

### ANTIBODY-BASED THERAPEUTIC STRATEGIES IN CLINICAL PHASE TRIALS FOR BLADDER CANCER: A SYSTEMATIC REVIEW

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**INTRODUCTION:** Antibody-based therapeutic strategies have become an established treatment option for over a decade in several types of cancer. However, bladder cancer has remained mostly an “orphan disease” regarding the introduction of these therapeutics, which has been translated in few improvements in patients’ overall survival.

**AIM:** This work provides a systematic review on antibody-based therapeutic strategies targeting the most prominent bladder cancer-related biomolecular pathways and immunological mediators currently undergoing clinical trial.

**MATERIAL & METHODS:** A comprehensive search of MEDLINE through PubMed and of Clinical Trials Registry was conducted and all procedures were conducted according to PRISMA guidelines.

**RESULTS & DISCUSSION:** Almost all studies involving antibody-based therapeutics concern advanced stage bladder tumors (90%), which are associated with poor prognosis and lack effective therapeutics. However, we must also note the few efforts to improve the management of BCG refractory non-muscle invasive tumors and patients showing intolerance to this immunotherapy, for which the remaining therapeutic option is radical cystectomy. Half of the approaches focused on targeting and inhibiting key molecules involved in oncogenic pathways, such as EGFR, HER2, VEGF, Ang, ALK1 and cell-adhesion, namely EpCAM. Other exciting emerging therapeutics focused on using antibodies for immune mediators aiming T cell cytotoxic activity stimulation, by blockage of CTLA-4, PD-1 and PD-L1. Such strategies have been proven capable of boosting highly specific immune responses against tumor cells and seem to be very promising as therapeutic agents. Antibodies may also be used to selectively deliver chemotherapy payloads to cancer cells; however only a preclinical study explored this strategy by the use of ado-trastuzumab emtansine, an antibody–drug conjugate that fuses the trastuzumab with DM1. Few novel therapeutics have transposed beyond phase II and only two phase III trials are currently being conducted targeting VEGF-A and both PD-L1 and PD-L2. Moreover, we note only modest improvements in patients’ survival (below 12 months), irrespectively of the strategies, which will likely translate into few developments in bladder cancer management in near future. However, we believe that the lessons learned from ongoing clinical trials will surely allow the design of more effective strategies and lead to groundbreaking advancements in bladder cancer management.