Background Mature tertiary lymphoid structures (mTLS) predict improved outcome in patients treated with immune checkpoint inhibitors (ICIs). However, a significant proportion of patients with TLS-positive tumors do not respond to ICI when used as a single agent and may therefore benefit from combination therapy. The multikinase inhibitor, regorafenib, deplete regulatory T cells, an immune population associated with resistance to ICI in TLS-positive tumors. We report the results of the PD-L1 inhibitor avelumab combined with regorafenib in patients with mTLS-positive advanced solid tumors.

Methods ‘Regomune’ is an open-label, multicenter phase II study assessing the combination of avelumab (10mg/kg IV every 14 days) with regorafenib (160 mg daily for 3 weeks in a 4-week cycle) in patients with advanced mTLS-positive solid tumors. The mTLS status was centrally assessed as previously described. All patients had confirmed progressive disease at inclusion, based on a central review of imaging. The primary efficacy endpoint was a 6-month non-progression rate using RECIST v1.1 based on blinded central review. 29 assessable patients were deemed necessary, and to meet the primary endpoint, at least 8 patients needed to be progression-free at 6 months.

Results Between January 2021 and July 2022, 132 patients (5 centers) underwent mTLS screening. Of these, 55 (41.7%) were identified as mTLS+, and 38 were included in the study. The top five histological subtypes were MSS colorectal cancer (15.8%), sarcoma (13.1%), oesogastric (10.5%), biliary tract (7.9%), and pancreatic cancer (7.9%). The most frequent grade 3/4 adverse events were palmar-plantar erythrodysesthesia syndrome (23.7%), maculo-papular rash (18.4%), fatigue, and oral mucositis (7.9%) each. No treatment-related deaths were reported. Of the 34 patients assessed for efficacy, 16 (47%) showed tumor shrinkage, with 9 achieving a partial response (26.7%) and 7 having stable disease (20.6%). The median duration of response was 6 months. Twelve patients (comprising various tumor types including MSS colorectal cancer, small bowel carcinomas, biliary tract cancer, sarcomas, thyroid and gynecological tumors.) were progression-free at 6 months, marking the study’s primary endpoint achievement. The median progression-free survival and overall survival were 3.6 months and 8.6 months, respectively.

Conclusions This is the pioneering histology-agnostic clinical trial employing mTLS as a biomarker for patient selection for treatment with an immune checkpoint inhibitor-based regimen. Durable responses were recorded, even in cases typically resistant to immunotherapy. Additional data from tumor and blood samples will be presented during the meeting.

Trial Registration NCT03475953

REFERENCES

Ethics Approval The REGOMINE study obtained ANSM and ethics approval (CPP Sud-Ouest Bordeaux) as per European Regulation. All participants gave informed consent before taking part.

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