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MEETING SUMMARY
ASCO 2020, VIRTUAL MEETING

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HIGHLIGHTS FROM NTRK CONNECT
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UPDATED ENTRECTINIB DATA IN CHILDREN AND ADOLESCENTS WITH RECURRENT OR REFRACTORY SOLID TUMOURS, INCLUDING PRIMARY CNS TUMOURS

Desai AV, et al.
ASCO 2020, Abstract #107. Oral presentation

CNS, central nervous system

BACKGROUND

Entrectinib = oral TRK/ROS1/ALK inhibitor

Entrectinib in adults: **efficacy data confirmed**[1]

leading to **approval in US and Japan in 2019**

STARTRK-NG (RXDX-101-03) study: Preliminary data of entrectinib in children with recurrent/refractory solid tumours were reported in 2019

(**Data cut-off: 31 October 2018; N=29**)[2]

Updated results are presented during ASCO 2020

(**Data cut-off: 1 July 2019; N=35**)

16 patients with fusion-positive tumours were alive and 9 were still on treatment

ALK, anaplastic lymphoma kinase; ASCO, American Society of Clinical Oncology; ROS1, ROS proto-oncogene 1; TRK, tropomyosin receptor kinase

[1]Doebele RC, et al. Lancet Oncol 2020;21:271-82; [2]Robinson GW, et al. J Clin Oncol 2019;37(15_suppl):10009-10009

TRIAL DESIGN

STARTRK-NG (NCT02650401): open-label, expansion cohorts phase 2 study

Phase 1 part of STARTRK-NG: the dose escalation to define dose for phase 2 (**n=16**)

Expansion Phase 2* part of STARTRK-NG (**n=19**) is presented below

Cohort B:
Primary CNS tumour with *NTRK*/*ROS1*+ fusion
(n=6)

discontinued

Cohort C:
Neuroblastoma
(n=3)

Cohort D:
Extracranial solid tumour *NTRK*/*ROS1*+ fusion
(n=1)

discontinued

Cohort E:**
Unable to swallow capsule
(n=9)

Entrectinib
Dose level 550 mg/m^2 (n=10)
OR
400 mg/m^2 in patients unable to swallow capsules (n=9)

Primary endpoint:
ORR RECIST v1.1

Secondary endpoints:
OS, PFS, DoR, TTR, CBR RECIST v1.1 and safety

*enrolment of *ALK* gene fusions discontinued since protocol amendment v6 dated May 2019; ** Primary CNS tumours (n=5), extracranial solid tumours (n=4)

ALK, anaplastic lymphoma kinase; CBR, clinical benefit rate; CNS, central nervous system; DoR, duration of response; NTRK, neurotrophic tyrosine receptor kinase; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours; ROS1, ROS proto-oncogene 1; TTR, time to response

RESULTS

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Data cut-off: 1 July 2019, N=35

Fusion-positive tumours (n=17)

Primary CNS (n=11)

- High grade glioma (n=8): *NTRK1* (2), *NTRK2** (2) and *NTRK3* (2) gene fusions, and other gene fusions** (2)
- Low grade glioma (n=1): other gene fusions (1)
- Medulloblastoma (n=1): fusion not in frame (1)
- CNS embryonal tumour (n=1): *NTRK2* gene fusions (1x)

Extracranial solid (n=9)

- Salivary gland tumour (n=1): no fusion identified (1)
- Melanoma (n=1): *NTRK3* gene fusions (1)
- Sarcoma, IFS (n=2): *NTRK3* gene fusions (2)
- Sarcoma; inflammatory myofibroblastic tumours (n=4): other gene fusions** (4)
- Sarcoma; synovial (n=1): no fusion identified (1)

Neuroblastoma (n=15)

- other gene fusions (1); No fusion identified (14)

	ORR, % (n)
Fusion-positive tumours	76% (13/17
Primary CNS tumours	70% (7/10)
Extracranial solid tumours	86% (6/7)

	Median DoR, months
Fusion-positive tumours	NR (95% CI: 14.3-NE)

*one *NTRK2* gene fusions not evaluable at data cut-off; ** other gene fusions are: *ROS1* or *ALK*

ALK, anaplastic lymphoma kinase; CNS, central nervous system; DoR, duration of response; IFS, infantile fibrosarcoma; NE, not estimable; NR, not reached; NTRK, neurotrophic tyrosine receptor kinase; ORR, objective response rate; ROS1, ROS proto-oncogene 1

CONCLUSION

- Efficacy data, with longer follow-up, confirm the durable objective response
- Safety profile remains consistent
  - Bone fractures (n=7, 20.6%) under investigation
- Overall benefit-risk ratio looks positive

A PHASE 2 STUDY OF LAROTRECTINIB FOR CHILDREN WITH NEWLY DIAGNOSED SOLID TUMOURS AND RELAPSED ACUTE LEUKAEMIAS HARBORING TRK FUSIONS: CHILDREN'S ONCOLOGY GROUP STUDY ADVL1823

Laetsch TW, et al.

ASCO 2020, Abstract #TPS10560. Poster presentation

TRK, tropomyosin receptor kinase

BACKGROUND

Larotrectinib = highly selective **TRK inhibitor**

US FDA approval on 26 November 2018

US indication:
for the treatment of adult and pediatric patients with solid tumors that:

- have a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion without a known acquired resistance mutation,
- are metastatic or where surgical resection is likely to result in severe morbidity, and
- have no satisfactory alternative treatments or that have progressed following treatment

EU decision on 19 September 2019*

EU indication:
for the treatment of adult and paediatric patients with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (*NTRK*) gene fusion,

- who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and
- who have no satisfactory treatment options

Formulations: oral solution (20 mg/ml)
hard capsules (25 and 100 mg)

*A conditional marketing authorization was granted in EU

EU, European Union; NTRK, neurotrophic tyrosine receptor kinase; TRK, tropomyosin receptor kinase; US, United States

TRIAL DESIGN ADVL1823

ADVL1823 (NCT03834961): single group, open-label, phase 2 study

Key eligibility:
NTRK gene fusions+

Cohort A:
newly diagnosed IFS

Cohort B:
other newly diagnosed TRK fusion solid tumour

Cohort C:
Relapsed/refractory TRK fusion acute leukeamia

n=70

larotrectinib 100mg/m^2/dose BID (max 100mg/dose) in continuous 28-day cycles

up to 26 cycles in the absence of disease progression or unacceptable toxicity, or complete surgical resection of tumour

Primary endpoint:
ORR (only in cohort A)

Secondary endpoints:
OS, DoR and EFS
ORR (only for cohorts B and C)
Safety

BID, twice a day; EFS, event-free survival; DoR, duration of response; IFS; infantile fibrosarcoma; NTRK, neurotrophic tyrosine receptor kinase; ORR, objective response rate; OS, Overall survival; TRK, tropomyosin receptor kinase

SUMMARY/KEY POINTS

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ADVL1823 COULD BRING NEW EVIDENCE IN THE ROLE OF LAROTRECTINIB IN IFS AND LEUKAEMIA PAEDIATRIC PATIENTS

- The selection of patients is based on histological diagnosis of *NTRK* gene fusion in a Clinical Laboratory Improvement Act/College of American Pathologists certified laboratory
- First patient enrolment occurred in October 2019
- The study is ongoing and preliminary data will soon be available/reported

IFS, infantile fibrosarcoma; NTRK, neurotrophic tyrosine receptor kinase

TRIDENT-1: A GLOBAL, MULTICENTER, OPEN-LABEL PHASE 2 STUDY INVESTIGATING THE ACTIVITY OF REPOTRECTINIB IN ADVANCED SOLID TUMOURS HARBORING *ROS1* OR *NTRK1-3* REARRANGEMENTS

Doebele RC, et al.

ASCO 2020, Abstract #TPS9637. Poster oral presentation

ROS1, ROS proto-oncogene 1; NTRK, neurotrophic tyrosine receptor kinase

BACKGROUND

ROS1 and *NTRK* gene fusions = identified as oncogenic drivers

Crizotinib and **entrectinib** = current standard of care in *ROS1* gene fusions positive NSCLC patients

Entrectinib and **larotrectinib** = for adults and paediatric patients with *NTRK* gene fusions positive solid tumours

Resistance mechanism occurred to *ROS1*/*NTRK* targeted therapies:

Most common = **Solvent front mutations**

Repotrectinib = next generation of ROS1/TRK tyrosine kinase inhibitor

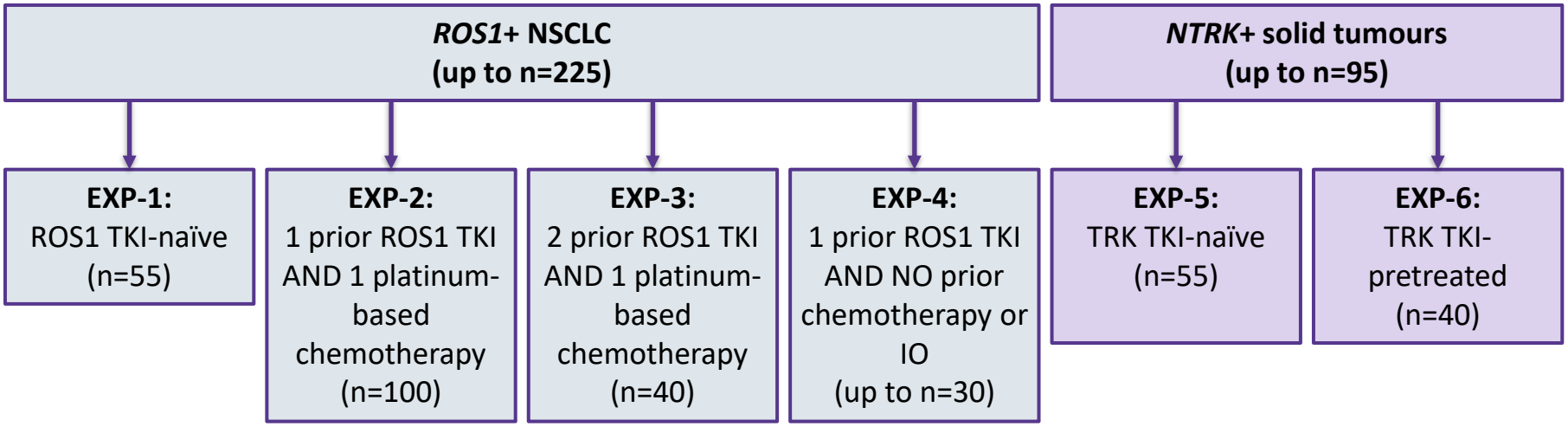
NSCLC, non-small-cell lung carcinoma; NTRK, neurotrophic tyrosine receptor kinase; ROS1, ROS proto-oncogene 1; TRK, tropomyosin receptor kinase

TRIAL DESIGN

TRIDENT-1 (NCT03093116): open-label, phase 2 study

Phase 1 part of TRIDENT-1 showed:
repotrectinib = well tolerated with promising antitumour activity

Phase 2 part of TRIDENT-1: study design is presented below



Treatment: Repotrectinib 160 mg QD for the first 14 days and dose may increase to 160 mg BID

Primary endpoint: ORR assessed by BICR RECIST v1.1

Secondary endpoints: DoR, TTR, CBR, CNS-PFS, PFS, OS, QoL

BICR, blinded independent central review; BID, twice a day; CBR, clinical benefit rate; CNS, central nervous system; DoR, duration of response; IO, immuno-oncology; NSCLC, non-small-cell lung carcinoma; NTRK, neurotrophic tyrosine receptor kinase; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QD, one a day; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumours; ROS1, ROS proto-oncogene 1; TKI, tyrosine kinase inhibitor; TRK, tropomyosin receptor kinase; TTR, time to response

SUMMARY/KEY POINTS

IF CONFIRMED, TRIDENT-1 COULD PROVIDE A NEXT-GENERATION TRK INHIBITOR TO OVERCOME RESISTANCE IN PATIENTS WITH ADVANCED SOLID TUMOURS HARBOURING *ROS1* OR *NTRK1-3* REARRANGEMENTS

- Preliminary efficacy data of repotrectinib in *ROS1*+ NSCLC patients are promising:
  - In TKI naïve (n=11) :
    - ORR = 91% (10/11)
    - DoR (% ≥18 months (range) = 65% (3.7+ - 23.3+ months)
    - Clinical benefit rate = 100 % (11/11)
  - In pretreated patients (n=29):
    - ORR, 1 prior TKI = 39% (7/18)
    - ORR, 1 prior TKI at 160 mg QD or above= 55% (6/11)
    - Clinical benefit rate, 1 prior TKI = 78% (14/18)
- Expecting data in TKI naïve and TKI pretreated patients with solid tumours who are positive for *NTRK* gene fusions

DoR, duration of response; NSCLC, Non-small-cell lung carcinoma; NTRK, neurotrophic tyrosine receptor kinase; ORR; overall response rate; QD, one a day; ROS1, ROS proto-oncogene 1; TRK, tropomyosin receptor kinase; TKI, tyrosine kinase inhibitor

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