Algorithmic precision in immune checkpoint therapy response prediction for lung cancer: Evaluating the Digital Drug Assignment model's clinical performance.

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Background: Despite the potential of immune checkpoint therapy (ICT) in oncology, its clinical effectiveness is limited, with only 15-35% of patients showing benefit. This inefficacy is compounded by the significant financial burden it poses. Here we tested the predictive performance of the computational reasoning model, the Digital Drug Assignment (DDA) published before (1) based on Next-Generation Sequencing (NGS) results of lung cancer patients treated with various ICTs. **Methods:** A cohort of 328 lung cancer cases was analyzed, all of which had tumor NGS results and documented outcomes following treatment with immune checkpoint inhibitors, sourced from cBioPortal. Treatment DDA scores were computed using the Genomate AI platform. DDA score thresholds were established to categorize response probability into low (<0, indicating potential resistance), intermediate (0 to 1000), and high (≥1000), or negative (<0) and positive (≥0) groups. Kaplan-Meier survival analysis was conducted, employing log-rank statistics for significance testing. **Results:** The collective Objective Response Rate (ORR) to ICT was 28%. Patients receiving low-DDA-score ICTs (n=34) showed an ORR of 0%, contrasted with 36% in the DDA-high group (n=212), and 18% in the intermediate group, demonstrating significant differences (Chi-square $p<0.0001$). Median Progression-Free Survival (mPFS) was 2.2 months in the DDA-low category, significantly shorter than the 7.0 months observed in the DDA-high group ($p<0.0001$, HR=0.40, 95% CI 0.23-0.72) or the 5.6 months in the overall positive DDA-score group ($p<0.0001$, HR=0.43, 95% CI 0.24-0.75). The intermediate group had a mPFS of 4.2 months, with a pooled mPFS of 5.0 months for all cases. Notably, median Overall Survival (mOS) also differed significantly between the DDA-low and DDA-high categories, 11.9 months vs. 26.3 months, respectively ($p=0.0038$, HR=0.52, 95% CI 0.30-0.92), with the intermediate group at 18.5 and all cases at 20.6 months. Even in the non-TMB-High/MSI-High/PD-L1+ subgroup, DDA was predictive of the outcome: mPFS of 2.2 vs 4.2 months in the negative (n=31) versus positive (n=108) DDA categories ($p=0.0066$, HR=0.55, 95% CI 0.32-0.95). By administering chemotherapy instead of ICT to the DDA-low cohort, we can not only potentially enhance the ORR but also reduce expenditures, resulting in an Incremental Cost-Effectiveness Ratio (ICER) of negative USD 121,816. **Conclusions:** The DDA demonstrates efficacy in predicting response to immunotherapy based on NGS data, offering a potential pathway to optimize treatment costs and outcomes. Our findings suggest that routine NGS panels could be leveraged for this purpose without necessitating additional testing. This highlights the potential economic impact of using predictive algorithms like DDA to optimize ICT utilization. 1. Petak et al. *npj Precis. Onc.* **5**, 59, 2021.

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