Supplementary data

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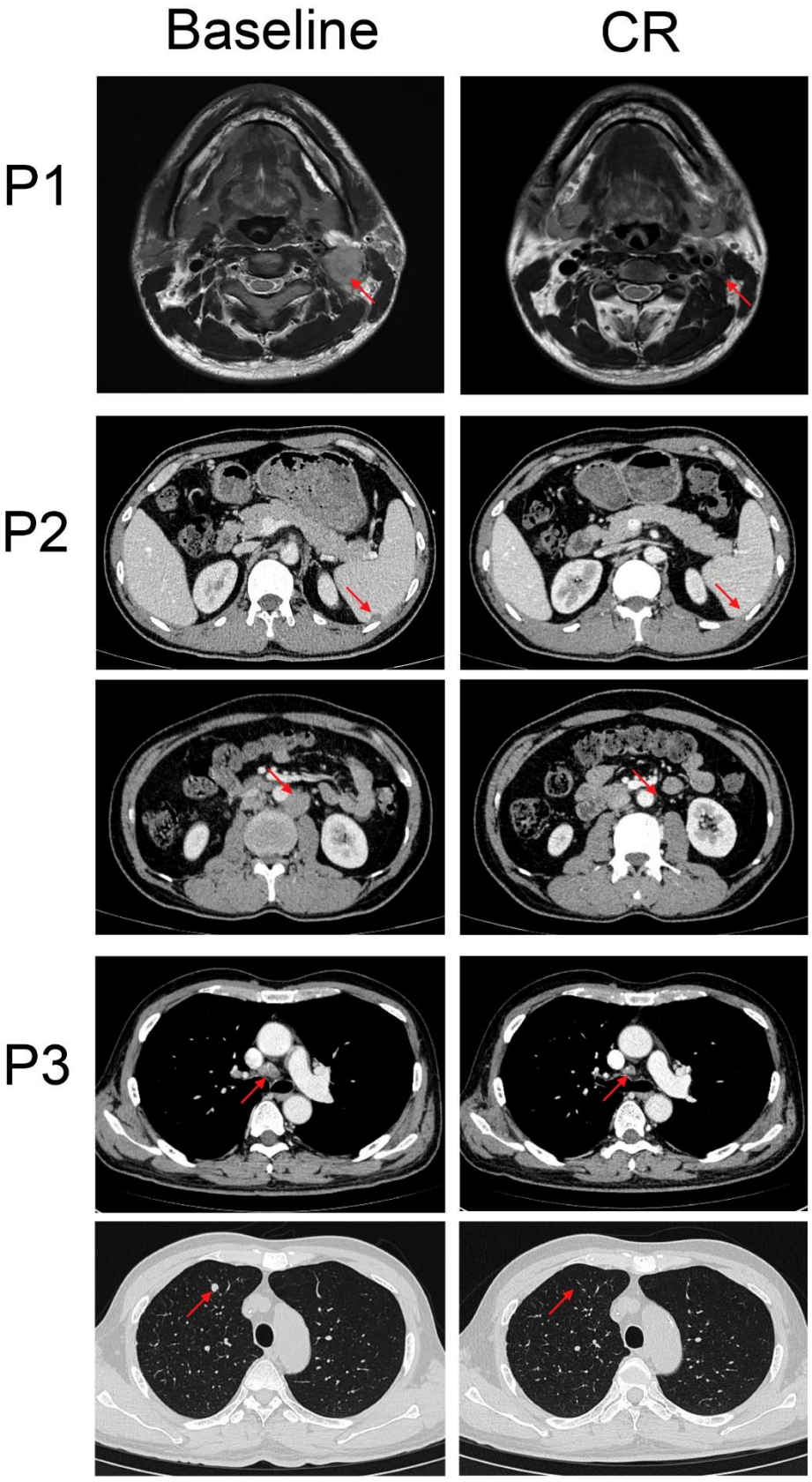
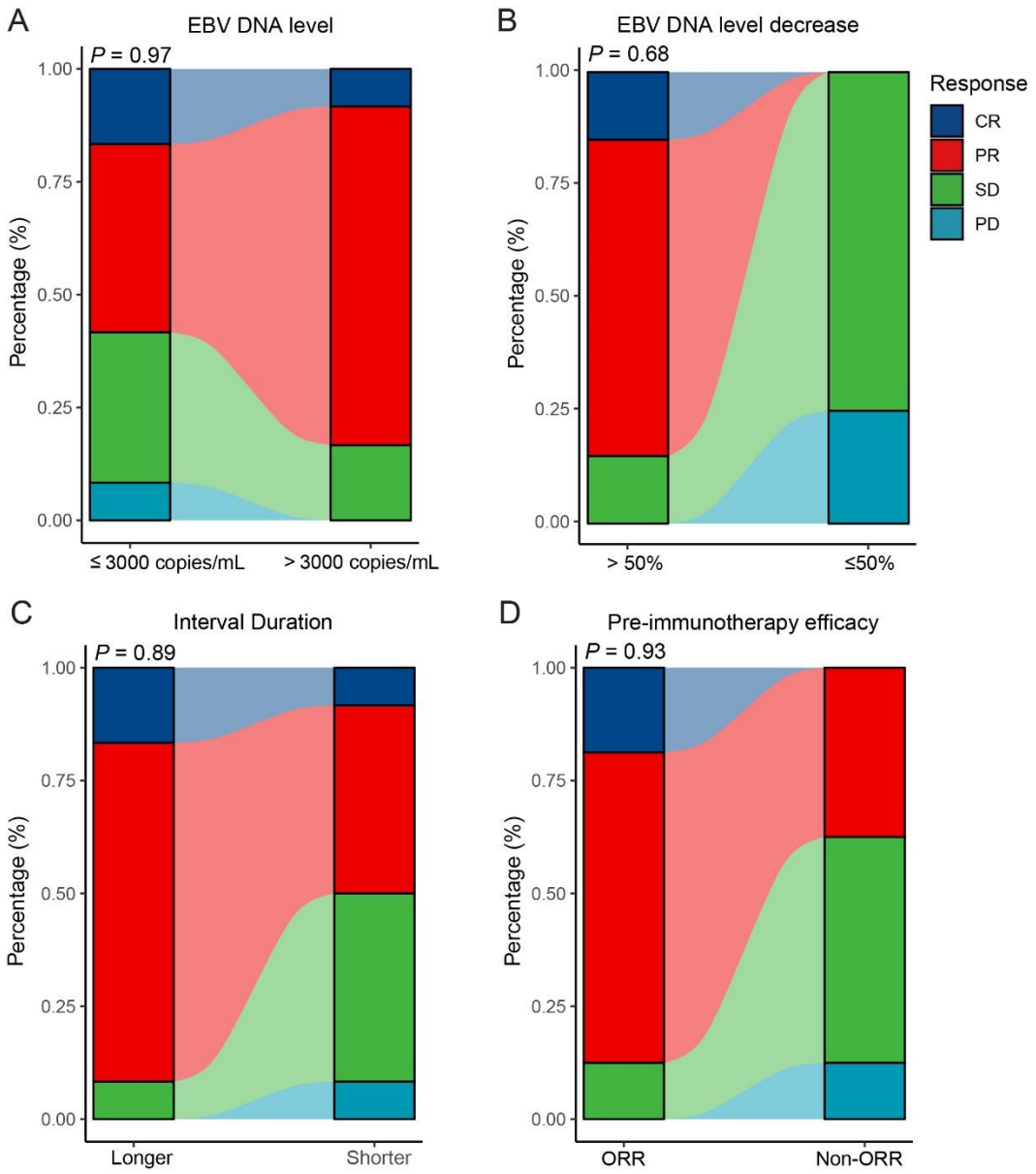
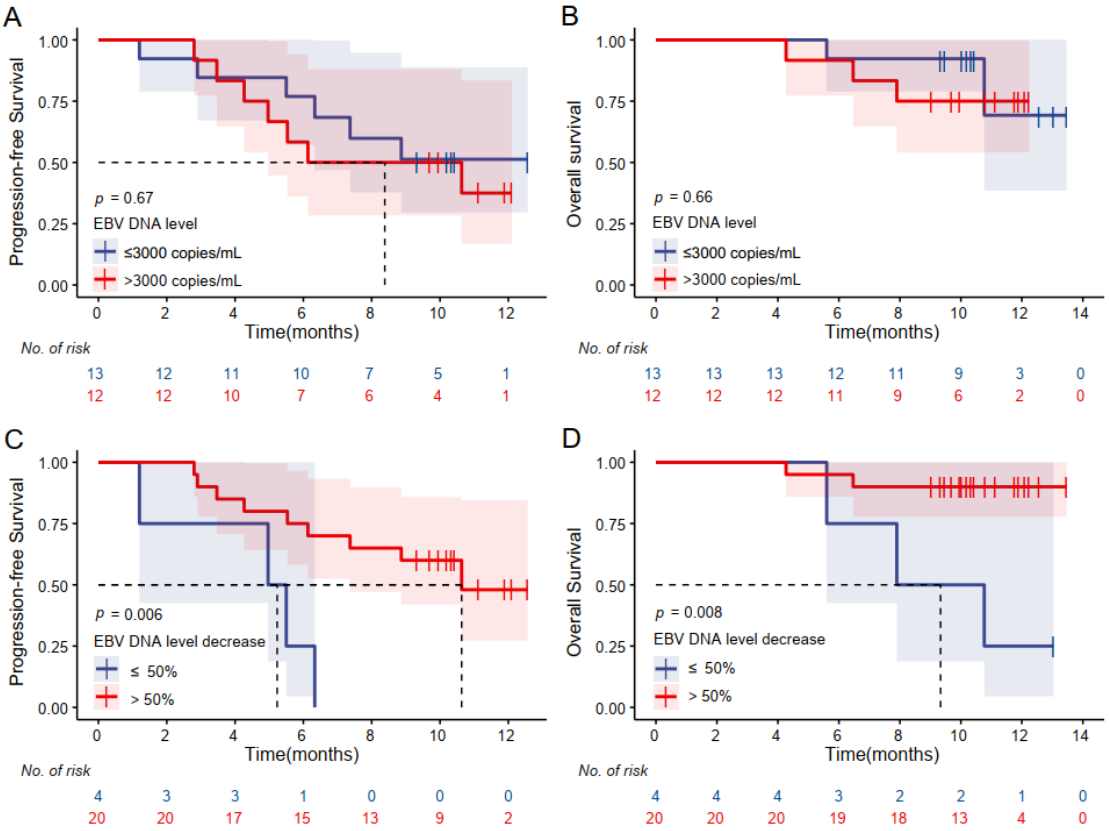
Appendix History of the patient who received PD at first time of post-baseline tumor assessment. A 33-year-old male patient, who was admitted to Sun Yat-sen University Cancer Center on September 2021 due to lost vision in his right eye and was diagnosed with undifferentiated non-keratinous nasopharyngeal carcinoma (T4N2M0, IVa stage), with immunohistochemistry showed CK (+), EGFR (+), and in situ hybridization showed EBERs (-), received two cycles of induction chemotherapy (nab-paclitaxel, cisplatin, and capecitabine) followed by cisplatin-based concurrent chemoradiotherapy. In February, 2023, imaging examination indicated that the patient had multiple bone metastases. Then, four cycles of gemcitabine and cisplatin chemotherapy in combination with camrelizumab were performed, with the best curative effect SD. The imaging examination in June 2023 indicated liver metastasis, and the liver needle biopsy showed undifferentiated non-keratinous carcinoma with immunohistochemistry showed CK (+), and in situ hybridization EBERs (-). This patient was enrolled in this trial on June 7, 2023, with plasma EBV DNA level was 0 copies/ml. After two cycles of treatment with cadonilimab and TPC chemotherapy, the tumor assessment was PD. The patient died on November 22, 2023.



Supplementary Figure 1. Typical imaging of complete response of metastatic lesions.



Supplementary Figure 2. Cochran-Armitage trend test to assess the relationship between the response and, **A** plasma EBV DNA level at baseline by cut-off of 3000 copies/mL; **B** decrease of EBV DNA level from baseline to the first post-treatment assessment by cut-off of 50%; **C** internal duration from latest immunotherapy by cut-off of median time of patients; and **D** best previous immunotherapy efficacy.



Supplementary Figure 3. Kaplan-Meier plots of progression-free survival (PFS) and overall survival (OS). **A and B**, PFS and OS stratified by the plasma EBV DNA level at baseline (cut-off of 3000 copies/mL); **C and D**, PFS and OS stratified by the decrease of plasma EBV DNA level from baseline to the first post-treatment assessment (cut-off of 50%).

Supplementary Table S1. Summary of previous treatment for advanced disease.

	Value (N = 25)
PD-1 inhibitor, no. (%)	
Toripalimab	13 (52)
Camrelizumab	8 (32)
Sintilimab	5 (20)
Palivizumab	2 (8)
Tislelizumab	1 (4)
Other therapy, no. (%)	
Cisplatin	24 (96)
Gemcitabine	22 (88)
Paclitaxel	10 (40)
Capecitabine	5 (20)
Nimotuzumab	4 (16)
Carboplatin	2 (8)
Tegafur	2 (8)
Apatinib	1 (4)
Cetuximab	1 (4)
Anlotinib	1 (4)
Bevacizumab	1 (4)

Supplementary Table S2. Compliance to the study regimen.

Variable	No. (%) of patients
Induction stage	**25 (100)**
Patients evaluated for TPC chemotherapy	25 (100)
Patients completing one cycle	25 (100)
Patients completing two cycles	24 (96)
Patients completing three cycles	23 (92)
Patients completing four cycles	21 (84)
Patients completing five cycles	15 (60)
Patients completing six cycles	12 (48)
Reason for not receive six cycles chemotherapy	
Treatment-related adverse event	5 (20)
Personal reason	4 (16)
Progression	3 (12)
Drop out	1 (4)
Patients with chemotherapy dose reductions	11 (44)
Dose reductions of NAB-paclitaxel	4 (16)
Dose reductions of cisplatin	5 (20)
Dose reductions of capecitabine	10 (40)
Reason for dose modification	
Gastrointestinal	5 (20)
Hand-foot syndrome	3 (12)
Hematologic adverse events	3 (12)
Patients with cadonilimab interruption	1 (4)
Fall-induce femoral fracture	1 (4)
Maintenance stage	**19 (76)**
Patients with capecitabine reduction	2 (8)
Hand-foot syndrome	2 (8)
Patients with cadonilimab interruption	2 (8)
Musculoskeletal	1 (4)
Diarrhea and colitis	1 (4)
Patients discontinued study	**14 (56)**
Reason for discontinued study	
Progression	13 (52)
Drop out*	1 (4)

* One patient withdrew his consent and refused to come back to continue the treatment after the first cycle of study regimen due to economic reason and received Chinese herb therapy at home. No intolerable adverse event occurred to her.

Note: Lobaplatin was used in three patients who had a clear history of prior cisplatin intolerance, and lobaplatin dose modification did not occurred.