Activity of bevacizumab combined with chemotherapy in advanced *RET*-rearranged non-small cell lung cancer

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Introduction: Selective RET inhibitors (SRIs) are standard for *RET*-rearranged (RET+) non-small cell lung cancer (NSCLC), yet post-SRI options are limited and global access to SRIs remains uneven. We investigated whether VEGF-pathway blockade with bevacizumab plus chemotherapy (Beva-CH) could be leveraged in this setting.

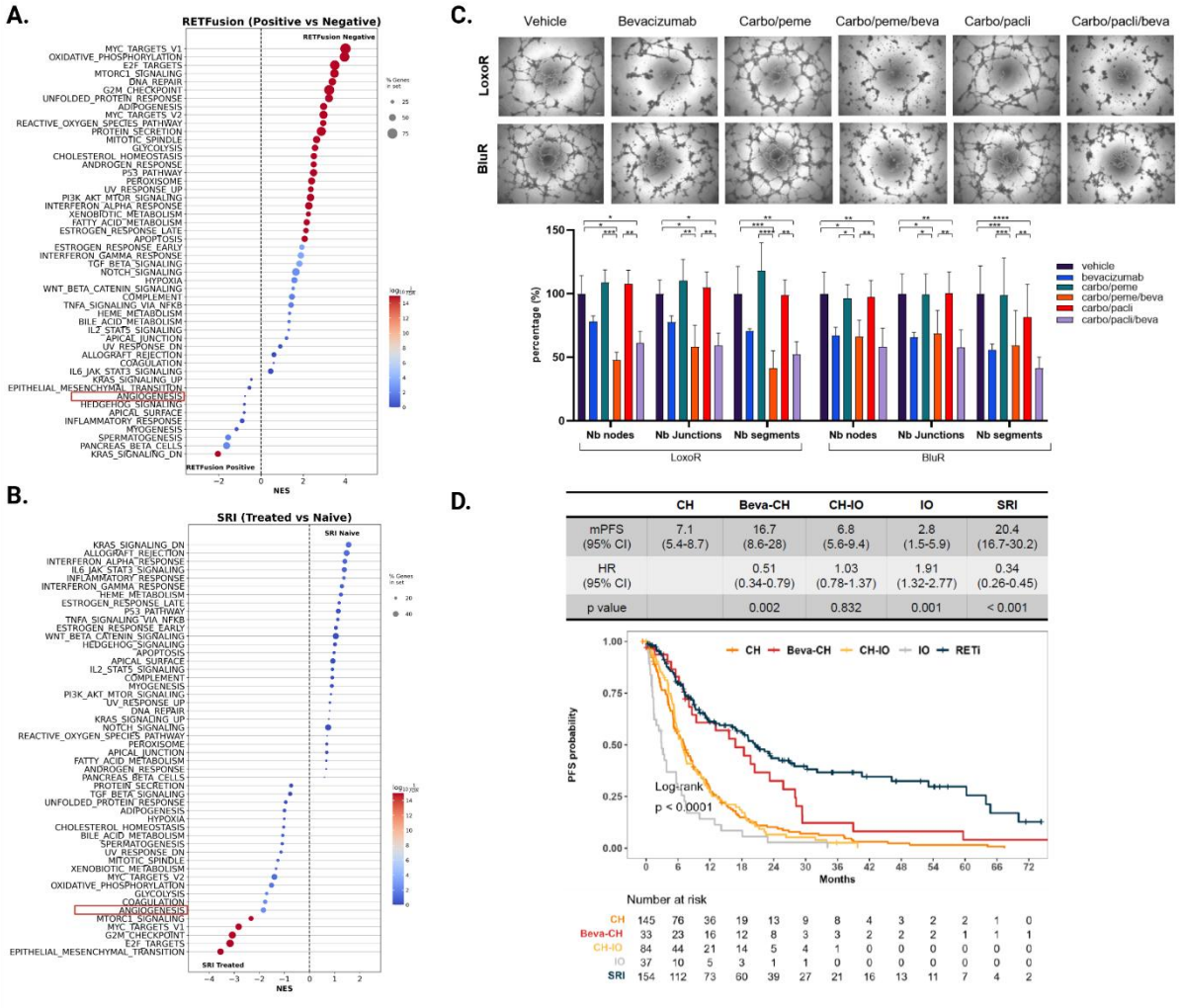
Methods: Whole-transcriptome data from a commercial CLIA-certified database (19,782 lung adenocarcinomas, 203 *RET*+) were interrogated for Hallmark angiogenesis and predefined VEGF-pathway genes, including *RET*+ samples before (n=66) and after (n=10) SRI. Functional studies used selpercatinib- and pralsetinib-resistant Lc2/AD-derived cell lines (BluR, LoxoR) exposed to bevacizumab ± platinum-based chemotherapy, assessing vasculogenic mimicry, 3D spheroid viability, apoptosis and migration. Clinically, we assembled a retrospective first-line cohort from the RET-MAP registry (465 patients across 48 centers) comparing Beva-CH with chemotherapy (CH), chemo-immunotherapy (CH-IO), immunotherapy (IO), and SRIs. Outcomes were objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). Multivariable Cox models and inverse probability of treatment weighting (IPTW; weights derived from propensity scores to balance baseline covariates) were applied.

Results: *RET*+ adenocarcinomas showed enrichment of angiogenesis hallmarks vs *RET* wild-type lung adenocarcinomas, with higher *KDR (VEGFR2)* expression (median transcript per million 25.4 vs 15.7; q<0.0001). In *RET*+ samples, SRI-treated tumors had higher angiogenesis ssGSEA scores than SRI-naïve tumors (median normalized enrichment score 0.45 vs 0.42; q=0.0483) (Figure A-B). SRI-resistant cells exhibited VEGF-axis hyperactivation (↑VEGFA/VEGFC; ↑p-VEGFR1/2) and intrinsic vasculogenic mimicry; bevacizumab impaired mimicry dose-dependently and, combined with carboplatin/pemetrexed or carboplatin/paclitaxel, reduced viability, increased apoptosis, limited migration, and shrank viable spheroid cores (Figure C).

Among 465 patients, first-line Beva-CH (n=34) achieved an ORR of 65% versus 52% with CH, 51% with CH-IO, 24% with IO, and 72% with SRIs. Median PFS was 16.7 months with Beva-CH vs 7.1 with CH, 6.8 with CH-IO, 2.8 with IO, and 20.4 with SRIs (Figure D). In adjusted analyses, Beva-CH was associated with longer PFS vs CH (multivariable HR 0.50, 95% CI 0.28–0.89; IPTW HR 0.40, 95% CI 0.23–0.67). In patients without subsequent SRI, median OS was 34.0 months with Beva-CH vs 15.7 with CH±IO (HR 0.56, 95% CI 0.31–1.02). Grade ≥3 adverse events occurred in 5/29 Beva-CH patients (two hypertension).

Conclusion: These findings reveal angiogenesis as a therapeutic vulnerability in RET-rearranged NSCLC and support bevacizumab plus chemotherapy as a clinically meaningful strategy where selective RET inhibitors are unavailable or after resistance, providing a compelling rationale for clinical trials testing angiogenesis inhibition in this underserved population.

Figure



	CH	Beva-CH	CH-IO	IO	SRI
mPFS (95% CI)	7.1 (5.4-8.7)	16.7 (8.6-28)	6.8 (5.6-9.4)	2.8 (1.5-5.9)	20.4 (16.7-30.2)
HR (95% CI)		0.51 (0.34-0.79)	1.03 (0.78-1.37)	1.91 (1.32-2.77)	0.34 (0.26-0.45)
p value		0.002	0.832	0.001	< 0.001

CH	145	76	36	19	13	9	8	4	3	2	2	1	0
Beva-CH	33	23	16	12	8	3	3	2	2	2	1	1	1
CH-IO	84	44	21	14	5	4	1	0	0	0	0	0	0
IO	37	10	5	3	1	1	0	0	0	0	0	0	0
SRI	154	112	73	60	39	27	21	16	13	11	7	4	2