

Checkmate 274 trial: Is Nivolumab the new standard in adjuvant setting for high-risk muscle invasive urothelial carcinoma?

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SUMMARY

Checkmate 274 is a phase 3, multicenter, double-blind, randomized controlled trial recently published in the *New England Journal of Medicine*, comparing nivolumab with placebo in adjuvant setting in patients with muscle-invasive urothelial carcinoma.^[1] Patients included were those with Eastern Cooperative Oncology Group performance status score of 0 or 1 and who underwent radical surgery with pathological evidence of urothelial carcinoma (originating in the bladder, ureter, or renal pelvis) with or without neoadjuvant cisplatin-based chemotherapy with a high risk of recurrence (pT3, pT4a, or pN⁺ and patient not eligible for, or declined, adjuvant cisplatin-based chemotherapy for patients who had not received neoadjuvant cisplatin-based chemotherapy; and ypT2 to ypT4a or ypN⁺ for patients who received neoadjuvant cisplatin).

Through a 1:1 randomization, nivolumab (240 mg) or placebo every 2 weeks was administered for up to 1 year or until disease recurrence or discontinuation from trial, with stratification according to tumor programmed death ligand-1 (PD-L1) expression level ($\geq 1\%$ vs. $< 1\%$ or indeterminate), pathological nodal status (N⁺ vs. N0 or NX with < 10 nodes removed vs. N0 with ≥ 10 nodes removed), and the use of neoadjuvant cisplatin-based chemotherapy (yes vs. no).

Primary end points were disease-free survival (DFS) among intention-to-treat (ITT) population and among those with a tumor PD-L1 expression $\geq 1\%$. Secondary end points included survival free from recurrence outside the urothelial tract, overall survival, and disease-specific survival.

Three hundred and fifty-three patients were included in the nivolumab arm and 356 in placebo arm. 140 patients in nivolumab arm and 142 patients in placebo arm had PD-L1 expression of $\geq 1\%$. Median DFS in the ITT population was 20.8 months with nivolumab (95% confidence interval [CI], 16.5–27.6) and 10.8 months with placebo (95% CI, 8.3–13.9). At 6 months, 74.9% of patients were alive and disease free with nivolumab and 60.3% with placebo (hazard ratio [HR] for disease recurrence or death, 0.70; 98.22% CI, 0.55–0.90; $P < 0.001$). For those with a PD-L1 expression level of $\geq 1\%$, the percentage of alive and disease-free patients was 74.5% and 55.7%, respectively, in nivolumab and placebo arms (HR: 0.55; 98.72% CI: 0.35–0.85; $P < 0.001$). Median survival free from recurrence outside the urothelial tract in the ITT population was 22.9 months (95% CI: 19.2–33.4) with nivolumab and 13.7 months (95% CI: 8.4–20.3) with placebo.

The percentage of patients who were alive and recurrence free outside the urothelial tract at 6 months was 77.0% with nivolumab and 62.7% with placebo (HR for recurrence outside the urothelial tract or death, 0.72; 95% CI: 0.59–0.89). Among patients with a PD-L1 expression level of 1% or more, the percentage of patients was 75.3% and 56.7%, respectively (HR: 0.55; 95% CI: 0.39–0.79). Grade 3 or higher treatment-related adverse events were more in nivolumab group (17.9% vs. 7.2%). Two treatment-related deaths due to pneumonitis occurred in the nivolumab group.

COMMENTS

Nivolumab, a monoclonal antibody directed against PD-1, has been approved by the Food and Drug Administration (FDA) for locally advanced or metastatic urothelial carcinoma with disease progression during/following platinum-containing chemotherapy or disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Five-year survival in high-risk muscle-invasive urothelial carcinoma is $\leq 60\%$;^[1] however, adjuvant therapy after radical surgery for such patients is still not standard of care.^[2] A recent meta-analysis has shown a therapeutic benefit of adjuvant cisplatin-based chemotherapy, but the statistical power of the included studies is very low.^[3] The National Comprehensive Cancer Network and European Association of Urology guidelines recommend adjuvant cisplatin-based chemotherapy in high-risk muscle-invasive bladder cancer only if neoadjuvant chemotherapy was not given. For cisplatin ineligibility, there is no evidence to recommend any perioperative chemotherapy.^[4]

IMvigor010 was the first phase 3 trial to evaluate any checkpoint inhibitor (atezolizumab) as adjuvant therapy in high-risk muscle-invasive urothelial carcinoma.^[5] Median DFS with atezolizumab was not significantly higher compared to observation ($P = 0.24$); thus, adjuvant checkpoint inhibitor therapy was not recommended then. Checkmate 274 is the first trial with positive results on adjuvant checkpoint inhibitor in high-risk muscle-invasive bladder cancer. The reasons for contradicting results between both trials are speculative and may be due to different drugs and regimen of drug administration, different targets of action (PD-1 vs. PD-L1), and different thresholds of PD1 positivity. Hence, the results of Checkmate 274 even though clinically significant need to be evaluated in perspective given the prior negative study.

In Checkmate 274 trial, in the ITT population, the median DFS with nivolumab was nearly double than with placebo, which was seen across all subgroups. Distant metastasis-free survival was also significantly higher with nivolumab. With nivolumab, adverse events were also higher and two patients died of pneumonitis. There was no difference in decline in the quality of life between both groups. The safety and toxicity profile of nivolumab in this study was comparable to that in the previous studies.^[6]

Patients with upper tract urothelial carcinoma were capped at approximately 20% to replicate the natural prevalence of urothelial carcinoma to decrease the skewness of data. On subgroup analysis, placebo had favorable results over nivolumab in ureteric and renal pelvic tumors ($HR > 1$). The reason for this difference is also not clear; however, this requires further analysis.

The limitation of this trial is it being an interim analysis with a short follow-up of 20 months. About 48.2% of patients in the nivolumab arm and 57.3% of patients in the placebo group had disease recurrence or died during follow-up. The secondary end point of overall survival was not achieved at the time of analysis, for which longer follow-up is required. However, DFS at 2–3 years is considered a surrogate of overall survival among patients with muscle-invasive urothelial carcinoma and thus, further follow-up may consolidate these findings by providing overall survival data.^[7,8]

Based on Checkmate 274 trial, FDA has granted a priority review designation to nivolumab for use as adjuvant treatment in patients with surgically resected, high-risk, muscle-invasive urothelial carcinoma.^[9] This can bring a paradigm shift in the treatment of muscle-invasive urothelial carcinoma, by providing a therapeutic option to patients not eligible for cisplatin or in those with pathological evidence of residual disease despite neoadjuvant cisplatin-based chemotherapy.

REFERENCES

1. Bajorin DF, Witjes JA, Gschwend JE, Schenker M, Valderrama BP, Tomita Y, *et al.* Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma. *N Engl J Med* 2021;384:2102-14.
2. Witjes JA, Bruins HM, Cathomas R, Comp erat EM, Cowan NC, Gakis G, *et al.* European association of urology guidelines on muscle-invasive and metastatic bladder cancer: Summary of the 2020 guidelines. *Eur Urol* 2021;79:82-104.
3. Leow JJ, Martin-Doyle W, Rajagopal PS, Patel CG, Anderson EM, Rothman AT, *et al.* Adjuvant chemotherapy for invasive bladder cancer: A 2013 updated systematic review and meta-analysis of randomized trials. *Eur Urol* 2014;66:42-54.
4. National Comprehensive Cancer Network. Bladder Cancer (Version 3.2021). Available from: http://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf. [Last accessed on 2021 Jul 09].
5. Bellmunt J, Hussain M, Gschwend JE, Albers P, Oudard S, Castellano D, *et al.* Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma (IMvigor010): A multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2021;22:525-37.
6. Sharma P, Retz M, Siefker-Radtke A, Baron A, Necchi A, Bedke J, *et al.* Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): A multicentre, single-arm, phase 2 trial. *Lancet Oncol* 2017;18:312-22.
7. Fajkovic H, Cha EK, Xylinas E, Rink M, Pycha A, Seitz C, *et al.* Disease-free survival as a surrogate for overall survival in upper tract urothelial carcinoma. *World J Urol* 2013;31:5-11.
8. Sonpavde G, Khan MM, Lerner SP, Svatek RS, Novara G, Karakiewicz PI, *et al.* Disease-free survival at 2 or 3 years correlates with 5-year overall survival of patients undergoing radical cystectomy for muscle invasive bladder cancer. *J Urol* 2011;185:456-61.

9. US Food and Drug Administration Accepts for Priority Review Bristol Myers Squibb's Application for Opdivo (Nivolumab) as Adjuvant Treatment for Patients with Muscle-Invasive Urothelial Carcinoma. News Release. Bristol Myers Squibb; April 30, 2021. Available from: <https://bit.ly/2R9Swic>. [Last accessed on 2021 Apr 30].

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