Meeting Abstract: ASCO Breakthrough: A Global Summit for Oncology Innovators
FREE ACCESS Developmental Therapeutics August 12, 2024

Efficacy of combination of immune checkpoint inhibitors, chemotherapy, and targeted therapy in advanced/refractory cancer.

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Publication: Journal of Clinical Oncology. Volume 42, Number 23_suppl
https://doi.org/10.1200/JCO.2024.42.23_suppl.41

Abstract
41

Background: The treatment of advanced/refractory malignancies continues to pose a major challenge, and it is associated with poor outcome. It has been shown that in some cancers, the combination of chemotherapy (CT) with immune checkpoint inhibitors (ICIs), or CT with targeted therapy (TT), are superior to chemotherapy alone. Consequently, in our treatment program (ICTriplex), TT was added to CT plus ICIs. These three modalities have convergent efficacy with divergent toxicity. Our prior data were previously reported (1-3). **Methods:** Treatment with ICTriplex was highly personalized and was tailored to the individual patient and their specific cancer. It was designed based on diagnosis, prior therapy, and genomic profiling. Between March 2017 and January 2024, 56 patients (pts) with advanced malignancies were treated: 31 females and 25 males, with a median age of 58. Tumor types included: lung (12), pancreas (8), colorectal (8), biliary tract (5), breast (4), stomach (4), melanoma (3), ovary (3), sarcoma (3), cervix (2), glioblastoma (2), Hodgkin's (1), and

thymoma (1). 43 pts received prior therapy: 14 received ICIs, 23 TT, and 42 CT. The agents used in ICTriplex were: 6 ICIs primarily nivolumab and pembrolizumab, 12 CT primarily taxanes, gemcitabine, and platinum, and 23 TT, primarily bevacizumab and erlotinib. Response was evaluated by both PET/CT and CT scans. A complete remission was achieved when metabolic activity completely resolved on PET/CT. Progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan-Meier estimator. **Results:** The overall response rate (ORR) was 88%. A complete remission (CR) occurred in 29 pts (52%), and a partial remission (PR) in 20 pts (36%). Of the 12 pts with lung cancer, 9 (75%) achieved CR and of these, 4 pts had brain metastases that completely resolved without radiation. Of the 8 pts with pancreatic cancer, 4 (50%) achieved CR. 4 of 5 pts with biliary tract cancer achieved CR. Toxicity was reasonable in all pts except for 3 who died from complications possibly related to ICIs. The median PFS was 11 months, and the median OS was 15 months. The achievement of CR and the PD-L1 + status, resulted in a statistically significant better PFS (p= 0.00; p= 0.02) and OS (p=0.00; p= 0.005). Patients with lung cancer showed a better PFS (p= 0.02) with the median at 19 months, and the median OS was 36 months. Potential predictors of unfavorable prognosis, such as receiving prior treatment, did not impact patients' clinical outcome. **Conclusions:** ICTriplex is a very effective treatment for advanced cancer that has become resistant to conventional therapy or with no available standard therapy. We strongly recommend this therapeutic approach for the treatment of such patients. 1. ASCO 2019 (e14254) 2. ASCO 2020 (e15150) 3. ASCO 2022 (e14590).

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