknown EGFR TKI–resistance mechanisms.

Hematologic toxicities were the most common TRAEs of grade 3 or greater. Treatment-related ILDs were reported in 5% of patients; all cased resolved after treatment was discontinued.[9]

HERTHENA-LUNG 01

In the ongoing, multicenter, open-label, phase 2 HERTHENA-Lung01 trial (NCT04619004), patritumab deruxtecan is being evaluated in patients with metastatic or locally advanced NSCLC with an activating *EGFR* mutation (exon 19 deletion [ex19del] or L858R) who have received and experienced progression while on, or after receiving, at least 1 EGFR TKI and 1 platinum-based chemotherapy-containing regimen.[2] Patients are randomly assigned to receive a fixed-dose regimen or gradually increased dose of patritumab deruxtecan. The primary end point is ORR by BICR, and secondary end points are DOR, PFS, investigator-assessed ORR, DCR, time to tumor response (TTR), OS, TEAEs, and best percentage change in the sum of diameters of measurable tumors.

HERTHENA LUNG-02

The primary objective of the HERTHENA Lung-02 study (NCT05338970) is to compare the efficacy of patritumab deruxtecan with platinum-based chemotherapy, as measured by PFS and the key secondary end point of OS in patients with metastatic or locally advanced NSCLC with an *EGFR* activating mutation (ex19del or L858R) after failure of third-generation EGFR TKI therapy.[3] Other secondary outcome measures include investigator-assessed PFS, ORR, DOR, CBR, DCR, TTR, TEAEs, and quality of life (QOL).

STAKEHOLDER INSIGHTS

Lin and **Mekhail** noted that patritumab deruxtecan has clinical activity in EGFR TKI-resistant cancers independent of resistance mechanisms, which makes the drug an exciting option for patients without on-target resistance. The panelists agreed that patritumab deruxtecan is a reasonable choice in the second-line setting and beyond given its efficacy and safety profile, but ILD is a concern as a potential AE.

ADCs Targeting CEACAM5

CEACAM5 belongs to a family of glycoproteins involved in cell adhesion, migration, and the inhibition of anoikis in humans.[23,24] CEACAM5 is believed to facilitate tumorigenesis and metastasis, as inhibition of anoikis is a known characteristic of cancer cells.

This emerging biomarker is differentially expressed in lung tissue; low expression has been noted in healthy lung tissue, and high expression (IHC intensity ≥ 2+ in ≥ 50% of tumor cells) has been found in up to 20% of nonsquamous NSCLC tissue.[5,23,25,26] In patients with NSCLC, no correlations have been found between CEACAM5 expression and patient sex, age, smoking history, or histologic grade.[23] However, CEACAM5 expression has been correlated with TNM stage, lymph node invasion, and histologic grade; therefore, CEACAM5 potentially is targetable by ADCs.

Tusamitamab ravtansine is a humanized mAb covalently bound »

to a potent antitubulin maytansinoid payload via a cleavable linker, allowing the selective targeting of CEACAM5-expressing tumor cells.[14,27]

NCT02187848 TRIAL

The efficacy and safety of tusamitamab ravtansine in patients with heavily pretreated, nonsquamous NSCLC expressing CEACAM5 were examined in a first-in-human, dose-escalation, phase 1/2 trial (NCT02187848).[5] Results in 2 cohorts, consisting of 28 patients exhibiting moderate expression (IHC ≥ 2+ in ≥ 1% to < 50% of tumor cells) and 64 patients exhibiting high expression (IHC ≥ 2+ in ≥ 50% of tumor cells), were analyzed; the primary end point was ORR. Patients had a median of 3 prior treatments for advanced disease; these included antitubulin agents (60.9%) and anti–PD1/PD-L1 agents (75%). Two confirmed PRs were observed (ORR, 7.1%) in the moderate expressor cohort. Interim results demonstrated that in the high expressor cohort, 13 patients had confirmed PRs (ORR, 20.3%), and 27 patients (ORR, 42.2%) had stable disease; an ORR of 17.8% was observed in 45 patients who had prior anti–PD1/PD-L1 therapy. Six patients discontinued due to TEAEs, of which the most frequent (all grades) were asthenia (38.0%), keratopathy/keratitis (38.0%), peripheral neuropathy (26.1%), dyspnea (23.9%), and diarrhea (22.8%). Dose modification due to a TEAE was necessary for 31 patients; 10 were due to keratopathy/keratitis, which was reversible and manageable with the modification. Reported hematologic toxicities included leukopenia (14.4%), neutropenia (4.4%), and thrombocytopenia (13.3%). TEAEs of grade 3 or greater occurred in 47.8% of patients, of which 15.2% were deemed to be drug related.

Sustained PR was observed in 67% of patients treated for at least 6 months, 53% of those treated for at least 9 months, and 47% of those treated for at least 12 months.[21] In patients treated for at least 12 months, sustained PR appeared to occur regardless of CEACAM5 expression level. Corneal TEAEs occurred in 73% of patients (≥ grade 3 keratitis, 36%; ≥ grade 3 keratopathy, 18%); there were no treatment discontinuations due to corneal AEs, which were easily managed with dose modifications.

CARMEN-LC05

The ongoing, open-label, phase 2, 3-part CARMEN-LC05 trial (NCT04524689) will investigate the safety and efficacy of frontline tusamitamab ravtansine plus pembrolizumab compared with tusamitamab ravtansine plus pembrolizumab and platinum-based chemotherapy with or without pemetrexed, in patients with CEACAM5-positive (CEACAM5 intensity ≥ 2+ in ≥ 1% of tumor cells by IHC), metastatic, nonsquamous NSCLC.[14]

Interim data demonstrated that among 25 patients treated for a median of 11 weeks across all cohorts, the ORR was 40%, and the DCR was 88%.[28] The most frequent TEAEs were nausea (44%), diarrhea (36%), and asthenia (32%). TEAEs of grade 3 or greater were reported in 68% of patients, and corneal TEAEs of any grade occurred in 24% of patients.

CARMEN-LC03

The ongoing, open-label, phase 3 CARMEN-LC03 trial (NCT04154956) is evaluating the safety and efficacy of tusamitamab ravtansine in the second-line setting compared with docetaxel in patients with CEACAM5-positive, metastatic, nonsquamous NSCLC who previously were treated with platinum-based chemotherapy and an immune checkpoint inhibitor.[10] The primary objectives are PFS and OS, with secondary objectives of ORR, DOR, health-related QOL, and safety. The trial is currently recruiting.

STAKEHOLDER INSIGHTS

Participants noted they do not yet routinely test for CEACAM5; those with experience with tusamitamab ravtansine discussed the drug's TEAEs. **Cohen** and **Rai** mentioned the importance of coordinating care with an experienced ophthalmologist or optometrist for the initial screening examination, prescription of ocular lubricants, and periodic ophthalmologic assessments for those taking tusamitamab ravtansine to prevent keratopathy.

Some panelists noted that the CARMEN-LC05 study lacks clarity of design. **Tarek Mekhail, MD, MS, FRCSI, FRCSEd,** explained that the trial lacked a comparative arm and, instead, involved 3 studies running in parallel; the arm yielding the most interesting results would be chosen to move into a phase 3 study.

Cohen and **Iams** believed that tusamitamab ravtansine could fit into the NSCLC treatment paradigm as a second-line treatment in patients with high CEACAM expression, if they were followed concurrently by an ophthalmologist. Participants expressed that further data are needed to determine the utility of this treatment for patients with moderate CEACAM5 expression. **Rai** and **Alan P. Lyss, MD,** had reservations about its use due to toxicities and noncompliance issues.

ADCs targeting TROP2

TROP2, a cell-surface glycoprotein, promotes malignant potential in several cancers, including NSCLC.[29-31] Increased TROP2 expression is associated with poor prognosis in NSCLC that is classified as adenocarcinoma but not in squamous cell NSCLC.[29,30] Results of recent work implicate TROP2 as an actionable biomarker in solid tumors, including NSCLC.[31]

Two agents under investigation are datopotamab deruxtecan, which is composed of the humanized, TROP2-

targeted mAb datopotamab conjugated to the topoisomerase I inhibitor deruxtecan via a tetrapeptide-based cleavable linker, and sacituzumab govitecan (IMMU-132), which contains the TROP2-directed mAb sacituzumab coupled to the cytotoxic SN-38 payload (a potent topoisomerase inhibitor and active metabolite of irinotecan) via a hydrolysable linker.[32-35]

TROPION-PANTUMOR01

The phase 1, 2-part, dose-escalation and expansion study (NCT03401385) of datopotamab deruxtecan in patients with advanced/metastatic solid tumors included a cohort with NSCLC.[4] Eligible patients were unselected for TROP2 expression, and they had measurable disease per RECIST v1.1; patients with stable or treated brain metastases were permitted. The primary objective was safety and tolerability, and the secondary objectives were efficacy and pharmacokinetics. In the NSCLC cohort, 180 patients from the dose-escalation and -expansion phases were treated with datopotamab deruxtecan 4 mg/kg (50 patients), 6 mg/kg (50 patients), or 8 mg/kg (80 patients), with a median follow-up of 11.4 months. ORR by BICR by dose was 24% for those given 4 mg/kg, 26% for those given 6 mg/kg, and 24% for those given 8 mg/kg; 4 patients (2 each at the 4- and 6-mg/kg doses) still are being treated. Grade 3 or greater TEAEs were reported in 47% of patients across doses.

TEAEs were predominantly nonhematologic; those of all grades that were seen in more than 30% of patients included nausea (52%), stomatitis (48%), alopecia (39%), and fatigue (32%). Of these, TEAEs that were greater than grade 3 included stomatitis (2%) and nausea and fatigue (each 1%). Drug-related ILD occurred in 19 patients (11%). A subset analysis of the NSCLC cohort after the data cutoff revealed that 34 patients had actionable genetic mutations (AGAs), including *EGFR* mutation (85%), *ALK* fusion (9%), *ROS1* fusion (3%), and *RET* fusion (3%).[36] Clinical activity was observed in *EGFR*-sensitizing mutations (ex19del, L858R), after osimertinib use, and across other AGAs.

TROPION-LUNG02

TROPION-Lung02 (NCT04526691) is an ongoing, open-label, phase 1b trial evaluating the safety and efficacy of datopotamab deruxtecan in patients with advanced or metastatic NSCLC.[11] Primary objectives were to assess the safety and tolerability of datopotamab deruxtecan. Secondary objectives were to evaluate efficacy, pharmacokinetics, and antidrug antibodies.

Patients were treated with datopotamab deruxtecan plus pembrolizumab with or without carboplatin or cisplatin. At a median treatment duration of 2.7 months, the ORR among all 46 patients was 39.0%, and the DCR was 82.6%. Among the cohort of 16 patients receiving first-line therapy, the ORR was 69%, and the DCR was 100%. The most commonly observed TEAEs of any grade included stomatitis (42%), nausea (38%), and fatigue (27%). There were no reported cases of ILD.

An interim analysis demonstrated that patients receiving datopotamab deruxtecan plus pembrolizumab (doublet cohort) had an ORR of 37% at a median follow-up of 6.5 months and a DCR of 84%; patients receiving datopotamab deruxtecan plus pembrolizumab and carboplatin or cisplatin (triplet cohort) had an ORR of 41% and a DCR of 84%.[36] The most frequent TEAEs of any grade in the doublet and triplet cohorts, respectively, were stomatitis (56% and 29%), nausea (41% and 48%), decreased appetite (28% and 38%), fatigue (25% and 36%), and anemia (16% and 36%). There were 4 ILD events determined as drug-related by an independent adjudication committee across cohorts; 2 were adjudicated as grade 1 or 2, and 2 were adjudicated as grade 3.

IMMU-132-01 TRIAL

A single-arm, multicenter trial (NCT01631552) evaluated the efficacy and safety of sacituzumab govitecan in patients with pretreated, metastatic NSCLC.[8] Patients received sacituzumab govitecan (either 8 or 10 mg/kg) on days 1 and 8 of 21-day cycles. The primary end points were safety and ORR; PFS and OS were secondary end points. The response-assessable study population of 47 patients, who had a median of 3 prior therapies, had an ORR of 19%, mDOR of 6.0 months, and a CBR (objective response plus stable disease lasting ≥ 4 months) of 43%. ORR in the intention-to-treat (ITT) population was 17%. The median onset of response was 3.8 months, the median ITT PFS was 5.2 months, and the median ITT OS was 9.5 months.

TEAEs of grade 3 or greater included neutropenia (28%), leukopenia (9%), pneumonia (9%), diarrhea (7%), nausea (7%), fatigue (6%), and febrile neutropenia (4%). More than 90% of 26 assessable archival tumor specimens showed increased expression of TROP2 (IHC 2+, 3+).

TROPICS-03

TROPiCS-03 (NCT03964727) is a phase 2, multicohort, open-label study of sacituzumab govitecan in patients with solid metastatic tumors (including NSCLC) to test a biomarker-enrichment strategy with TROP2.[16] Patients will be treated with sacituzumab govitecan 10 mg/kg IV on days 1 and 8 of a 21-day cycle until disease progression or toxicity occurs. The primary outcome measure is ORR (investigator assessed).

EVOKE-01

EVOKE-01 (NCT05089734) is an open-label, global, multicenter, randomized, phase 3 study of sacituzumab govitecan vs docetaxel in patients with advanced stage IV NSCLC with progression on or after platinum-based chemotherapy and anti–PD-1/PD-L1 immunotherapy.[8] Patients with AGAs must have received »

treatment with at least 1 TKI. The primary end point is OS; secondary end points include PFS, ORR, DOR, DCR, TEAEs, abnormal laboratory test results, and mean change in score from baseline on the NSCLC Symptom Assessment Questionnaire.

STAKEHOLDER INSIGHTS

The panelists expressed interest in exploring TROP2 expression in NSCLC and using TROP2 as a biomarker of ADC targeting. Datopotamab deruxtecan may be beneficial in the anti-EGFR setting. Data from the TROPION trials were promising for the use of datopotamab deruxtecan as a first-line treatment, but they want to see more data.

The panelists believed that sacituzumab govitecan has a place in the second-line treatment of NSCLC. The participants would like to see more stratified data to support the consideration of TROP2 expression as part of standard care. They agreed that datopotamab deruxtecan and sacituzumab govitecan are powerful agents, but patient tolerability remains a concern.

LOOKING AHEAD

The panelists expressed that with the advent of more biomarker-driven therapeutic options, second biopsies might be needed due to changes in gene expression that can occur after the initial cancer diagnosis. **Mekhail** pointed out that second biopsies may be considered problematic, yet a patient seeking active treatment with good performance status would be unlikely to decline a biopsy. **Lyss** noted that referral of North American patients to international studies on ADCs may be an issue, and he raised the question of how data on new drugs developed exclusively outside North America should be approached. **Iams** noted that the motivation to obtain biomarker specimens primarily would be affected by the timing of approval of particular ADCs, such as an unselected ADC vs a biomarker-specific ADC. **Dietrich** believed that screening for CEACAM5 and, perhaps, HER2 and HER3 is warranted, but data do not yet support screening for TROP2. When asked whether they would collect biomarker data from patients in anticipation of upcoming ADC approvals, **Iams, Rai,** and **Cohen** concurred that these tests were unlikely to be covered by insurance companies prior to approvals. **Lin** pointed out that some large reference laboratories process samples for biomarkers that are not currently actionable. **Cohen, Iams, Mekhail,** and **Rai** reiterated the importance of recording any biomarkers present, whether actionable or nonactionable, to avoid potential medicolegal issues. ■

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