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A Phase 1 Study of the Next-Generation ALK/ROS1/TRK Inhibitor Ropotrectinib (TPX-0005) in Patients with Advanced *ALK*/*ROS1*/*NTRK*+ Cancers (TRIDENT-1)

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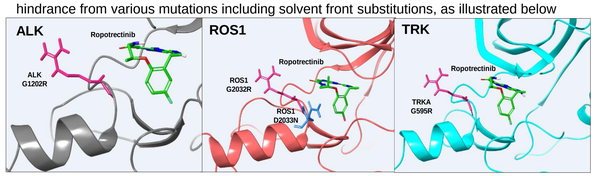
INTRODUCTION

- *ALK*, *ROS1* and *NTRK1/2/3* fusions are oncogenic drivers across multiple tumor types[1]
- Acquired resistance including solvent front mutations (i.e. ALK G1202R, ROS1 G2032R & D2033N, TRKA G595R, TRKB G639R and TRKC G623R) are difficult to overcome with current therapies[2]
- Ropotrectinib is designed to reside within the ATP adenine binding pocket and avoid steric hindrance from various mutations including solvent front substitutions, as illustrated below



- Ropotrectinib is a next-generation ALK/ROS1/TRKA-C inhibitor and exhibits potent activity against both wild-type (WT) and a variety of mutations (including solvent front mutations)

Table 1. Ropotrectinib Potently Inhibited WT and Mutant ALK/ROS1/TRK in Ba/F3 Cell Proliferation IC_{50} (nM)

	EML4-ALK V1		CD74-ROS1			LMNA-TRKA		ETV6-TRKB		ETV6-TRKC		
Inhibitor	**WT**	**G1202R**	**WT**	**G2032R**	**D2033N**	**WT**	**G595R**	**WT**	**G639R**	**WT**	**G623R**	**G623E**
Ropotrectinib	**27**	**63.6**	**<0.2**	**3.3**	**1.3**	**<0.2**	**0.4**	**<0.2**	**0.6**	**<0.2**	**3**	**1.4**
Crizotinib	55.7	400	14.6	266.2	200.9							
Ceritinib	7.1	965	42.8	1813	169.2							
Alectinib	11.6	417										
Brigatinib	10.9	190.5	21	1172	128.4							
Lorlatinib	0.5	41.5	0.2	160.7	3.3							
Ensartinib			39.5	371.8	401.9							
Entrectinib			10.5	1813	169.2	0.5	705	<0.5	1384	0.6	1623	1351
Larotrectinib						4	1024	10.9	3000	10.2	3293	742.3

OBJECTIVES

Primary Objectives: Determine 1st cycle DLTs, MTD and RP2D of Ropotrectinib

Secondary Objectives: Evaluate the safety, tolerability, food effect on the PK, and preliminary confirmed objective response rate (cORR) of Ropotrectinib

METHOD

Key Eligibility Criteria

- Histologically or cytologically confirmed, locally advanced or metastatic solid tumors that harbor an *ALK*, *ROS1*, *NTRK1*, *NTRK2*, or *NTRK3* gene rearrangement
- At least 1 measurable target lesion; CNS-only measurable disease allowed per RECIST v1.1
- No limit on number of prior chemotherapy, immunotherapy, or TKI regimens
- Asymptomatic CNS metastases were allowed

Study Design

This Phase 1/2 Multicenter Study included Phase 1a and Phase 1b studies

- In Phase 1a, 6 evaluable patients were enrolled in each dose escalation cohort
- In Phase 1b, the effect of high fat-, high calorie-food on the PK of Ropotrectinib was evaluated

Assessments

- Dose-limiting toxicities (DLTs) were evaluated during Cycle 1
- CT scans at screening, and every 2 cycles until Cycle 18, then every 3 cycles until Cycle 36
- Tumors assessed per RECIST v1.1
  - Intracranial lesions could be considered as target lesions
- Adverse events (AEs) graded per Common Terminology Criteria for Adverse Events v4.03
- Archival tumor tissue specimens (or de novo tumor biopsy) collected at baseline
- Blood for molecular profiling (circulating free DNA) collected at screening and end of treatment

RESULTS

Patients and Treatment

- 72 subjects (31 *ALK*+, 33 *ROS1*+ and 8 *NTRK*+ by local test) received as least 1 dose of Ropotrectinib in 6 cohorts (**Tables 2 & 3**)
- As of the data cutoff date of April 16, 2018:
- 50 subjects have discontinued treatment:
  - 36 subjects due to disease progression
  - 8 subjects due to AEs
    - 6 subjects due to unrelated AEs
    - 2 subjects due to drug-related AEs
      - 1 subject at 160 mg BID had Grade 3 dyspnea and Grade 3 hypoxia (DLT)
      - 1 subject at 200 mg BID had Grade 3 pleural effusion
  - 5 subjects withdrew consent
  - 1 subject based on Investigator decision
- 22 subjects continuing treatment (duration of treatment: 70 − 402+ days)

Table 2. Dose Cohorts (Phase 1a + Phase 1b)

Cohort #	Phase	Dose	# Pts dosed	Total # Pts
1	1a	40 mg QD	6	13
	1b	40 mg QD	7[a]	
2	1a	80 mg QD	6	12
	1b	80 mg QD	6	
3	1a	160 mg QD	8[b]	23
	1b	160 mg QD	15[c]	
4	1a	240 mg QD	10[d]	10
5	1a	160 mg BID	12[e]	12
6	1a	200 mg BID	2[f]	2
Total			72	72

[a] 1 Additional (add'l) pt added due to inadequate PK collection; [b]2 Add'l pts added based on inadequate PK collection and to further evaluate PK; [c]Expansion of the cohort to 12 pts and 3 add'l pts added due to inadequate PK collection; [d]3 Add'l pts added (2 replaced as unevaluable and 1 with inadequate PK collection); 1 add'l pt who originally consented to 200 mg BID cohort added; [e]Expansion of the cohort to 12 pts; [f]Dose escalation stopped due to DLTs in the previous dose cohort (160 mg BID)

Table 3. Patient Demographics and Disease Characteristics

Demographics	Overall N=72
Age (Years)	52.0
Median (Min, Max)	(18, 79)
Age Group	
<65	60 (83.3)
≥65	12 (16.7)
Sex, n (%)	
Male	36 (50.0)
Female	36 (50.0)
Race, n (%)	
Caucasian	36 (50.0)
Asian	32 (44.4)
Black or African American	3 (4.2)
Other	1 (1.4)
ECOG at Baseline, n (%)	
0	24 (33.3)
1	48 (67.7)

Disease Characteristics	Overall N=72
Number of *ALK*+ Subjects	**31**
# Prior TKIs	2 (0,4)
Number of *ROS1*+ Subjects	**33**
# Prior TKIs	1 (0,3)
Number of *NTRK*+ Subjects	**8**
# Prior TKIs	1 (0,2)
Number of Subjects with CNS	**23 (31.9)**
Disease Tumor Type, n (%)	
Non-Small Cell Lung Cancer	60 (83.3)
Glioblastoma	3 (4.2)
Renal Cell Carcinoma	2 (2.8)
Cholangiocarcinoma	2 (2.8)
Soft Tissue Sarcoma	2 (2.8)
Melanoma	1 (1.4)
Salivary Gland Cancer	1 (1.4)
Uterine Cancer	1 (1.4)

Safety

- A total of 60 subjects experienced treatment-related AEs, the majority Grade 1 or 2 (**Table 4**)
- 4 DLTs at dose levels 240 mg QD (n=1) and 160 mg BID (n=3)
  - 1 Grade 3 dizziness (240 mg QD): treatment continued at 160 mg QD
  - 1 Grade 3 dizziness (160 mg BID): treatment continued at 160 mg QD
  - 1 Grade 2 dizziness (160 mg BID): treatment continued at 80 mg QD
  - 1 Grade 3 dyspnea/hypoxia (160 mg BID): resolved after treatment discontinuation
- There have been 15 deaths on study:
  - 3 deaths during the treatment period
    - 2 subjects due to disease progression
    - One 53-year-old subject with *ALK*+ TKI-refractory NSCLC and hypertension (requiring medical therapy), diabetes and obesity (BMI 44) developed atrial fibrillation on C1D8 and died on C1D10
  - 12 deaths during the 28-day follow-up period: 11 due to disease progression and 1 due to sepsis unrelated to Ropotrectinib

Preliminary Clinical Activity by Investigator Assessment

- As of the data cutoff, 56 subjects (18 *ALK*+, 31 *ROS1*+, 7 *NTRK*+ by local test) had both a baseline and at least 1 post-baseline tumor assessment and are evaluable for tumor response (**Figure 1**)
- **18 Evaluable *ALK*+ subjects:** 14 TKI-refractory NSCLC
- No PR or CR achieved to date; 4 subjects had durable stable disease: (83 -165 days)
- PK/PD relationship indicates incomplete target coverage at current dose levels
- **31 Evaluable *ROS1*+ subjects:** 1 *ROS1*+ TKI-refractory melanoma subject, 1 *ROS1* fusion-negative subject by central next gene sequence (NGS), 29 *ROS1*+ NSCLC subjects
- 10 TKI-naïve and 19 TKI-refractory NSCLC: median # prior TKIs = 1 (0-3)
  - For TKI-naïve subjects, cORR = 70% with 7 confirmed PR, 1 PR to be confirmed
    - Median follow up of 8 months with 90% of subjects remaining on treatment (**Figure 2**)
  - For TKI-refractory subjects, cORR = 11% with 2 cPR and 1 PR to be confirmed
    - A crizotinib-refractory *CD74-ROS1*+ NSCLC subject with solvent front mutation ROS1 G2032R achieved a confirmed PR with a duration of treatment 8.0+ months
    - Median follow up of 4 months with 53% of subjects remaining on treatment (**Figure 2**)
  - Intracranial antitumor activity was observed in *ROS1*+ NSCLC subjects (**Figure 3**)
- **7 Evaluable *NTRK*+ subjects:** 2 were *NTRK* fusion-negative by NGS
  - A confirmed PR (-82%) observed in a TKI-refractory subject with mammary analogue secretory carcinoma (MASC) with solvent front mutation ETV6-TRKC G623E (**Figure 4**) treated at 40 mg QD and has a treatment duration of 13.2+ months
    - Another PR in a TKI-refractory subject (cholangiocarcinoma) at 40 mg QD
    - 2 GBM subjects had SD

Figure 1. Maximum % Change in Target Lesion Size of 56 Response Evaluable Subjects in Advanced Cancers at All Dose Levels

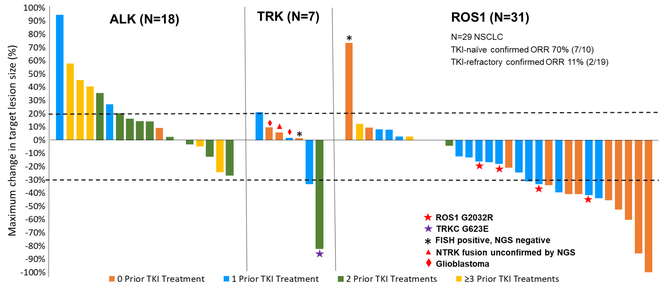


Figure 2. Duration of Treatment with Ropotrectinib in *ROS1*+ NSCLC (N=29)

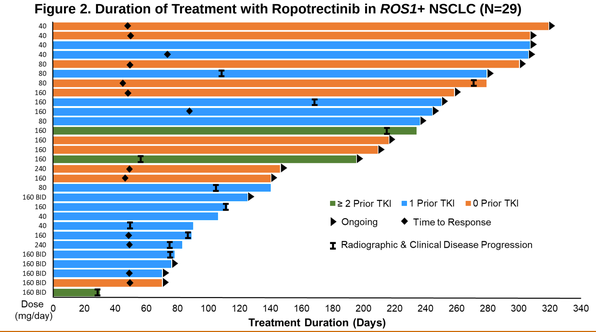


Table 4. Treatment-Related AEs (TRAE) in All Cycles (≥10%)

AEs	All Grades N (%)	Grade ≥ 3* N (%) (Gr #)
Dizziness	35 (48.6)	2 (2.8) (Gr3)
Dysgeusia	33 (45.8)	
Paraesthesia	21 (29.2)	
Constipation	14 (19.4)	
Fatigue	13 (18.1)	
Anemia	8 (11.1)	3 (4.2) (Gr3)
Nausea	8 (11.1)	
Ataxia	7 (9.7)	1 (1.4) (Gr3)
Oral hypoesthesia	7 (9.7)	

*Other Grade 3 TRAEs were increased weight, dyspnea/ hypoxia, pleural effusion, and hypophosphatemia (n=1 each)

Figure 3. CNS Response of a Crizotinib-Refractory, *CD74-ROS1* Fusion-Positive NSCLC Subject with Solvent Front Mutation ROS1 G2032R Having a Confirmed PR at 160 mg QD and a Duration of Therapy 8.0+ Months

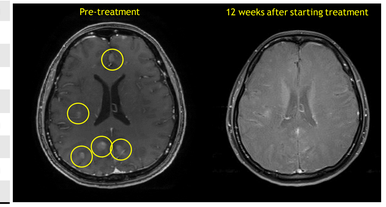
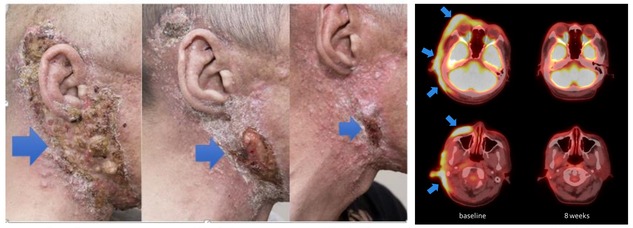


Figure 4. Response of a TKI-refractory *NTRK3* Fusion-Positive MASC Subject with Solvent Front Mutation ETV6-TRKC G623E Treated at 40 mg QD with a Duration of Therapy 13.2+ Months



CONCLUSIONS

- **Ropotrectinib is a next-generation ROS1/TRKA-C/ALK inhibitor with meaningful preliminary clinical activity**
  - **Preliminary antitumor activity observed in *ROS1* fusion-positive NSCLC patients across all doses with additional responders pending confirmation**
    - TKI-naïve patients, confirmed ORR 70% (7/10)
    - TKI-refractory patients, confirmed ORR 11% (2/19) with 1 durable responder with solvent front mutation *ROS1* G2032R
  - **Preliminary antitumor activity observed in *NTRK* fusion-positive solid tumors including 1 *NTRK3* fusion-positive MASC patient with a solvent front mutation TRKC G623E**
  - **Activity within heavily pre-treated *ALK* fusion-positive NSCLC patients currently limited**
    - Median prior TKIs = 2 (range 0-4): no responders to date
    - The lack of activity may be influenced by doses utilized & further dose exploration is ongoing
- **Ropotrectinib is well tolerated with primarily Grade 1 and Grade 2 TEAEs**
  - Dose-limiting dizziness is an on-target adverse event associated with TRK inhibition
  - Recommended phase 2 dose determination is ongoing
- **The preliminary TRIDENT-1 phase 1 data warrant further clinical testing of Ropotrectinib in *ROS1*+, *NTRK*+, and *ALK*+ advanced solid tumors**

REFERENCES

1. Yoshihara K, et al. *Oncogene*. 2015, 34: 4845–4854.
2. Schram AM, et al. *Nature Reviews Clinical Oncology* 2017, 14:735-748

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