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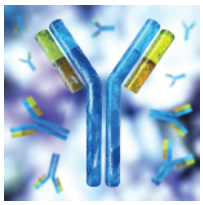
Clinical Trials

Major finding: The PD-1 antibody camrelizumab was well tolerated in patients with nasopharyngeal carcinoma.

Approach: Camrelizumab was assessed as a monotherapy and with platinum chemotherapy in two phase I trials.

Impact: Camrelizumab warrants further investigation for the treatment of patients with nasopharyngeal carcinoma.

CAMRELIZUMAB HAS ACTIVITY IN PATIENTS WITH NASOPHARYNGEAL CARCINOMA



Patients with nasopharyngeal carcinoma often respond to treatment with platinum-based chemotherapy such as gemcitabine plus cisplatin, but patients with recurrent or metastatic disease have few treatment options. Fang, Yang, Ma, and colleagues evaluated the anti–PD-1 antibody camrelizumab (SHR-1210) in patients with nasopharyngeal carcinoma in two single-arm phase I trials. The first (monotherapy) trial treated 93 patients with recurrent or metastatic disease with camrelizumab monotherapy in a dose-escalation and expansion cohort. The second (combination) trial enrolled 23 patients with treatment-naïve nasopharyngeal carcinoma. These patients were treated with camrelizumab in combination with gemcitabine and cisplatin. The primary endpoint of both trials was the safety and tolerability of the study treatment. Camrelizumab was well tolerated in the monotherapy trial, with 15 of 93 (16%) patients experiencing grade 3–4 adverse events, and 8 patients (9%) having treatment-related serious adverse events. Overall, 31 of the 91 evaluable patients (34%) achieved an overall response. In the camrelizumab combination trial, 20 of 23 (87%) patients experienced grade 3–4 adverse events, and two patients had treatment-related serious adverse events. Of the 22 evaluable patients, 20 (91%) achieved an overall response. Taken together, these trials indicate that camrelizumab is well tolerated and exhibits promising preliminary antitumor activity both as a monotherapy in patients with recurrent or metastatic nasopharyngeal carcinoma and in combination with platinum chemotherapy in patients with treatment-naïve nasopharyngeal carcinoma. These findings support further clinical investigation of camrelizumab in patients with nasopharyngeal carcinoma. ■

Fang W, Yang Y, Ma Y, Hong S, Lin L, He X, et al. Camrelizumab (SHR-1210) alone or in combination with gemcitabine plus cisplatin for nasopharyngeal carcinoma: results from two single-arm, phase 1 trials. Lancet Oncol 2018;19:1338–50.

Tumor Suppressors

Major finding: SPOP colocalizes with substrates in membraneless organelles, thereby enhancing ubiquitination.

Concept: Substrates drive the phase separation of SPOP into mesoscale assemblies that promote enzymatic activity.

Impact: Disruption of SPOP phase separation may underlie the oncogenicity of tumor-associated *SPOP* mutations.

SPOP MUTATIONS DISRUPT PHASE SEPARATION TO IMPAIR ITS ACTIVITY

SPOP is a tumor suppressor protein and substrate adaptor of the cullin3-RING ubiquitin ligase (CUL3) that is frequently mutated in a variety of tumor types. Tumor-associated *SPOP* mutations disrupt substrate binding and ubiquitination, leading to increased expression of oncogenic substrates, but the mechanisms by which SPOP assembles with its substrates and gets recruited to nuclear bodies remain poorly understood. Bouchard, Otero, and colleagues investigated the mechanisms underlying colocalization of SPOP and its substrates, including the death domain–associated protein (DAXX) and the androgen receptor (AR). When SPOP and DAXX were coexpressed, they both relocalized into nuclear bodies (termed SPOP/DAXX bodies) distinct from the PML bodies where DAXX usually resides and the nuclear speckles where SPOP generally localizes. These SPOP/DAXX bodies were characterized as liquid membraneless organelles, and the relocalization to these membraneless bodies was disrupted by prostate cancer–associated *SPOP* mutations. The phase separation was mediated by multiple weak interactions between DAXX and SPOP, which are facilitated by multiple SPOP-binding motifs in DAXX and oligomerization of SPOP. These features were required for SPOP/DAXX phase separation, as was shown by mutational analysis. Mutations in SPOP or DAXX disrupted phase separation, preventing the colocalization of SPOP and DAXX, and reducing ubiquitination of target proteins. The SPOP/DAXX bodies were active ubiquitination hubs, recruiting CUL3 to facilitate ubiquitination of DAXX. Similarly, other SPOP substrates harbored weak SB motifs, suggesting that SPOP may recruit them via phase separation. Consistent with this hypothesis, AR formed liquid droplet-like assemblies with SPOP, indicating a phase separation similar to DAXX. Taken together, these findings reveal that cancer-associated *SPOP* mutations disrupt the liquid–liquid phase separation that normally concentrates the components required for substrate ubiquitination, resulting in loss of function. ■

Bouchard JJ, Otero JH, Scott DC, Szulc E, Martin EW, Sabri N, et al. Cancer mutations of the tumor suppressor SPOP disrupt the formation of active, phase-separated compartments. Mol Cell 2018;72:19–36.e8.

AACR American Association for Cancer Research

CANCER DISCOVERY

SPOP Mutations Disrupt Phase Separation to Impair Its Activity

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