NTRK connect

POWERED BY COR2ED

MEETING SUMMARY
ESMO 2019, Barcelona, Spain

CATERINA MARCHIÒ
ASSOC. PROFESSOR OF PATHOLOGY
Department of Medical Sciences, University of Turin
Pathology Unit, FPO-IRCCS Candiolo Cancer Institute
Candiolo, Italy

NTRK FUSIONS POSITIVE SOLID TUMOURS

DISCLAIMER

Please note: The views expressed within this presentation are the personal opinions of the author. They do not necessarily represent the views of the author's academic institution or the rest of the NTRK CONNECT group.

This content is supported by an Independent Educational Grant from Bayer.

DURABILITY OF RESPONSE WITH LAROTRECTINIB IN ADULT AND PEDIATRIC PATIENTS WITH TRK FUSION CANCER

Hyman, et al. ESMO 2019 Abstract #445PD

LAROTRECTINIB IN *NTRK* GENE FUSIONS DEVELOPMENT PROGRAM

NTRK connect
POWERED BY COR2ED

Expanded cohort with 98 new *NTRK* gene fusions positive patients treated with larotrectinib

NCT02122913: Phase 1 dose escalation study in adults with advanced solid tumours[1]

SCOUT: NCT02637687: Phase 1/2 dose escalation study in paediatric with advanced solid tumours[2]

NAVIGATE: NCT02576431: Phase 2, open-label, basket study in adult/adolescent with advanced solid tumours and TRK fusion positive[3]

n=8

n=12

n=35

55 *NTRK* gene fusions positive patients

Primary endpoint
Best objective response rate (ORR)
RECIST v1.1 per investigator assessment

Secondary endpoints:
Duration of response
Progression-free survival
Safety

Dosing:
Larotrectinib 100mg BID predominantly

Data cut-off: 19 February 2019[4]

BID, twice a day; NTRK, neurotrophic tyrosine receptor kinase; ORR; overall response rate; RECIST, Response Evaluation Criteria in Solid Tumors; TRK, tropomyosin receptor kinase

1. Hong DS, et al. Ann Oncol 2019;30(2):325-31; 2. Laetsch TW, et al. Lancet Oncol 2018;19(5):705-14;
3. Drilon A, et al. N Engl J Med 2018;378(8):731-39; 4. Hyman, et al. ESMO 2019 Abstract #445PD.

LAROTRECTINIB IN *NTRK* GENE FUSIONS RESULTS

NTRK connect
POWERED BY COR2ED

- **In the primary cohort of 55 patients**
  - Median follow-up = **26 months** (Data cut-off: 19 February 2019)
  - The **median DOR** in 44 patients with complete or partial responses was **35.2 months** (95% CI 21.2–NE), with 17 progression events and 27 responses ongoing (range 1.6–44 months)
  - The **median PFS** in the primary cohort was **25.8 months** (95% CI 9.9–NE), with 27 patients having progressed
- **In the expanded combined dataset of 153 patients**
  - The most common tumor types = soft tissue sarcoma (n=36), infantile fibrosarcoma (n=29), thyroid carcinoma (n = 26), salivary gland carcinoma (n=21), and lung cancer (n=12)
  - The overall **ORR** = 79% (95% CI 72–85), with complete responses in 16%
  - **Adverse events** were primarily grade 1-2, with 13% of patients having had a grade 3-4 event related to larotrectinib
  - Only **one patient discontinued** due to an AE related to larotrectinib

AE, adverse event; CI, confidence interval; DOR, duration of response; NE, not estimated; NTRK, neurotrophic tyrosine receptor kinase; ORR, overall survival rate; PFS, progression-free survival

Hyman, et al. ESMO 2019 Abstract #445PD.

LAROTRECTINIB IN *NTRK* GENE FUSIONS
CONCLUSION

- These data confirm the marked tissue-agnostic efficacy and long durability of response in patients with TRK fusion cancer treated with larotrectinib
- Larotrectinib continued to demonstrate a favourable long-term safety profile
- Screening patients for *NTRK* gene fusions should be actively considered

NTRK, neurotrophic tyrosine receptor kinase; TRK, tropomyosin receptor kinase

Hyman, et al. ESMO 2019 Abstract #445PD.

UPDATED EFFICACY AND SAFETY OF ENTRECTINIB IN PATIENTS WITH NTRK FUSION-POSITIVE TUMORS: INTEGRATED ANALYSIS OF STARTRK-2, STARTRK-1 AND ALKA-372-001

Rolfo, et al. ESMO 2019 Abstract #476P

ENTRECTINIB IN *NTRK* GENE FUSIONS DEVELOPMENT PROGRAM

NTRK connect
POWERED BY COR2ED

ALKA-372-001 (EudraCT: 2012-000148-88): Italian multicenter Phase 1 study (n=54).

STARTRK-1 (NCT02097810): global multicenter, Phase 1 study (n=65).

In Study ALKA-372-001, different dosing regimens (intermittent dosing [Schedules A and C] and continuous daily dosing [Schedule B] were evaluated under fasted and fed conditions.

In Study STARTRK-1, all patients were treated on a continuous daily dosing regimen, under fed conditions.

All cycles were 28 days in duration.

STARTRK-2 (NCT02568267): open-label multicenter phase II basket study.

- Primary endpoints: Objective Response Rate assessed by blinded independent central review using RECIST v1.1

NTRK, neurotrophic tyrosine receptor kinase; RECIST, Response Evaluation Criteria in Solid Tumors

Drilon A, et al. Cancer Discov 2017;7(4):400-409; Rolfo, et al. ESMO 2019 Abstract #476P.

ENTRECTINIB IN *NTRK* GENE FUSIONS
RESULTS AND CONCLUSION

NTRK connect
POWERED BY COR2ED

- An additional **5 months of follow up** have shown that entrectinib induced systemic response in NTRK fusion positive tumours
  - **ORR** remained high (**59%**)
  - **PFS** was prolonged (**median 11.8 months**)
  - **DOR** was longer than that reported in the previous analysis (median **12.9 months** versus **10.4 months**), as was the **OS** (median **23.9 months** versus **20.9 months**)

- This analysis also showed **clinically meaningful intracranial responses** to entrectinib in patients with NTRK fusion positive solid tumours and CNS metastases, with **intracranial DOR of 54.5%**

CNS, central nervous system; DOR, duration of response; NTRK, neurotrophic tyrosine receptor kinase; ORR, overall survival rate; OS. Overall survival; PFS, progression-free survival

Rolfo, et al. ESMO 2019 Abstract #476P.

SAFETY AND PRELIMINARY CLINICAL ACTIVITY OF REPOTRECTINIB IN PATIENTS WITH ADVANCED ROS1/TRK FUSION-POSITIVE SOLID TUMORS (TRIDENT-1 STUDY)

Drilon, et al. ESMO 2019 Abstract #444PD

TRIDENT-1 STUDY DESIGN

NTRK connect
POWERED BY COR2ED

- **NCT03093116:** Open label, multicenter first-in-human phase 1/2 dose escalation study. Patients with locally advanced or metastatic solid tumours with ROS1, NTRK or ALK gene fusions were enrolled
  - **Phase 1**
    Phase 1a dose escalation / Phase 1b food-effect sub-study, / Phase 1c dose escalation with food / Midazolam drug-drug interaction sub-study.
  - **Phase 2**
    6 distinct expansion cohorts
    - ROS1 TKI-naïve ROS1+ NSCLC / 1 Prior ROS1 TKI ROS1+ NSCLC / 2 Prior ROS1 TKIs ROS1+ NSCLC
    - ROS1 or ALK TKI-naïve ROS1+ or ALK+ solid tumours (non-NSCLC)
    - **TRK TKI-naïve NTRK+ solid tumours / TRK TKI-pretreated NTRK+ solid tumours**
- As of 22 July 2019, 93 patients in 9 dose cohorts under fed and fasted conditions (Phase 1)
- **Primary endpoints:** Dose limiting toxicities (Phase 1) + Recommended Phase 2 Dose (Phase 1) + Overall Response Rate Phase 2
- Presentation of preliminary efficacy data

DOR, duration of response; NSCLC, non-small-cell lung carcinoma; NTRK, neurotrophic tyrosine receptor kinase; TKI, tyrosine kinase inhibitor

Drilon, et al. ESMO 2019 Abstract #444PD.

TRIDENT-1 STUDY
RESULTS AND CONCLUSION

- Preliminary clinical efficacy demonstrated in TKI-naive and TKI pretreated patients with ROS1+ in advanced NSCLC patients:
- TKI naive:
  - **cORR= 91%** (10/11) with **65% DOR≥18 months**
- TKI-pretreated with:
  - 1 prior TKI: **cORR 39%** (7/18)
    - cORR 57% (4/7) in crizotinib-pretreated patients at 160mg QD and above
  - 2 prior TKIs: **cORR 29%** (2/7)

=> Preliminary clinical efficacy activity also demonstrated in NTRK+ TKI-naive and TKI-pretreated patients with advanced solid tumours: 2 case studies presented, one of a patient with advanced *NTRK* fusion positive MASC with acquired *TRKC* G623E solvent front substitution

- **Manageable safety profile**
- Global registrational Phase 2 portion of the study is ongoing.

cORR, confirmed overall response rate; DOR, duration of response; MASC, Mammary analogue secretory carcinoma; NSCLC, non-small-cell lung carcinoma; NTRK, neurotrophic tyrosine receptor kinase; PFS, progression-free survival; QD, one a day; TKI, tyrosine kinase inhibitor

Drilon, et al. ESMO 2019 Abstract #444PD.

REACH NTRK CONNECT VIA TWITTER, LINKEDIN, VIMEO AND EMAIL OR VISIT THE GROUP'S WEBSITE

https://ntrkconnect.info

Follow us on Twitter
@ntrkconnectinfo

Join the
NTRK CONNECT
group on LinkedIn

Watch us on the
Vimeo Channel
NTRK CONNECT

Email
froukje.sosef@
cor2ed.com

NTRK CONNECT
Bodenackerstrasse 17
4103 Bottmingen
SWITZERLAND

Dr. Antoine Lacombe
Pharm D, MBA
Phone: +41 79 529 42 79
antoine.lacombe@cor2ed.com

Dr. Froukje Sosef
MD
Phone: +31 6 2324 3636
froukje.sosef@cor2ed.com