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LEADING ARTICLE

Clinical Overview of Enfortumab Vedotin in the Management of Locally Advanced or Metastatic Urothelial Carcinoma

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Abstract

The treatment landscape for locally advanced or metastatic urothelial carcinoma has broadened significantly over recent years. New therapeutic options include immunotherapy with checkpoint inhibitors and targeted therapy with erdafitinib. Despite these advances, gaps remain in the selection and sequencing of optimal therapies. Treatment decisions are often influenced by several patient-specific factors such as tolerability and biomarker expression. Following progression while receiving front- and second-line therapies, there is no widely accepted standard of care for patients. Enrollment into a clinical trial is recommended in all lines of therapy for advanced disease. Antibody–drug conjugates have recently emerged as novel therapeutics allowing for targeted delivery of chemotherapeutic agents. Enfortumab vedotin, a nectin-4-targeted antibody conjugated with monomethyl auristatin E, is the first-in-class therapeutic option and has demonstrated unprecedented response rates following progression on chemotherapy and immunotherapy for advanced disease with a tolerable safety profile. As a result, a biologics license application was submitted to the US FDA in July 2019. Ongoing clinical trials are aiming to further establish the role of enfortumab vedotin in urothelial carcinoma. In this article, we highlight the safety and efficacy of enfortumab vedotin for patients with advanced bladder cancer, ongoing clinical trials, clinical pharmacology, and pharmacokinetics.

Key Points

Enfortumab vedotin, a nectin-4-targeted antibody–drug conjugate, has demonstrated a safe and effective therapeutic profile for patients with locally advanced or metastatic bladder cancer following platinum-based chemotherapy and immunotherapy.

Peripheral neuropathy, hyperglycemia, and rash have been associated with enfortumab vedotin, and prompt management is required. Peripheral neuropathy is a known toxicity associated with monomethyl auristatin E, and rash is associated with nectin-4 expression in skin.

Ongoing clinical trials for advanced bladder cancer are investigating combination chemoimmunotherapy, targeted therapies, and sequencing of therapy, which will likely influence treatment decisions in the future.

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1 Introduction

Urothelial carcinoma (UC) is the sixth most common cancer in the USA, accounting for 80,470 (4.6%) new cases and 17,670 (2.9%) deaths in 2019 [1]. Although only approximately 5% of patients present with metastatic UC (mUC) at initial diagnosis, a large portion of patients treated for localized disease relapse or progress to advanced stages, with a 5-year relative survival of 4.6% [2, 3]. In recent years, significant advances in treatment options have been made using immunotherapies and targeted therapies for locally advanced UC or mUC, although cisplatin-based chemotherapy remains the front-line standard of care in eligible patients [2].

UC is a highly mutated tumor type, and several agents and combination therapies are under investigation in clinical trials [4]. Erdafitinib, a novel pan-fibroblast growth factor receptor (FGFR) inhibitor, was recently approved by the US FDA as a second-line treatment option for patients with susceptible FGFR2 or FGFR3 alterations following platinum-based chemotherapy based on an objective response rate (ORR) of 32.2% (95% confidence interval [CI] 22.4–42.0) [5]. However, FGFR aberrations occur in

approximately 10–20% of patients with mUC [6]. Furthermore, the development of immune checkpoint inhibitors as treatment options for mUC has led to two approved agents in the front-line setting (pembrolizumab and atezolizumab) and five agents in the second-line setting (pembrolizumab, nivolumab, avelumab, durvalumab, and atezolizumab). Currently, pembrolizumab is the only National Comprehensive Cancer Network (NCCN) category 1 recommendation in the second-line setting following progression after receiving platinum-based chemotherapy [3]. The ORR observed with immune checkpoint blockage in locally advanced UC or mUC ranges between 15 and 24%, and their use in the front-line setting for select patients was limited from the initial label by the FDA because of improved survival achieved with chemotherapy versus immune checkpoint blockade in patients whose tumors had low programmed death ligand 1 (PD-L1) expression [7, 8]. These changes were based on the interim survival analysis from the ongoing KEYNOTE-361 and IMvigor130 studies (ClinicalTrials.gov identifiers: NCT02853305 and NCT02807636), phase III trials of pembrolizumab and atezolizumab with or without chemotherapy compared with chemotherapy alone in advanced UC. For pembrolizumab, a combined positive score $\geq 10\%$ is now required using the PD-L1 IHC 22C3 pharmDx assay; for atezolizumab, $\geq 5\%$ PD-L1 expression in tumor-infiltrating immune cells by the VENTANA PD-L1(SP142) assay is required.

Patients with locally advanced UC or mUC have many unmet needs in terms of prioritizing front-line treatment according to the ability to tolerate platinum-based chemotherapy versus checkpoint ligand expression, as well as sequencing treatment following initial selection and tolerability in the second-line setting. No third-line standard-of-care option currently exists. The NCCN recommends enrollment into a clinical trial for all stages of advanced disease [3].

A notable investigational antibody–drug conjugate (ADC), enfortumab vedotin, was recently granted breakthrough therapy designation by the FDA for its preliminary clinical evidence, novel mechanism of action, and the need for improved therapies for UC [8, 9]. ADCs are an emerging class of agents providing a unique mechanism of targeted drug delivery of a cytotoxic agent through a targeted antibody and a linked therapeutic agent [10]. On 16 July 2019, the biologics license application (BLA) was submitted to the FDA, seeking accelerated approval of enfortumab vedotin for the treatment of patients with locally advanced UC or mUC who have received a checkpoint inhibitor and platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced, or metastatic setting [11]. Here, we review the clinical pharmacology, kinetics, clinical trials, efficacy and safety, and proposed place in therapy for enfortumab vedotin.

2 Clinical Pharmacology of Enfortumab Vedotin

Enfortumab vedotin is a fully humanized monoclonal antibody (AGS-22M6) targeting nectin-4 linked to the microtubule-disrupting agent monomethyl auristatin E (MMAE), similar to the FDA-approved brentuximab vedotin, which targets cluster of differentiation (CD)-30 and is also linked to MMAE [12, 13]. The AGS-22CE antibody is conjugated to MMAE through interchain disulfide bonds with tris (2-carboxyethyl)-phosphine in an approximate 4:1 ratio in enfortumab vedotin [14].

Nectins are immunoglobulin-like transmembrane proteins that are found in the adherens junctions of cells and mediate Ca^{2+}-independent cell–cell adhesion via both homophilic and heterophilic transinteractions. Nectin-4, specifically, has been shown to have strong affinity to nectin-1 and is highly expressed in urothelial, breast, lung, and pancreatic cancer tissues. Binding of nectin-4 to nectin-1 plays an important role in cell growth, cellular proliferation, and migration by recruiting cadherins and modulating cytoskeleton rearrangements. Nectin-4 has been proposed to signal through the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathway and has been correlated with vascular endothelial growth factor expression [15, 16]. Overexpression of nectin-4 is associated with disease progression and poor prognosis. In human tissue microarrays, moderate to strong staining of nectin-4 was observed in 60% of assessed bladder tissues [14]. Once bound to nectin-4, enfortumab vedotin internalizes into the cell. MMAE is then cleaved via proteolytic enzymes and binds to the tubules and disrupts the cellular microtubule network, inducing cell cycle arrest (G2/M phase) and apoptosis.

Initial preclinical data for enfortumab vedotin demonstrated that targeting of nectin-4 resulted in growth inhibition of multiple human xenografts with positive expression, and tumor regression in urothelial and breast cancers [14]. In vitro assays demonstrated the successful inhibition of the nectin-4/nectin-1 interaction. In vivo antitumor activity was dose dependent: ≤ 1 mg/kg inhibited the growth of bladder and breast cancer xenografts; ≥ 3 mg/kg inhibited subcutaneous bladder and breast cancer xenografts and orthotopic breast cancer xenografts. Of note, the unbound AGS-22CE antibody did not result in antitumor activity in any preclinical model; efficacy is correlated with the bound ADC and nectin-4 expression.

It is important to note that there are two antibodies of enfortumab vedotin; both the hybridoma-derived AGS-22M6E (also known as ASG-22ME) and the Chinese hamster ovary cell-derived ASG-22CE have shown eradication of established tumor xenografts, and different antibodies may be referenced in the literature [14].

3 Pharmacokinetics of Enfortumab Vedotin

When injected in mice at a single bolus of 10 mg/kg, enfortumab vedotin exhibited similar pharmacokinetic properties as the unbound AGS-22CE antibody: elimination half-life ($t_{½}$) = 1.53 versus 1.72 days, concentration maximum = 135 versus 177 µg/mL, area under the concentration–time curve (AUC) from time zero to last observable time point = 336 versus 324 day × µg/mL, AUC from time zero to observable time point = 339 versus 329 day × µg/mL, volume of distribution = 78.1 versus 82.4 mL/kg, and clearance 29.4 versus 30.3 mL/day/kg [14].

EV-101 (ClinicalTrials.gov identifier NCT02091999) is a phase I, dose-escalation and expansion trial in patients with solid tumors, including mUC, who were given enfortumab vedotin at four dose levels of 0.5, 0.75, 1, or 1.25 mg/kg on days 1, 8, and 15 every 28 days as a 30-min intravenous infusion [17]. Serum concentrations were dose proportional, and antitumor activity was seen at all dose levels. The serum $t_{½}$ of enfortumab vedotin is 1.5–2 days [14, 17].

MMAE, the cytotoxic component of enfortumab vedotin, exhibits additional kinetic properties: protein binding = 68–82%, $t_{½}$ = 3–4 days, and time to peak = 1–3 days after the end of infusion [13]. Steady-state concentrations of MMAE are generally achieved within 21 days. In vitro data indicate that MMAE metabolism occurs primarily via oxidation by cytochrome P450 (CYP)-3A4/5 but does not induce any CYP enzymatic processes. No dose adjustments for drug–drug interactions are provided for MMAE-containing ADCs. With the administration of brentuximab vedotin, the AUC of MMAE increased approximately twofold in patients with severe renal impairment and 2.3-fold in patients with hepatic impairment compared with those with healthy organ function.

4 Clinical Trials

4.1 EV-101 Trial

EV-101 is a phase I trial evaluating the pharmacokinetics, immunogenicity, safety, and antitumor activity of enfortumab vedotin in subjects with mUC and other malignant solid tumors that express nectin-4 [18]. A key secondary endpoint of this trial was tumor response, defined as a complete response (CR) or partial response (PR) per Response Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.1). Key inclusion criteria for subjects with mUC were failure of at least one prior chemotherapy regimen for metastatic disease unless deemed ineligible for cisplatin, availability of tumor tissue sampling for nectin-4 expression (an immunohistochemistry H-score ≥ 150 for nectin-4 expression was considered positive), and no grade ≥ 2 motor neuropathy. The study design consisted of three arms: arm A was a dose-escalation arm of enfortumab vedotin; arm B was a dose-expansion arm of three cohorts consisting of patients with (1) mUC and renal insufficiency, (2) non-small-cell lung cancer, and (3) ovarian cancer; arm C was a dose-expansion arm of patients who received checkpoint inhibitors in the metastatic setting. Of note, because of the universal expression of nectin-4, the trial protocol was amended during the enrollment phase to enroll all patients independent of immunohistochemistry using the H-score.

Mature results from EV-101 were assessed in 112 patients with mUC that received enfortumab vedotin 1.25 mg/kg on days 1, 8, and 15 every 28 days with a median follow up of 13.4 months [19]. The dosing schema of enfortumab vedotin was established from the preliminary results of this study that suggested activity and tolerability at the maximum tolerated dose (RP2D) of 1.25 mg/kg [20]. Patients were heavily pretreated, with nearly all patients having had prior exposure to platinum-based chemotherapy and 89 having received a prior checkpoint inhibitor. Additionally, 33 (29.5%) patients had liver metastasis. Enfortumab vedotin resulted in an ORR of 42% (CR, n = 5; PR, n = 42) in the intent-to-treat population. An ORR of 42% (95% CI 31.2–52.5) and 36% (95% CI 20.4–54.9) was seen in patients with prior checkpoint exposure and liver metastasis, respectively; overall survival (OS) at 1 year was 51.6% (95% CI 40.3–61.8) and 42% (95% CI 25.0–58.0), with a median OS of 12.2 months (95% CI 8.5–17.1) and 10.4 months (95% CI 6.4–14.1); median progression-free survival (PFS) was 5.4 months (95% CI 5.1–6.3) and 3.5 months (95% CI 1.6–6.6). The median duration of response (DoR) following checkpoint inhibitor therapy was 7.4 months (95% CI 4.2–9.4) and 7.7 months (95% CI 3.7 to –) in the liver metastasis arm; 23.4% of responses were ongoing at a median follow-up of 11.3 months.

The most commonly reported adverse drug reactions (ADRs) were fatigue (53%), alopecia (46%), and decreased appetite (42%). Grade ≥ 3 ADRs that occurred in ≥ 5% of patients included anemia (8%), hyponatremia (7%), urinary tract infection (7%), and hyperglycemia (6%); four fatal ADRs were reported (respiratory failure, urinary tract obstruction, diabetic ketoacidosis, and multiorgan failure).

4.2 EV-201 Trial

EV-201 (NCT03219333) is a global, phase II, two-cohort, single-arm trial aiming to establish the safety and efficacy of intravenous enfortumab vedotin 1.25 mg/kg on days 1, 8, and 15 of every 28-day cycle in patients with locally advanced UC or mUC who were previously treated with platinum-based chemotherapy and checkpoint inhibitor

therapy [21]. Cohort 1 of the trial enrolled patients who were exposed to both platinum-based chemotherapy and immunotherapy; cohort 2 is currently recruiting patients who have only received prior immunotherapy. Eligible subjects were patients aged ≥ 18 years who had an Eastern Cooperative Oncology Group performance status (ECOG PS) score of ≤ 1, adequate baseline organ function, and no grade ≥ 2 sensory or motor neuropathy. The primary endpoint of EV-201 was ORR by independent review, and secondary endpoints included DoR, PFS, ORR by investigator, OS, safety, and tolerability. Tumor response was assessed per the RECIST v1.1 criterion.

A total of 128 patients were enrolled in cohort 1, and 125 patients received treatment. The median age was 69 years (range 40–84), with 27% aged ≥ 75 years [22]. Visceral metastases were present in 90% of patients, and 40% had liver metastases. Patients were heavily pretreated, with a median of three systemic therapies (range 1–6); 26% had received taxanes. Confirmed ORR was 44% (95% CI 35.1–53.2) by independent review, with a 12% CR rate and 32% PR rate. Similar responses were observed in prespecified subgroups, which included responses to prior immunotherapy (56% in responders, 41% in nonresponders) and in patients with poor prognostic characteristics, including liver metastases (38%), and three or more prior lines of therapy (41%). Stable disease was the best response in 28% of patients, 18% had progressive disease, and 10% were not evaluable. The median DoR was 7.6 months (range 0.95–11.30 +; 95% CI 4.93–7.46). Objective responses occurred regardless of prior responses to checkpoint inhibitors.

Peripheral neuropathy, rash, and hyperglycemia were prespecified for analysis as composite terms. These ADRs are discussed in depth within the discussion section. The most common ADRs were fatigue (50% all grade and 6% grade ≥ 3), alopecia (49% all grade), decreased appetite (44% all grade and 1% grade ≥ 3), dysgeusia (40% all grade and none grade ≥ 3), and peripheral sensory neuropathy (40% all grade and 2% grade ≥ 3). The most common grade ≥ 3 ADRs were neutropenia (8%), anemia (7%), and fatigue (6%). Febrile neutropenia (4%) was the most common serious ADR; no routine growth factor treatment was used. Neuropathy resolved in most patients or was ongoing at grade 1 at the last follow-up. No deaths were reported during the safety reporting period.

4.3 Notable Ongoing Trials

The EV-301 trial (NCT03474107) is an ongoing phase III trial aiming to demonstrate a survival benefit of enfortumab vedotin [23]. With a similar intent to the Keynote 045 trial, which established a survival benefit of pembrolizumab over chemotherapy as a second-line option in immunotherapy-naïve patients, EV-301 is comparing enfortumab vedotin versus investigator's choice of chemotherapy following progression on front- and second-line treatment with chemotherapy and immune checkpoint blockade [23, 24]. Additionally, the EV-103 trial (NCT03288545) is a phase I, dose-escalation, dose-expansion trial looking at a broader use of enfortumab vedotin in combination with chemotherapy or immunotherapy in the front-line setting for locally advanced UC or mUC [25]. Various cohorts within the trial include cisplatin- and platinum-ineligible patients. Initial results from EV-103 demonstrated that the combination of enfortumab vedotin plus pembrolizumab shrank tumors in most patients, resulting in an ORR of 71% (32/45; 95% CI 55.7–83.6). The CR rate was 13% (6/45); 58% (26/45) of patients had a PR, and 22% (10/45) had stable disease [26]. In total, 91% of responses were observed at the first assessment. Grade ≥ 3 treatment-related adverse events of clinical interest were rash (11%; 5/45), hyperglycemia (7%; 3/45), and peripheral neuropathy (4%; 2/45); these rates were similar to those observed with enfortumab vedotin monotherapy [22, 26]. A total of 11% (5/45) of patients had grade ≥ 3 treatment-related immune-mediated adverse events of clinical interest that required the use of systemic steroids (one event each of pneumonitis, dermatitis bullous, hyperglycemia, tubulointerstitial nephritis, myasthenia gravis). None of the adverse events of clinical interest were grade 5 events. Lastly, the safety, tolerability, and pharmacokinetics were evaluated in a phase I open-label trial in 24 Japanese patients with locally advanced UC or mUC [27]. Enfortumab vedotin demonstrated an ORR of 35.3%. Findings from EV-201 and these trials will help establish the role of enfortumab vedotin in patients deemed ineligible for cisplatin and who have only received prior immunotherapy [21].

Table 1 highlights key efficacy outcomes from reported phase I and II trials of enfortumab vedotin for advanced bladder cancer.

5 Discussion

The treatment landscape for locally advanced UC or mUC continues to evolve. Despite numerous therapeutic advances in immunotherapy and targeted therapies, enrollment into a clinical trial is encouraged in all stages of advanced disease. Selection of therapy is often tailored to individual patients based on prior treatment, time between treatment and relapse, ECOG PS, tolerability, ligand expression, access to a clinical trial, end organ function, and preference [3]. Based on findings from EV-101 and EV-201, enfortumab vedotin has demonstrated therapeutic benefit following front-line chemotherapy and second-line immunotherapy [19, 22].

The preferred front-line therapy in patients with locally advanced UC or mUC is cisplatin-based chemotherapy with

Table 1 Efficacy of phase I and II trials of enfortumab vedotin for advanced bladder cancer

	EV-101 trial [19]	Phase I trial (Japanese) [27]	EV-103 trial [25, 26]	EV-201 trial [22]
ClinicalTrials.gov identifier	NCT02091999	NCT03070990	NCT03288545	NCT03219333
Phase	I	I	I	II
Aim	Pharmacokinetics, immunogenicity, safety, and antitumor activity in subjects with mUC and other malignant solid tumors expressing nectin-4	Safety, tolerability, and pharmacokinetics in Japanese patients with locally advanced UC or mUC	Dose-escalation, dose-expansion trial of enfortumab vedotin in combination with chemotherapy or immunotherapy in the front-line setting for locally advanced or mUC	Safety and efficacy of IV enfortumab vedotin 1.25 mg/kg on days 1, 8, and 15 of every 28 days in patients with locally advanced UC or mUC previously treated with platinum-based chemotherapy and checkpoint inhibitor therapy
Population	$n = 112$ (mUC)	$n = 24$	$n = 45$ (preliminary)	$n = 125$
Objective response rate	42% (95% CI 31.2–52.5)	35.3%	71% (32/45; 95% CI 55.7–83.6)	44% (95% CI 35.1–53.2)
Complete response	4.5%	–	13%	12%
Partial response	37.5%	–	58%	32%
Disease control rate	–	76.5%	–	–

CI confidence interval, *IV* intravenous, *mUC* metastatic urothelial carcinoma, *UC* urothelial carcinoma

dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (ddMVAC) or gemcitabine and cisplatin because of improved response rates and survival [3]. Patients who are unable to tolerate cisplatin-based chemotherapy (cisplatin ineligible) may receive carboplatin (i.e., platinum-based). As previously mentioned, pembrolizumab and atezolizumab are also appropriate front-line options but require patients to (1) have positive ligand expression or (2) be deemed ineligible for platinum-based chemotherapy (cisplatin and carboplatin) regardless of ligand expression [8]. Response rates with platinum-based chemotherapy in the front-line setting range between 40 and 60%.

The preferred second-line option is often dictated by the front-line choice of therapy. Patients who progress on platinum-based chemotherapy should receive pembrolizumab as second-line therapy [3]. The phase III Keynote 045 trial established pembrolizumab as the only category 1 option following chemotherapy because of improved OS rates [3, 24]. Patients who are deemed ineligible for platinum in the front-line setting often receive a checkpoint inhibitor, erdafitinib if harboring the indicated FGFR aberrations, or enroll into a clinical trial; however, patients are often frail since they were deemed ineligible for platinum therapy and treatment options are limited.

Enfortumab vedotin demonstrated an ORR that has not been seen in advanced UC to date without requiring biomarker testing because of uniform expression of nectin-4 on bladder cancer cells. Based on the BLA submitted to the FDA, the place in therapy of enfortumab vedotin is aimed as a third-line treatment option [11]. In select patients, enfortumab vedotin may provide a second-line option should patients progress on front-line immunotherapy and lack an FGFR aberration. In addition, enfortumab vedotin was well-tolerated in clinical trials.

Outside of the clinical trials discussed in this article, several studies are evaluating additional FGFR inhibitors, combination chemoimmunotherapy, and various novel targets, including additional ADCs such as sacituzumab govitecan (IMMU-132), RC48-ADC, and trastuzumab deruxtecan (DS-8201a). The maturation of and data from EV-201, EV-301, and EV-103 will help establish and refine the place in therapy for enfortumab vedotin.

On the basis of safety, the monitoring and management of peripheral neuropathy, rash, and hyperglycemia should be noted. In EV-201, treatment-related peripheral neuropathy, a known toxicity associated with MMAE-containing ADCs, occurred in 50% of patients, almost all (94%) of which were grade ≤ 2 [22, 28]. Peripheral sensory neuropathy was more common than motor neuropathy. The median time to onset was 2.43 months (range 0.03–7.39), and most patients (76%) had resolution of or ongoing grade 1 peripheral neuropathy at last follow-up. As seen with brentuximab vedotin, general management of neuropathy includes dose

reductions and/or withholding therapy until recovery [13]. Treatment-related rash occurred in 48% of patients, most of which were low grade (75% grade ≤ 2), with a median time to onset of 0.53 months (range 0.03–7.39) [22]. Of all patients who experienced rash, 73% experienced complete resolution and 20% had some improvement at last follow-up. Rash, often demonstrating as maculopapular and diffuse in appearance, is an expected on-target toxicity with enfortumab vedotin because of nectin-4 expression in the skin [14]. Management of rash includes topical or systemic corticosteroids, oral antihistamines, and enfortumab vedotin dose reductions and delays [22]. Lastly, hyperglycemia occurred in 11% of patients, regardless of known hyperglycemia at baseline, with a median time to onset of 0.58 months (range 0.26–9.23). In patients who experienced hyperglycemia, 57% achieved complete resolution and 14% experienced some improvement. The etiology of the hyperglycemia is unknown at this time but is unlikely to be an on-target effect. Close monitoring of changes in glucose levels should be considered for patients receiving treatment.

The treatment landscape of advanced UC will continue to evolve. As novel therapeutic modalities continue to expand treatment options for UC, an assessment of the cost effectiveness of therapies, key biomarkers of response and resistance, and sequencing of therapies would be of great value.

6 Conclusion

Clinical trials of enfortumab vedotin have demonstrated a safe and effective therapeutic profile in a difficult-to-treat population of patients with locally advanced UC or mUC. To date, there is no widely accepted standard-of-care option for patients with advanced bladder cancer following progression on chemotherapy, immunotherapy, and erdafitinib. Ongoing clinical trials aim to further establish the place of enfortumab vedotin in the treatment paradigm of bladder cancer. Treatment options for UC have significantly changed in recent years, and clinicians should be aware of up-to-date regimens and pipeline agents to provide optimal patient care, select appropriate treatments, manage ADRs, and properly sequence therapies when indicated.

Compliance with Ethical Standards

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