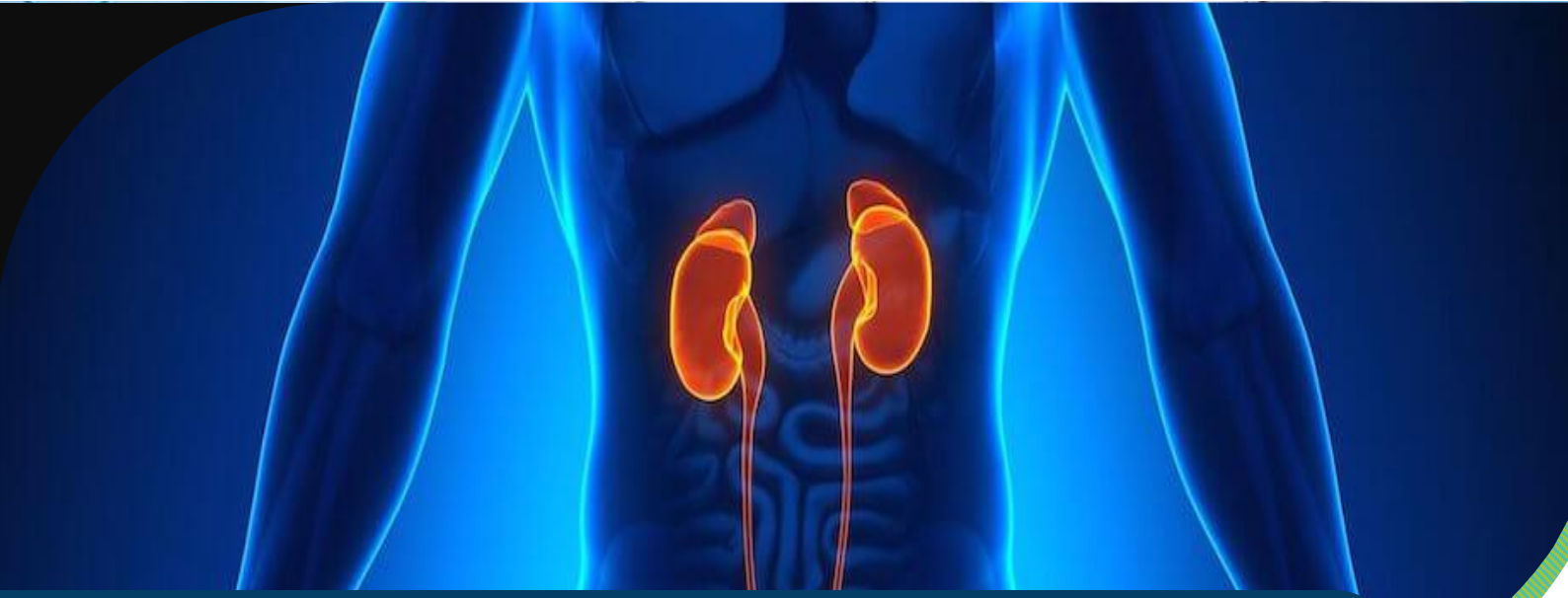

NU Rounds

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Dear Doctor,

Greetings from Micro Labs limited. We are happy to bring you "**NU Rounds**" which contains latest and interesting news in the field of Urology.

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Should you require any specific article or medical information, please feel free to contact us at medicalservices@microlabs.in

Looking forward to your valuable feedback

Best Regards,

Medical Team, Micro Labs Ltd

^{18}F-FDG imaging better for PSMA-suppressed prostate cancer patients

In prostate cancer patients with poor to no expression of the prostate-specific membrane antigen (PSMA), scientists have discovered the genomic signature to understand why 18F-FDG imaging works better than PSMA-targeted imaging. Researchers reported in a research published in the Journal of Nuclear Medicine that a neuroendocrine gene signature (common in prostate cancers with low PSMA expression) interacts with a distinct differential expression of glucose transporters and hexokinase proteins, which makes a more desirable 18F-FDG absorption than PSMA-targeted radioligans. In addition, the research revealed that tumor models of xenograft zebrafish are a reliable and efficient preclinical tool for measuring non-radioactive glucose uptake.

Researchers used data-mining methods, cell lines and patient-derived xenographic templates to research the expression rates of glucose-associated genes, including 14 members of the SLC2A family (encoding glucose transporter proteins), four members of the family of hexokinase (genes HK1-HK3 and GCK) and PSMA (gene FOLH1) after androgen-driven therapy and in conjunction with neuroendocrine hallmarks. One community of main and metastatic prostate cancer patients with no neuroendocrine histopathology was characterized by a neuroendocrine-like subset. Glucose uptake was assessed through the non-radioactive visualization of glucose absorption utilizing a fluorescent glucose bioprobe in a neuroendocrine-induced in vitro model and a zebrafish experiment.

Researchers find increased expression of GCK and reduced expression of SLC2A12, which suggests that a hallmark of a neuroendocrine gene interacts with differential production of glucose transporters and hexokinase proteins. The inhibition of PSMA in neuroendocrine prostate cancer is consistent with increased glucose absorption, in line with this term.

Early diagnosis of the progression of neuroendocrine prostate cancer is important for patients, because these cancers do not follow the standard of treatment and need additional therapies. Such results indicate that these tumors express genes in favour of enhanced glucose intake, offering genomic evidence to help the 18F-FDG positron emission tomography as an appealing imaging method for these conditions.

In addition to researching the rate of expression of glucose uptake-associated genes, researchers tried to assess the viability of utilizing glucose uptake in a zebrafish model of non-radioactive in vivo imaging. Using a fluorescent glucose bioprobe to photograph embryo-larval zebrafish, researchers have shown that the xenograft tumor models of zebrafish are a simple and cost-effective way of measuring non-radioactive glucose uptake.

Lisa A. Porter, PhD, Professor at the University of Windsor, Ontario, Canada, said that the application of FDG imaging in mice could be restricted by a variety of considerations, such as running costs and short-lived radioactive material and non-radioactive glucose samples of special concern. Human xenographs in mice often pose difficulties in the pace of engraftment and are also costly and time-consuming. From a scientific point of view, this study shows the zebrafish paradigm as a potential avenue for speeding in vivo research on molecular imaging.

Source: Bakht MK, et al. Differential Expression of Glucose Transporters and Hexokinases in Prostate Cancer with a Neuroendocrine Gene Signature: A Mechanistic Perspective for 18F-FDG Imaging of PSMA-Suppressed Tumors. J Nucl Med. 2020;61(6):904-910.

Primary progression-free survival and interim overall survival results from Atezolizumab with or without chemotherapy in metastatic urothelial cancer

INTRODUCTION

In the 1980s, cisplatin-based chemotherapy became the standard first-line treatment for metastatic urothelial carcinoma, with long-term remission in about 10 per cent of patients possible. Although tolerability has improved, there have been no further significant improvements in efficacy. In addition, due to poor performance status, comorbidities or impaired renal function, around 50 percent of patients with metastatic urothelial carcinoma are ineligible for cisplatin treatment. These patients generally receive lesser regimens based on carboplatin. The first modern systemic therapies for metastatic urothelial carcinoma are programmed death-ligand 1 (PD-L1) and programmed death-1 (PD-1) antagonists, both for first-line management of cisplatin-ineligible patients and for patients with cancer development following platinum-based chemotherapies.

Regimens which combine platinum-based chemotherapy with inhibitors of PD-L1 and PD-1 are attractive for several reasons. Chemotherapy based on platinum will cause immunomodulatory symptoms, thus growing the concomitant blockage of PD-L1 and PD-1. This combination may also be advantageous due to the absence of professional cross-resistance within such medical groups, as a fraction of patients seek care outside first-line therapy. Phase 3, national, multicenter, randomized, partly blinded study IMvigor130 assessed the effectiveness of atezolizumab alone or in conjunction with platinum-based chemotherapy against placebo with platinum-based chemotherapy in untreated metastatic urothelial carcinoma patients. Preliminary findings have seen clinical procedure already impacted. Based on unplanned reviews by both IMvigor130 and KEYNOTE-361 independent data management committees (IDMC), the FDA and the European Medicines Agency (EMA) updated the labeling for atezolizumab and pembrolizumab monotherapy in the first-line setting to restrict diagnosis to biomarker-expressing PD-L1 tumours. Here, the authors report the primary progression-free survival and interim overall survival results from IMvigor130.

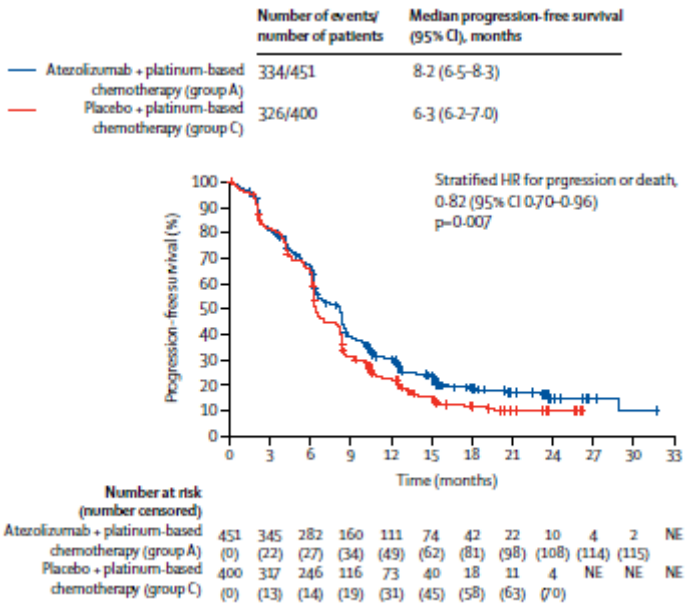
METHODS

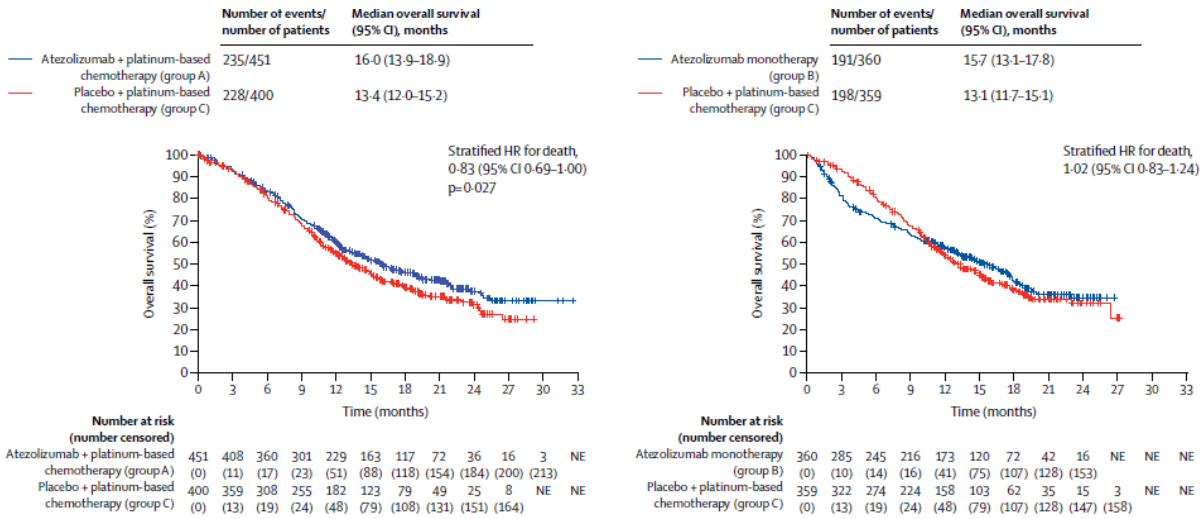
In this multicentre, phase 3, randomised trial, untreated patients aged 18 years or older with locally advanced or metastatic urothelial carcinoma, from 221 sites in 35 countries, were randomly assigned to receive atezolizumab plus platinum-based chemotherapy (group A), atezolizumab monotherapy (group B), or placebo plus platinum-based chemotherapy (group C).

Patients received 21-day cycles of gemcitabine (1000 mg/m² body surface area, administered intravenously on days 1 and 8 of each cycle), plus either carboplatin (area under the curve of 4.5 mg/mL per min administered intravenously) or cisplatin (70 mg/m² body surface area administered intravenously) on day 1 of each cycle with either atezolizumab (1200 mg administered intravenously on day 1 of each cycle) or placebo. Group B patients received 1200 mg atezolizumab, administered intravenously on day 1 of each 21-day cycle. The co-primary efficacy endpoints for the intention-to-treat population were investigator-assessed Response Evaluation Criteria in Solid Tumours 1.1 progression-free survival and overall survival (group A vs group C) and overall survival (group B vs group C), which was to be tested only if overall survival was positive for group A versus group C.

RESULTS

They enrolled 1213 patients. 451 (37%) were randomly assigned to group A, 362 (30%) to group B, and 400 (33%) to group C. Median follow-up for survival was 11·8 months (IQR 6·1–17·2) for all patients. At the time of final progression-free survival analysis and interim overall survival analysis (May 31, 2019), median progression-free survival in the intention-to-treat population was 8·2 months (95% CI 6·5–8·3) in group A and 6·3 months (6·2–7·0) in group C (stratified hazard ratio [HR] 0·82, 95% CI 0·70–0·96; one-sided p=0·007). Median overall survival was 16·0 months (13·9–18·9) in group A and 13·4 months (12·0–15·2) in group C (0·83, 0·69–1·00; one-sided p=0·027). Median overall survival was 15·7 months (13·1–17·8) for group B and 13·1 months (11·7–15·1) for group C (1·02, 0·83–1·24). Adverse events that led to withdrawal of any agent occurred in 156 (34%) patients in group A, 22 (6%) patients in group B, and 132 (34%) patients in group C. 50 (11%) patients in group A, 21 (6%) patients in group B, and 27 (7%) patients in group C had adverse events that led to discontinuation of atezolizumab or placebo.





Investigator-assessed progression-free survival and overall survival

CONCLUSIONS

The application of atezolizumab as first-line medication of platinum-based chemotherapy improved progression-free survival in patients with metastatic urothelial carcinoma. The combination's health profile has been as demonstrated in human officers. Such findings encourage the usage of atezolizumab + platinum-based chemotherapy to treat metastatic urothelial carcinoma as a new first-line treatment choice.

REFERENCE

Galsky MD, Arija JÁA, Bamias A, et al. Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): a multicentre, randomised, placebo-controlled phase 3 trial. Lancet. 2020;395(10236):1547-1557

Primary chemoablation of low-grade upper tract urothelial carcinoma using UGN-101, a mitomycin-containing reverse thermal gel

INTRODUCTION

Upper tract urothelial cancer is a severe, most frequently identified malignancy in patients over 70 years of age, and is typically handled with aggressive nephroureterectomy. Biopsy classification coupled with cross-sectional imaging results and urinary cytology is introduced into the criteria for clinical stage stratification by the European Association of Urology (EAU). Extirpative surgery that may involve segmental elimination of parts of the ureter or, more specifically, extreme nephroureterectomy is typically given to patients with high-grade cancers. In comparison, kidney-preserving strategies such as endoscopic ablation is given to 10–20 per cent of patients with low-grade disease presented as a single, narrow, and ideally positioned lesion inside the upper tract. Endoscopic surgery poses different medical complications and is related to a high incidence of recurrence of the local condition. Eventually, 70–80 per cent of low-grade and low-stage urothelial cancer patients undergo severe nephroureterectomy. It technique is related to the usual dangers of large operations and the additional long-term deleterious consequences of renal insufficiency, exacerbation of pre-existing comorbidities and the possible need for reliance on dialysis.

Early results on genomic study of low-grade urothelial cancer of the bladder and low-grade urothelial cancer of the upper tract indicate that low-grade urothelial malignancies share similar genetic features, independent of the place of origin. Low-grade urothelial bladder cancer is susceptible to numerous chemotherapeutic drugs, such as mitomycin and gemcitabine, widely prescribed after transurethral resection of bladder tumors as adjuvant intravesical therapies. Concentration of the medication and dwelling period at the target are main features of effective topical therapy for urothelial bladder cancer; however, constant dilution of the product due to urinary discharge reduces the advantage of topical aqueous therapy to urothelial cancer in the upper tract. The authors previously documented proof of principle and tentative efficacy for UGN-101, a reverse thermal gel formulation of mitomycin, in a compassionate use system in the care of 22 patients with upper-tract urothelial cancer. UGN-101 consists of mitomycin and a sterile RTGel reverse thermogelation hydrogel (UroGen Pharma, Ra'anana, Israel), used before instillation to reconstitute mitomycin. UGN-101 's reverse thermal properties permit local administration of mitomycin as a stream, with eventual conversion to a semi-solid gel depot upon instillation into the upper tract.

The regular flow of urine dissolves the gel depot, allowing for tissue access to mitomycin over a 4–6 h duration. DNA alkylation and the consequent suppression of DNA replication were generally due to the process of tumor cell death by mitomycin. Other mitomycin functions include regulation of redox cycling, RNA inhibition, and control of thioredoxin reductase function.

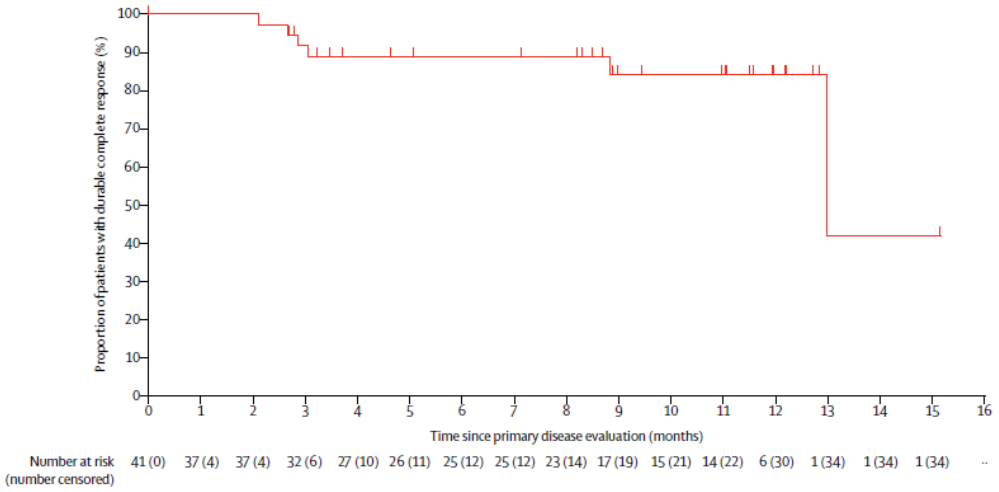
The current study also evaluated UGN-101 's efficacy and effectiveness in chemotherapeutically ablate main and persistent low-grade urothelial cancer of the upper tract.

METHODS

In this open-label, single-arm, phase 3 trial, participants were recruited from 24 academic sites in the USA and Israel. Patients (aged ≥18 years) with primary or recurrent biopsy-proven, low-grade upper tract urothelial cancer (measuring 5–15 mm in maximum diameter) and an Eastern Cooperative Oncology Group performance status score of less than 3 (Karnofsky Performance Status score >40) were registered to receive six instillations of once-weekly UGN-101 (mitomycin 4 mg per mL; dosed according to volume of patient's renal pelvis and calyces, maximum 60 mg per instillation) via retrograde catheter to the renal pelvis and calyces. All patients had a planned primary disease evaluation 4–6 weeks after the completion of initial therapy, in which the primary outcome of complete response was assessed, defined as negative 3-month ureteroscopic evaluation, negative cytology, and negative for-cause biopsy. Activity (complete response, expected to occur in >15% of patients) and safety were assessed by the investigator in all patients who received at least one dose of UGN-101.

RESULTS

74 enrolled patients received at least one dose of UGN-101. 42 (59%, 95% CI 47–71; p<0. 0001) patients had a complete response at the primary disease evaluation visit. The median follow-up for patients with a complete response was 11 months. The most frequently reported all-cause adverse events were ureteric stenosis in 31 (44%) of 71 patients, urinary tract infection in 23 (32%), haematuria in 22 (31%), flank pain in 21 (30%), and nausea in 17 (24%). 19 (27%) of 71 patients had study drug-related or procedure-related serious adverse events. No deaths were regarded as related to treatment.



CONCLUSION

Primary chemoablation of low-grade urothelial cancer of the upper tract with intracavitary UGN-101 helps in the eradication of clinically important diseases and can give such patients a kidney-sparing alternate therapy.

REFERENCE

Kleinmann N, et al. Primary chemoablation of low-grade upper tract urothelial carcinoma using UGN-101, a mitomycin-containing reverse thermal gel (OLYMPUS): an open-label, single-arm, phase 3 trial. Lancet Oncol. 2020;21(6):776-785.