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Updated Results of CABINET Trial/Alliance A021602: Cabozantinib Versus Placebo for Advanced Neuroendocrine Tumors (NET) after Progression on Prior Therapy

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BACKGROUND

NETs are sensitive to VEGF pathway inhibitors. We compared cabozantinib (CABO), a multi-kinase inhibitor targeting VEGFR, c-MET, AXL and RET, with placebo (PB) in a phase 3 trial including previously treated patients (pts) with advanced NET (NCT03375320). The study was stopped early and unblinded, per DSMB recommendations, based on interim results showing improvement in PFS by local radiology assessment (ESMO 2023). Final analyses of PFS by blinded independent central review (BICR), objective response rate (ORR), subgroup analyses, and safety are presented.

METHODS

Pts with locally advanced or metastatic extra-pancreatic NET (epNET) or pancreatic NET (pNET) were randomized 2:1 in separately powered cohorts to receive CABO 60 mg daily vs PB. Eligibility: progression by RECIST within 12 months (mo) prior to registration, ≥ 1 prior therapy. Prespecified primary endpoint: PFS by BICR. Secondary endpoints: ORR, overall survival (OS), safety.

RESULTS

203 pts with epNET and 95 pts with pNET were randomized through the data cutoff of 8/24/2023. Primary tumor sites for pts with epNET included GI tract 57%, lung 19%, unknown 12%. In both cohorts, CABO significantly improved PFS by BICR and resulted in higher confirmed ORR (Table). Across clinical subgroups, including primary tumor site and prior anticancer therapy, PFS favored CABO. Grade 3+ treatment-related adverse events (AEs) were higher in the CABO arm; no new safety signals were noted. The most common \geq grade 3 treatment-related adverse events in the epNET cohort included

hypertension (21%), fatigue (13%) and diarrhea (11%); in the pNET cohort, they included hypertension (22%), fatigue (11%) and thromboembolic events (11%).

Table. Progression-free survival and objective tumor response by BICR of patients enrolled in the epNET and pNET cohorts

| | CABO - epNET (N=134) | PB - epNET (N=69) | CABO - pNET (N=64) | PB - pNET (N=31) |
|-----------------------------|-------------------------|----------------------|-----------------------|---------------------|
| Median PFS (BICR), months | 8.5 | 4.0 | 13.8 | 4.5 |
| Stratified HR (95% CI) | 0.38 (0.25-0.58) | Ref | 0.23 (0.12-0.42) | Ref |
| Stratified log-rank p-value | p<0.0001 | | p<0.0001 | |
| | | | | |
| Confirmed ORR (BICR), n (%) | | | | |
| Partial response | 7 (5%) | 0 | 12 (19%) | 0 |
| Stable disease | 87 (65%) | 37 (54%) | 39 (61%) | 17 (55%) |
| Progressive disease | 15 (11%) | 24 (35%) | 5 (8%) | 12 (39%) |
| Not evaluable/missing | 25 (19%) | 8 (12%) | 8 (13%) | 2 (6%) |

CONCLUSIONS

CABO demonstrates significant improvement in PFS by BICR in epNET and pNET. AEs are consistent with the known safety profile of CABO. CABO may be a new treatment option for pts with previously treated, advanced NET.

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