Anlotinib as a Third-Line or Further Treatment for Recurrent or Metastatic Nasopharyngeal Carcinoma: A Single-arm, Phase 2 Clinical Trial

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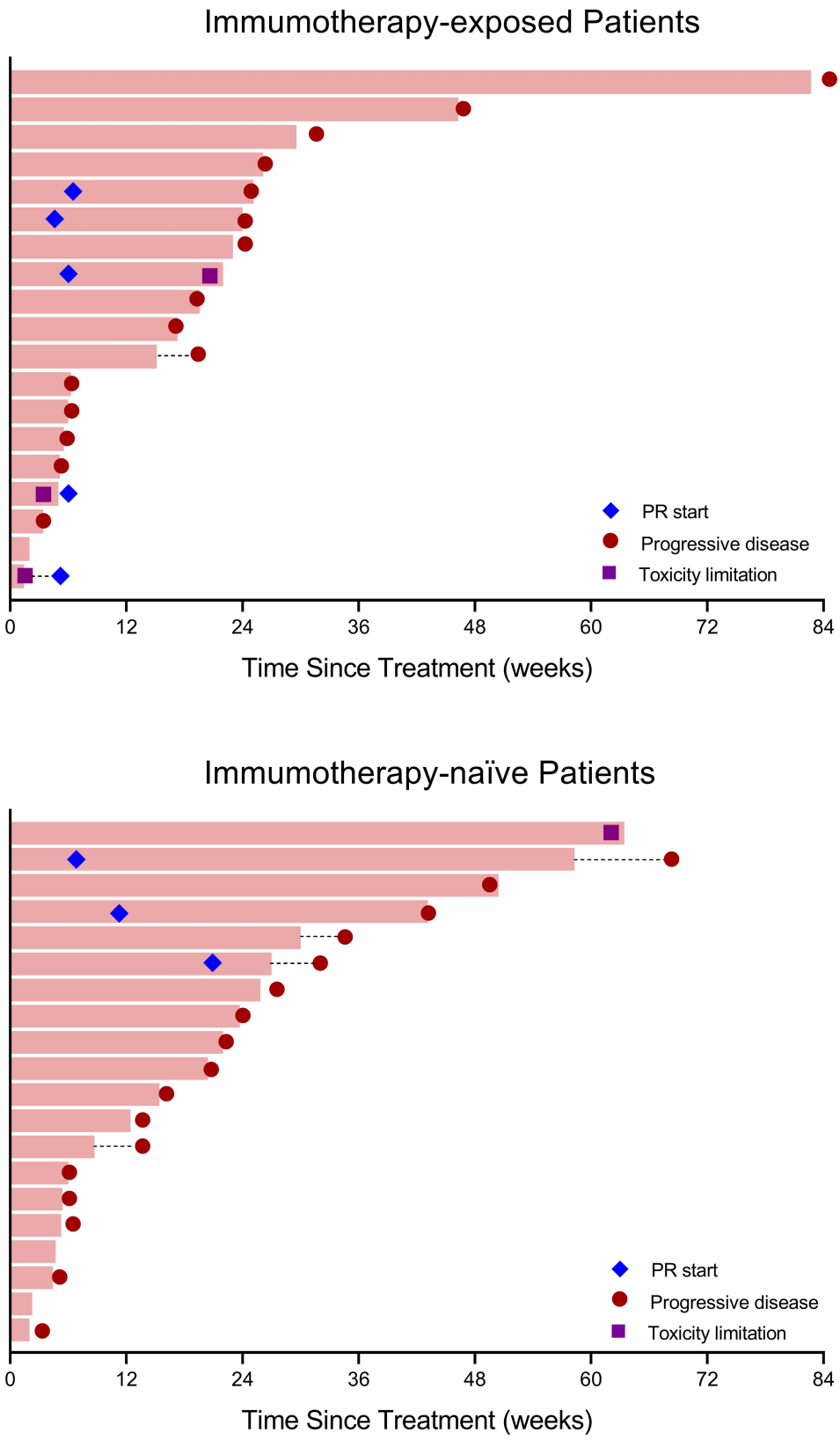

Figure S1. Treatment exposure and response duration of immunotherapy -exposed and immunotherapy-naïve patients.

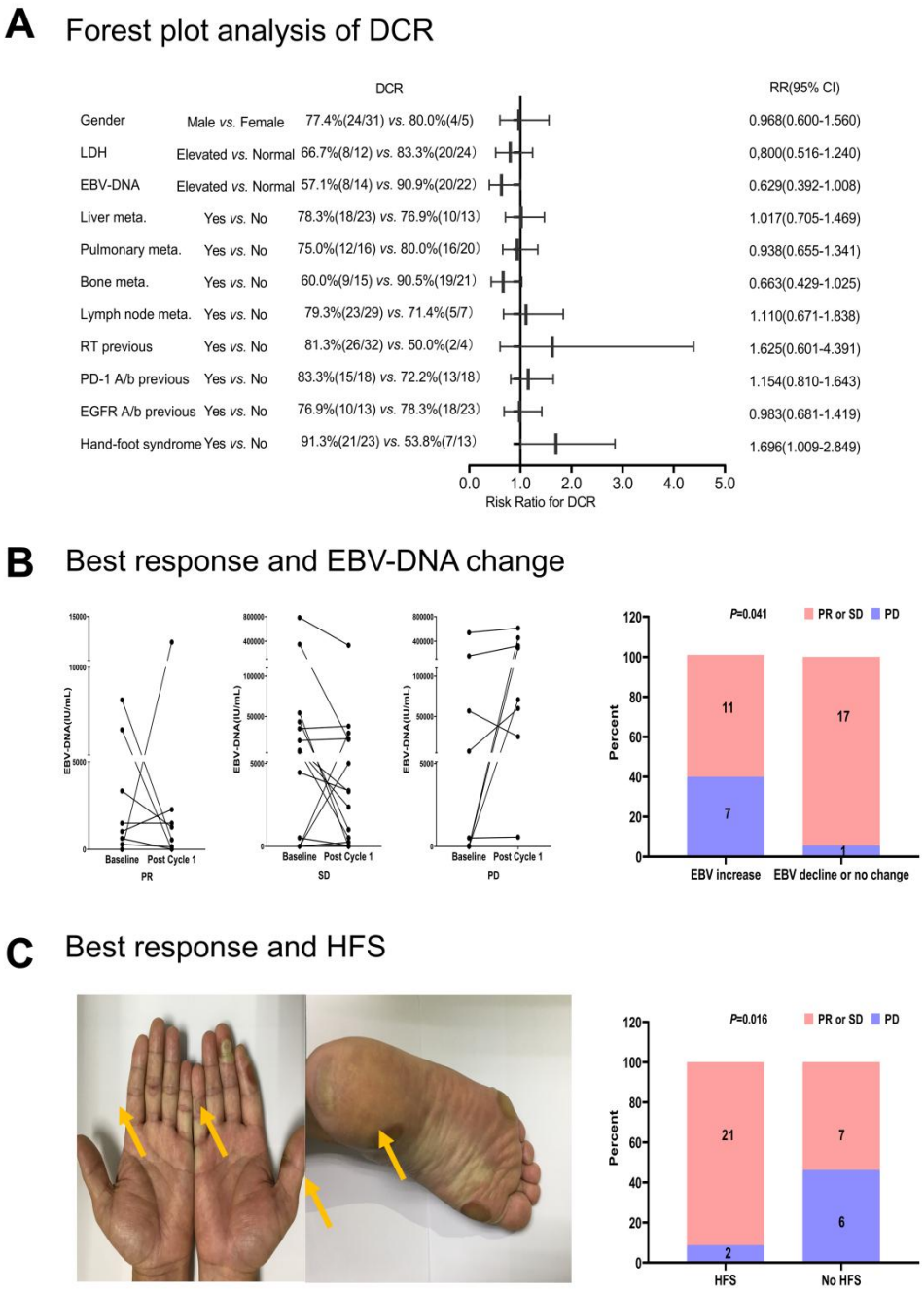

Figure S2. Subgroup Analysis. (A) Forest plot analysis of DCR by patient subgroups. (B) Best response and EBV-DNA change. Changes in plasma EBV DNA copy number post cycle 1 from baseline (left panel) and treatment responses of patients (right panel). (C) Hand-foot syndrome in patients treated with anlotinib (left panel) and treatment responses of patients per occurrence of hand-foot syndrome (right panel). Patient responses are colored coded. EBV, Epstein-Barr virus; PD, progressive disease; PR, partial response; SD, stable disease.

Table S1. Studies of antiangiogenic multikinase inhibitors in recurrent and metastatic nasopharyngeal narcinoma.

Agent	Type	Number	Efficacy	Toxicity
Sorafenib[23]	Prospective phase II	7 NPC + 20 SCCHN	ORR (3.7%), DCR (37.0%), mPFS (3.4 mos), mOS (4.2 mos).	Grade 3 lymphopenia (17%), fatigue (7%), hyponatremia (3%), leucopenia (3%), and lipase elevation (3%). One death for epistaxis.
Sunitinib[11]	Prospective phase II	13	ORR (10.0%), DCR (30.0%), mPFS (3.5 mos), mOS (10.5 mos).	Grade 3/4 hemorrhage (28.6%), leucopenia (28.6%), fatigue (21.4%), neutropenia (21.4%) and dysphagia (14.3%). Two death for grade 5 hemorrhage.
Pazopanib[7]	Prospective phase II	33	ORR (6.1%), DCR (54.5%) at 12 weeks, mPFS (4.4 mos), mOS (10.8 mos).	Grade 3/4 fatigue (15.2%), hand-foot syndrome (15.2%), anorexia (9.1%), diarrhea (6.1%), and vomiting (6.1%).
Axitinib[8]	Prospective phase II	40	ORR (3.7%), DCR (78.4%) at 3 months, mPFS (5.0 mos), mOS (10.4 mos).	Grade 3/4 hypertension (8%), diarrhea (5%), weight loss (5%), and pain (5%). All hemorrhage were grade 1 -2.
Apatinib[24]	Prospective phase II	33	ORR (36.4%), DCR (54.5%) at 5 months, mPFS (5.0 mos), mOS (16.0 mos).	Grade 3/4 hand-foot syndrome (15.2%), oral ulcer (15.2%), proteinuria (6.1%), leukopenia (6.1%), thrombocytopenia (6.1%) and hemorrhage (3.0%).
Lucitanib[9]	Prospective phase Ib	10 in the continuous arm, 10 in the continuous arm.	ORR (20%), DCR (90%), mPFS (3.73 mos) for the continuous arm; ORR (10%), DCR (60%), mPFS (3.68 mos) for the intermittent arm.	Grade 3/4 hypertension (30% vs 0%), proteinuria (20% vs 0%), increased AST (10% vs 0%), and decreased platelet count (10% vs 0%),

Anlotinib	Prospective phase II	39	ORR (20.5%), DCR (71.8%), mPFS (5.7 mos), mOS (NR), 12-month OS (58.3%).	Grade 3/4 hand-foot syndrome (23.7%), oral mucositis (21.0%) and hypertension (7.9%). All hemorrhage were grade 1-2.

AST, aspertate aminotransferase; DCR, disease control rate; mPFS, median progression-free survival; mos, months; mOS, median overall survival; NPC, nasopharyngeal narcinoma; NR, not reached; ORR, objective response rate; SCCHN, squamous cell carcinoma of the head and neck.