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Review Article

Neoadjuvant Chemotherapy for Bladder Cancer

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Abstract

Background: Muscle invasive bladder cancer (MIBC) is an aggressive malignancy, with 5-year survival rates ranging from 36% to 48% for pT_{3-4}/pN^+ tumors. Radical cystectomy (RC) remains the gold-standard treatment for the management of MIBC. Perioperative treatment can improve overall survival (OS), with more robust evidence favoring neoadjuvant chemotherapy (NAC). **Objective:** This review aims to discuss the historical perspectives, recent advances, experimental therapies, and current evidence for the use of various chemotherapeutic drugs in a neo-adjuvant setting for the treatment of MIBC. **Data Sources:** We searched and analyzed research articles, reviews, clinical trials, and meta-analyses addressing NAC in the management of MIBC. **Results:** The advantages of NAC in MIBC include the delivery of chemotherapy at the earliest time point when the micrometastatic burden is presumed to be the lowest. It has improved patient compliance and better tolerability in preoperative period with more number of patients completing the therapy. It reflects *in vivo* chemosensitivity of urothelial cancer along with favorable pathological outcomes in individual showing response. Delay in RC in nonresponders and overtreatment in low-stage disease are the potential disadvantages. **Conclusion**: NAC in MIBC is associated with improved OS. Cisplatin-based NAC is the current standard of care in eligible patients.

Keywords: Bladder cancer, Neoadjuvant chemotherapy, Urothelial carcinoma

Introduction

Bladder cancer is the fourth most commonly diagnosed cancer in men and the eighth in women in the United States.[1] The American Cancer Society's estimates for bladder cancer in the United States for 2020 are about 81,400 (62,100 in men and 19,300 in women) new cases and about 17,980 deaths (13,050 men and 4,930 women).[2] Worldwide, bladder cancer remains the ninth most common malignancy. Estimated annual incidences of 382,660 cases and 150,282 deaths were reported in 2008.[3,4] Tumors that are nonmuscle invasive ($<pT_2$) can be effectively treated with transurethral resection and intravesical therapy.[5] Cystoscopic surveillance at regular intervals is required because of the high rate of recurrence and subsequent progression to more advanced disease, particularly in those with high-grade urothelial carcinoma. Tumors that are muscle

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invasive (approximately 20%) are usually treated with radical cystectomy (RC). However, there is a substantial rate of recurrence[6] (56% among patients with pT_3 disease), most commonly as distant metastases.[5]

The stage of the disease at the presentation has a significant impact on individual outcomes and long-term survival in patients managed with primary cystectomy and lymph node dissection. In a retrospective study of 1054 patients, the 5-year and 10-year recurrence-free survival and overall survival (OS) rates in organ-confined, lymph-node-negative bladder cancer were 85% and 82%, and 78%, and 56%, respectively. Patients with lymph node-positive disease had considerably worse survival outcomes, with 5-year and 10-year recurrence-free survival rates of 35% and 35%, and OS rates of 31% and 23%, respectively.[7] Research has focused on the early eradication of micrometastatic spread with perioperative chemotherapy, as positive lymph node status or distant metastatic disease carries an abysmal prognosis. The use of neoadjuvant chemotherapy (NAC) seems to be an attractive treatment option for muscle-invasive bladder cancer (MIBC), given the general chemosensitivity of urothelial carcinoma and the lack of NAC-associated surgical complications.[7] Several studies have reported difficulty in administering chemotherapy in an adjuvant setting owing to surgical morbidity and postoperative complications.[8,9]

In this article, we review several clinical articles, review articles, and analyses to assess the significance of achieving a tumor response following NAC, the preferred drug combinations in a neoadjuvant setting, the role of NAC in cisplatin-ineligible patients, and a brief note on the novel agents under evaluation for neoadjuvant therapy.

The Implications of Achieving a Tumor Response to Neoadjuvant Chemotherapy

NAC is widely used in the treatment of several solid tumors, including breast,[10] rectum,[11] lung,[12] and many more. The goal of using NAC in all such settings is to improve patient outcomes through tumor down-staging, elimination of micrometastatic disease, and improving the ability to administer the effective doses of chemotherapeutic agents compared with the postoperative setting. As far as bladder cancer is concerned, achieving any degree of pathological response translates into improved survival rates. This benefit was demonstrated by Splinter *et al*.[13] in a retrospective analysis of patients who received NAC before RC. The 5-year survival rate for patients achieving a pathological response ($<pT_2$) was 75% versus 20% in the patients who did not show a pathological response ($P < 0.0001$).[14] Similarly, in another retrospective study of patients receiving combination chemotherapy (methotrexate, vinblastine, adriamycin and cisplatin; MVAC) preoperatively, achieving a pathological response in organ-confined disease versus nonorgan-confined disease was associated with improved 5-year survival (61% vs. 35%, respectively).[15] Another perceived benefit of achieving a tumor response is the application of bladder preservation protocols in the management of MIBC. The primary aim of bladder preservation is to achieve oncological outcomes comparable to RC and maintain the patient's quality of life. NAC can help realize these goals in appropriately selected patients. An ideal patient to consider for bladder preservation would be one with a unifocal tumor ($\leq pT_2$ disease) with the absence of Carcinoma in situ (CIS), absence of hydronephrosis, and macroscopically complete TURBT with good bladder capacity.[16]

Historical Perspective of Neoadjuvant Chemotherapy

Grossman *et al*.[15] assessed the capability of NAC to enhance the disease outcome in patients with locally advanced bladder cancer who were managed with RC. They enrolled 317 patients over 11 years, of whom 154 were subjected to surgery alone, and 153 were assigned to receive combination chemotherapy. In intention-to-treat analysis, the median survival times among patients assigned to the surgical and NAC arms were 46 months and 77 months, respectively ($P = 0.06$). In both groups, improved survival was associated with the absence of residual disease in the RC specimen. Considerably, more patients in the NAC arm had an absence of residual disease than those assigned to the cystectomy group (38% vs. 15%, $P < 0.001$) [Table 1].

The Nordic Cystectomy Trial I recruited 311 eligible patients with MIBC (Stage $T_{2\text{-}4a}$ N_X M_0). The participants were randomized to receive two cycles of NAC (cisplatin and doxorubicin) at 3-weekly intervals followed by radiation therapy versus radiation and RC alone. Subset analysis revealed a 15% absolute survival benefit in patients with $T_{3\text{-}4a}$ disease receiving NAC ($P = 0.03$).[17]

In the largest phase III randomized clinical trial conducted to date by the International Collaboration of Trialists investigating the role of NAC in MIBC, three cycles of cisplatin, methotrexate, and vinblastine (CMV) NAC administered every 3 weeks was compared to nonneoadjuvant therapy.[18] A total of 976 patients with Stage $T_{2\text{-}T4a}$ $N_{0/X}$ M_0 urothelial bladder cancer and a glomerular filtration rate >50 ml/min were randomized to receive NAC or no therapy before definitive treatment (RC, radiotherapy or radiotherapy plus RC). In the final analysis, 43% of the patients received radiation therapy, 49% underwent RC, and 8% received a combination of the two. At 3 years of follow-up, a nonsignificant 5.5% absolute difference in survival was observed in favor of NAC ($P = 0.075$). However, at a longer median follow-up of 8 years, a statistically significant 16% reduction in the risk of death ($P = 0.037$) was demonstrated, corresponding to a 10-year survival improvement from 30% to 36%.[19]

Preferred Neoadjuvant Chemotherapy Drug Combinations

A South West Oncology Group (SWOG) trial explored the

Table 1: Select phase III randomized controlled trials for neoadjuvant chemotherapy in muscle invasive bladder cancer

Author	Number of patients	Neoadjuvant arm	Control arm	Findings
Kitamura *et al*., 2014[44]	130	MVAC	Radical cystectomy	Favourable OS in NAC arm
Griffiths *et al*., 2011[19]	976	CMV/RT Radical cystectomy	RT or radical cystectomy	6% survival advantage in favour of NAC
Sherif *et al*., 2004[43]	620	AC/RT/radical cystectomy	RT or radical cystectomy	20% reduction in death in NAC arm
Grossman *et al*., 2003[15]	298	MVAC/radical cystectomy	Radical cystectomy	Favourable results with MVAC NAC
Sengeløv *et al*., 2002[42]	153	M/C/RT/radical cystectomy	RT or radical cystectomy	No difference noted

MVAC: Methotrexate, vinblastine, doxorubicin, and cisplatin, OS: Overall survival, CMV: Cisplatin, methotrexate, and vinblastine, RT: Radiation therapy, NAC: Neo adjuvant chemotherapy, AC: Adriamycin, cisplatin, CA: Cisplatin, adriamycin; C, 5FU: Cisplatin, 5-fluorouracil

role of four drugs in the neoadjuvant setting for chemotherapy. The MVAC regimen was originally studied at Memorial Sloan-Kettering Cancer Center (MSKCC) in the 1980s, with a significant response reported in patients with advanced disease. An early retrospective analysis of the MSKCC experience with neoadjuvant MVAC demonstrated promising activity. In this review, 111 patients with T_{2-3} N_0 M_0 MIBC received neoadjuvant MVAC, of whom 60 (54%) showed a complete clinical response (cCR). Of these patients, 43 (71.66%) underwent bladder-preserving surgery, and 74% were still alive after an average follow-up of 10 years, with 58% having a functioning bladder.[20] Another prospective phase III randomized trial (SWOG 8710/INT-0080) investigated the role of neoadjuvant MVAC followed by RC. A total of 317 patients with MIBC eligible for RC and cisplatin-based chemotherapy were randomized to receive NAC (methotrexate [30 mg/m^2], vinblastine [3 mg/m^2], doxorubicin [30 mg/m^2] and cisplatin [70 mg/m^2]) for three cycles followed by RC versus RC alone.[15] In intention-to-treat analysis of 307 patients, the median survival in the combination therapy arm was 77 months versus 46 months in surgery alone arm ($P = 0.06$).

The gemcitabine and cisplatin (GC) chemotherapy regimen carries significant toxicity. When given in a neoadjuvant setting, patients have been reported to experience granulocytopenia (Grade 4: 33%), stomatitis (Grade 3: 10%), and combined gastrointestinal toxicity of nausea, vomiting, diarrhea or constipation (Grade 3: 10%).[15] For these reasons alone, the GC regimen has mostly been replaced by the MVAC regimen for metastatic disease based on a phase III trial. The use of GC stems from the desire to avoid the toxicity profile of the MVAC regimen while maintaining efficacy. The efficacy of the combination of GC for metastatic disease was established by von der Maase *et al*.,[21] who reported similar progression-free survival (PFS) (7.7 vs. 8.3 months) and OS (14.0 vs. 15.2 months; HR: 1.09; 95% CI: 0.88-1.34; $P = 0.66$) between GC and MVAC, respectively. Although an increased incidence of Grade 3 or 4 anemia (27% vs. 18%) and Grade 3 or 4 thrombocytopenia (57% vs. 21%) was noted in the GC regimen, the toxicity profile was better.

GC has also been evaluated in the neoadjuvant setting. The first retrospective analysis reported by the MSKCC group compared the outcomes of 42 patients who received GC with 54 patients who received MVAC. The proportion of patients who achieved a pathologic complete response (pCR) (26% vs. 28%) and $<pT_2$ response (36% vs 35%) was equivalent between GC and MVAC, respectively.[22] A small prospective phase II trial of neoadjuvant GC regimen including 22 patients reported a pCR rate of 26.7%. The median PFS was 26 months, and the median OS was 36 months.[23] Comparable rates of pCR between GC and MVAC regimens indicates the long-term treatment effectiveness and improved survival. These results support the use of GC in a neoadjuvant setting.

Meta-Analysis

The Advanced Bladder Cancer Meta-Analysis Collaboration analyzed 3005 patients from 11 different trials, integrated 98% of all patients from these randomized clinical trials, and summarized the survival benefits associated with NAC.[24] The pooled results revealed a 14% reduction in the risk of death, translating into a 5% absolute survival benefit at 5 years of follow-up (hazard ratio = 0.86; 95% confidence interval: 0.77–0.95; $P = 0.003$) for patients treated with cisplatin-based NAC. This benefit was consistent across various subgroups irrespective of age, clinical stage, and performance status. The Advanced Bladder Cancer meta-analysis firmly established the benefit of NAC and its role in the management of locally advanced MIBC [Figures 1 and 2].

Dosing Schedule Options

Several alternate dosing schedules of cisplatin-based NAC have been explored as a means of further improving disease response and survival outcomes. A collective strategy has been to intensify the dosing frequency from every 3 or 4 weeks to every 2 weeks. Several studies have also evaluated the efficacy and safety of this dose-dense (DD) schedule in both advanced and the neoadjuvant settings for urothelial carcinoma.

In the advanced setting, Sternberg *et al*. reported an improved cCR (25% vs. 11%; $P = 0.006$) and PFS (9.5 vs. 8.1 months; $P = 0.017$) with similar safety in a 2-week versus 4-week MVAC schedule, respectively.[25] Similarly, the Hellenic Oncology Group compared DD-MVAC and DD-GC in the advanced/metastatic setting and reported comparable PFS (8.5 vs. 7.8 months; $P = 0.36$) and OS (19 vs. 18 months; $P = 0.098$), respectively, between the regimens and improved tolerability and less toxicity with the DD-GC regimen.[26]

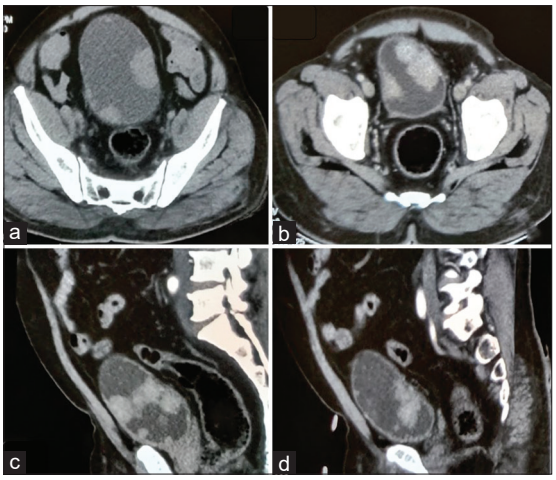

Figure 1: Computed tomography (a and b: Axial cuts; c and d: Sagittal cuts) of a patient presenting with gross hematuria showing multiple tumours over the anterior, posterior and lateral walls of the urinary bladder

Elmongy *et al*. reported a 50% pCR rate in a small feasibility study of 12 patients who received DD-MVAC before RC.[27] A retrospective analysis of 80 patients with T_{2-4a} N_{0-2} M_0 disease managed with DD-MVAC (three or four cycles) followed by RC or radiation therapy indicated that out of the 60 subjects who underwent RC, 24 (40%) were disease free. Additionally, 52% of the patients had <pT_2 disease, and the 2-year disease-free survival and OS rates were 65% and 77%, respectively.[28]

Role of Neoadjuvant Chemotherapy in Cisplatin-Ineligible Patients

Cisplatin-based regimens with either GC or MVAC have served as the first-line options in the treatment of advanced, unresectable, or metastatic bladder cancer and remain the standard of care. Up to 50% of cases ineligible for cisplatin-based chemotherapy are due to a number of medical comorbidities.[29] One consensus review suggested that patients with the following conditions should be considered ineligible for chemotherapy[30] [Figure 3]:

1. Impaired renal function (CrCl <60 ml/min)
2. Poor performance status (Eastern Cooperative Oncology Group of 2 or Karnofsky performance status ≤60%–70%)
3. Common Terminology Criteria for Adverse Events version 4 (CTCAE v4) Grade ≥2 hearing loss by audiometry
4. CTCAE version 4 Grade ≥2 peripheral neuropathy, and
5. New York Health Association Class III heart failure

Multiple randomized trials have tested the effectiveness of carboplatin-based regimens in the neoadjuvant setting. One small phase II trial assessed neoadjuvant paclitaxel, carboplatin, and gemcitabine (PCaG) in patients with CrCl > 40 ml/min, adequate bone marrow, and liver function. Patients were registered into two arms according to stage [T_{2-3} N_0 M_0 (arm 1) or T_{2-4} $N_{1-3}$$M_0$ (arm 2)] with primary endpoints of pCR (arm 1) and resectability (arm 2), respectively.[31] An analogous SWOG 0219 phase II trial evaluated the efficacy of three cycles of PCaG followed by surveillance or RC. Of 74 patients who were evaluable after NAC, 34 (46%) were clinically disease-free on follow-up TURBT. Of these patients, 10 underwent RC, of whom four had a pCR and the remaining six had residual pT_{2-4} malignancies.[32]

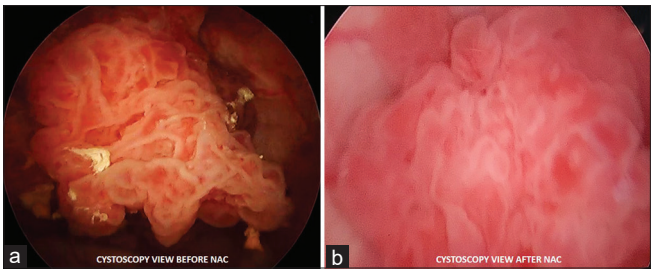

Figure 2: (a) Cystoscopic view of bladder tumours at diagnosis showing multiple sessile tumours along with increased vascularity. (b) A patient received three cycles of MVAC. Postchemotherapy cystoscopy showed marginally reduced size and decreased vascularity of the tumour and surrounding bladder mucosa

A separate phase II trial in patients eligible for cisplatin-based therapy assessed the effectiveness of methotrexate, vinblastine, and carboplatin in the neoadjuvant setting, and it therefore serves as a potential reference for a similar regimen in cisplatin-ineligible patients.[33] In this trial, patients with T_{2-4} N_0 M_0 bladder cancer received the three-drug regimen on a 28-day schedule for four cycles, with the principal outcome of pCR. A pathological response was noted in 40% of the 47 patients treated, of whom 12 (26.5%) achieved a pCR with a disease-specific survival rate of 42% at 2 years of follow-up.

In summary, cisplatin-ineligible patients can be offered alternative chemotherapy regimens; however, the survival benefit is far superior in patients who receive cisplatin-based chemotherapy. At present, numerous clinical trials are being conducted to address this issue. It would be apt to say that the results from these studies will further clarify whether cisplatin-ineligible patients benefit from novel immune-checkpoint inhibitor therapy.

Novel Agents in the Neoadjuvant Setting

VEGF inhibitors

Several trials have evaluated anti-VEGF therapy for urothelial carcinoma of the bladder. A phase II trial in advanced urothelial carcinoma assessed the effectiveness of GC plus bevacizumab (GC-Bev) combination therapy. A median PFS of 8.2 months, median OS, and overall response rates of 19.1 months and 72%, respectively, were reported.[34] Based on these data, a randomized, double-blind, placebo-controlled phase III trial is presently being conducted to define the role of GC-Bev in advanced urothelial carcinoma as a first-line therapy. Researchers are also reviewing the role of neoadjuvant bevacizumab in many small, single-institutional studies. An interim analysis of a phase II trial evaluating neoadjuvant

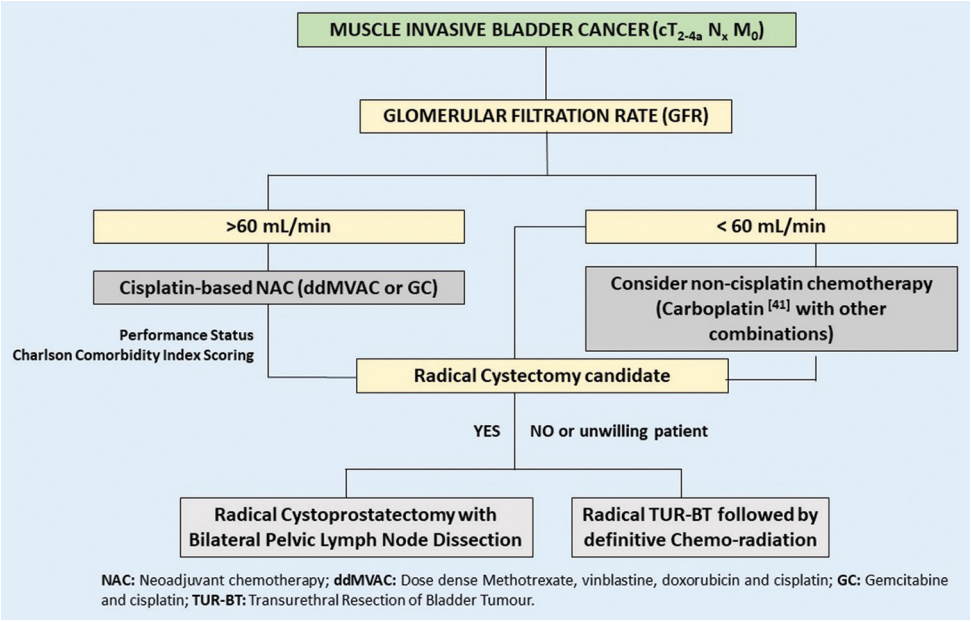

Figure 3: Management algorithm for nonmetastatic muscle invasive bladder cancer

GC-Bev followed by surgery has provided some insight into the role of neoadjuvant anti-angiogenic therapy. Patients with evidence of persistent disease on RC specimens were subjected to adjuvant paclitaxel plus bevacizumab therapy.[35]

Sunitinib is an oral multi-target receptor tyrosine kinase inhibitor with potent VEGF inhibition. It was tested in combination with GC in a neoadjuvant setting with the primary endpoint of pCR. Although closed early due to incomplete accrual (18 out of a planned 45 patients), one patient attained a pCR (6.6%), and five (33%) patients had $<pT_2$ disease; and of these latter five, four exhibited pT_{is} responses.[36]

Single-agent erlotinib, an oral epidermal growth factor receptor (EGFR) inhibitor, was studied in a small phase II trial in patients with MIBC (clinical T_2 N_0 M_0) with a principal outcome of pCR. Out of the 20 evaluable patients treated with erlotinib (150 mg daily for 4 weeks), five (25%) had a pCR and seven (35%) had a ≤pT1 response and an overall organ-confined response rate of 75%.[37] The most common side effect was rash; notably, every patient who exhibited any degree of disease down-staging also experienced a rash. More extensive phase II or confirmatory phase III trials are essential to determine the usefulness of this EGFR inhibitor in a neoadjuvant setting and also to explore the relationship between skin toxicity and response to chemotherapy.

Similarly, dasatinib, an oral tyrosine kinase inhibitor of Src-mediated signalling, was studied in a phase II neoadjuvant trial in patients unsuitable for or reluctant to accept cisplatin-based therapy. A daily oral dose of 100 mg dasatinib was used for 28 ± 7 days, followed by RC 8-24 h after the last dose of treatment.[38] The primary endpoint was the feasibility of >60% of the patients completing RC without dose-limiting toxicity. Although the trial did reach its goal with 15 of 25 patients (68%) achieving surgical resection, the pathological response was T_1 or T_{is} in three patients (14%) and $\geq T_2$ in 19 patients (86%) with node-positive disease in six patients (27%).

Future Perspectives

NAC represents a standard of care for the treatment of muscle-invasive urothelial cancer. Immune checkpoint inhibitors, including anti-PD1 and anti-PDL1 agents (targeted therapy), have shown efficacy in the treatment of advanced bladder cancer, and the use of these drugs in a neoadjuvant setting seems reasonable. These agents are currently under clinical trials. Given the dismal prognosis of patients with advanced disease, the neoadjuvant setting represents a critical opportunity to prevent the development of metastatic urothelial cancer and/or eradicate preexisting micro-metastases. Several studies are underway to identify whether molecular profiles or biologic markers can identify which patients are more likely to respond or should be excluded from NAC based on predicted resistance.[39] One such approach is the co-expression extrapolation (COXEN) methodology which utilizes gene expression models derived from *in vitro* drug testing of established cell line panels, such as NCI-60, to generate the predictive biomarkers of response to standard chemotherapy.[40,41] If successful, COXEN could represent a patient-specific biomarker that can be used to predict a response to neoadjuvant treatment and survival.

Conclusion

Cisplatin-based NAC is the current standard of care in eligible patients. There are several advantages of NAC before RC in patients with MIBC. The most prominent advantage is delivering chemotherapy at the earliest time-point when

the burden of micro-metastatic disease is expected to be the lowest. This ensures better tolerability and patient compliance in the preoperative period, which in turn ensures that more patients can complete the planned chemotherapy. NAC also reflects the *in vivo* chemosensitivity of bladder tumours. Patients responding to NAC have a favorable prognosis and long-term survival as determined by pathological staging of RC specimens. Novel immunotherapeutic agents targeting VEGF and EGFR inhibition also have shown promising results.

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Conflicts of interest

There are no conflicts of interest.

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