Collaborative clinical registries in rare cancers: the ETOP-NTRK registry

Rolf A. Stahel
Rare Cancers Europe, Milan, 29.11.2019

A multicentre retrospective and prospective non-interventional study of NTRK/ROS1 fusions in Lung Cancer, Breast Cancer and Sarcoma
Conflict of Interest

Consultant or advisory role in the last two years
I have received honoraria as a consultant at advisory boards from Abbvie, AstraZeneca, Boehringer Ingelheim, MSD, Pfizer, Seattle Genetics, Roche and Takeda

Speaker honoraria in the last two years
I have received honoraria as a speaker from AstraZeneca, Boehringer Ingelheim, Lilly, MSD and Roche

DMC in the last two years
Roche and Takeda

Financial support of ETOP trials (president and scientific chair)
AstraZeneca, BMS, Boehringer Ingelheim, Genentech, MSD, Pfizer, Roche, and Ventana
Non-Interventional Study NTRK, ROS1 – an Intergroup Collaboration

ETOP - European Thoracic Oncology Platform

Coordinating group and sponsor
Countries: 24, Centers: 220

IBCSG – International Breast Cancer Study Group

Coordinating group
Countries: 41, Centers: 1006

Collaborative groups

GECP – Spanish Lung Cancer Group
GEIS – Spanish Group of Sarcoma Research
GSF– GETO – French Sarcoma Group (TBC)
SPOG - Swiss Paediatric Oncology Group (Endorsement TBC)
ESBB for German sites (TBC)
other

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Non-interventional study NTRK, ROS1 Objectives

Primary objective

1. Evaluate the natural history defined as clinical characteristics, molecular data, standard of care treatment and clinical outcome of NSCLC, TNBC / SBC and STS, CFS patients harboring NTRK or ROS1 fusions.

Secondary objectives

2. Understand the biomarker testing landscape and tests currently being used in clinical practice to identify NTRK and ROS1 gene fusions, primarily across Europe.

3. Evaluate the natural history in clinically relevant subgroups of patients (e.g. early versus late breast cancer).

NSCLC: non-small cell lung cancer; TNBC: triple negative breast cancer; SBC: secretory breast cancer; STS: sarcomas; CFS: congenital fibrosarcoma
Exploratory objectives

4. Assess changes in QoL and functioning as measured by the EORTC QLQ-C30 questionnaire.

5. Conduct additional central molecular analyses of patients with remaining biological material.
Non-Interventional Study for NTRK, ROS1 - Overview

Lung Cancer
- SCLC, non-squamous 125 Pts, locally advanced
- Stage IIIB, IIIC, IV
- Local testing NTRK, ROS1

Breast Cancer
- TNBC / SBC
- 25 Pts, early-late stage
- Central or local testing NTRK

Sarcoma
- STS / CFS
- 35 Pts, locally advanced or metastatic
- Local testing NTRK

Clinical data, NTRK or ROS1 fusion results, and tumor tissue collection
NIS may be extended to pan-cancer in the future

EC approval based on earlier general broad consent

Prospective
- With explicit patient consent for NIS (w/QoL)

Retrospective
- EC approval based on earlier general broad consent

Study Start
- 0
- 1 yr
- 2 yr
- 3 yr

-3 yr
-2 yr
-1 yr

55 Patients
- 15 NTRK
- 40 ROS1

70 Patients
- 20 NTRK
- 50 ROS1

15 Patients
- 15 NTRK
- 0 ROS1

10 Patients
- 10 NTRK
- 0 ROS1

15 Patients
- 15 NTRK
- 0 ROS1

20 Patients
- 20 NTRK
- 0 ROS1

Rare Cancers Europe | Milan | November 29th, 2019

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Rationale for focus on NSCLC, breast, sarcoma based on NTRK NIS in a collaborative groups network

54% of solid tumours in adults

Entrectinib integrated efficacy analysis
Adult patients with NTRK fusion-positive solid tumours (n=54)

Larotrectinib integrated efficacy analysis
Adult patients with NTRK fusion-positive solid tumours (n=55)
NTRK-gene fusions are found in a wide range of adult and pediatric tumors.

Cancer types include:
- Lung cancer
- Breast cancer
- Secreatory breast carcinoma
- Gastrointestinal stromal tumour (pan-negative)
- Cholangiocarcinoma
- Melanoma
- Spitzoid tumours

Adult cancers:
- High-grade glioma
- Head and neck cancer
- Thyroid cancer
- MASC

Paediatric cancers:
- High-grade glioma
- Papillary thyroid cancer
- Secretory breast carcinoma
- Infantile fibrosarcoma
- Cellular and mixed congenital mesoblastic nephroma

Cocco et al, Nat Rev Clin Onc 2018

MASC mammary analogue secretory carcinoma
NTRK fusions are frequent in some rare cancers, and rare in some frequent cancers

- **≤5%**
  - Lung Adenocarcinoma
  - Breast-invasive carcinoma

- **5-25%**
  - Paediatric and young adult Soft Tissue Sarcoma

- **>75%**
  - Secretory breast carcinoma
    - <0.15% of all BC
  - Infantile fibrosarcoma
    - 2% of all paediatric solid malignant cancers

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3. Morosini D et al, 2015, ASCO.
Precision oncology for patients with non-small cell lung cancer

Histological subtyping of NSCLC: SqCC versus AdC
- NSCLC
- Vor 2004
- 2004-2008
- SQCC 34%
- AdC 55%
- Others 11%

Molecular subtyping of AdC
- KRAS mutation 25%
- EGFR mutation 10%
- ALK fusion 4%
- ROS1 fusion 1.9%
- RET fusion 0.9%
- NTRK1 fusion 1%
- HER2 mutation 3%
- BRAF mutation 3%
- PIK3CA mutation 2%
- HRAS mutation 1%
- NRAS mutation 1%
- AKT mutation 1.1%
- MET exon 14 mutation 3%
- MAP3K1 mutation 1%
- Unknown 42%

Molecular subtyping of SqCC
- FGFR1 amplification 22%
- DDR2 mutation 4%
- PIK3CA amplification 33%
- MET amplification 5%
- MET mutation 1%
- BRAF mutation 2%
- Others or unknown 33%

Bubendorf, Europ Resp Review 2017
Precision oncology for patients with non-small cell lung cancer

Molecular subgroups of lung adenocarcinoma and targeted agents

- **KRAS** mutation 25%
- **EGFR** mutation 10%
- **ALK** fusion 4%
- **ROS1** fusion 1.9%
- **RET** fusion 0.9%
- **NTRK1** fusion 1%
- **HER2** mutation 3%
- **BRAF** mutation 3%
- **PI3KCA** mutation 2%
- **HRAS** mutation 1%
- **NRAS** mutation 1%
- **AKT** mutation 1.1%
- **MET exon 14** mutation 3%
- **MAP3K1** mutation 1%
- Unknown 42%

**Targeted agents**

- **AMG510, MRTX849**
- Gefitinib, Erlotinib, Afatinib, Osimertinib, JNJ-372
- Crizotinib, Ceritinib, Alectinib, Brigatinib, Lorlatinib
- Crizotinib Selparcatinib, Pralsetinib
- Entrectinib, Larotrectinib, Repotrectinib
- TDM-1, Trastuzumab deruxtecan
- Vemurafenib/Trametinib

Bubendorf, Europ Resp Review 2017
Larotrectinib in NTRK-Fusion Positive Cancers

<table>
<thead>
<tr>
<th>Tumor type — no. (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Salivary-gland tumor</td>
<td>12 (22)</td>
</tr>
<tr>
<td>Other soft-tissue sarcoma</td>
<td>11 (20)</td>
</tr>
<tr>
<td>Infantile fibrosarcoma</td>
<td>7 (13)</td>
</tr>
<tr>
<td>Thyroid tumor</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Colon tumor</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Lung tumor</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>4 (7)</td>
</tr>
<tr>
<td>GIST</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Appendix tumor</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Breast tumor</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Pancreatic tumor</td>
<td>1 (2)</td>
</tr>
<tr>
<td>CNS metastases — no. (%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>54 (98)</td>
</tr>
<tr>
<td>Yes</td>
<td>1 (2)</td>
</tr>
<tr>
<td>TRK gene — no. (%)</td>
<td></td>
</tr>
<tr>
<td>NTRK1</td>
<td>25 (45)</td>
</tr>
<tr>
<td>NTRK2</td>
<td>1 (2)</td>
</tr>
<tr>
<td>NTRK3</td>
<td>29 (53)</td>
</tr>
</tbody>
</table>
Entrectinib in NTRK- and ROS1-Fusion Positive Cancers

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>NTRK+ solid tumors (N=54)</th>
<th>ROS1+ NSCLC (N=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>Median (range)</td>
<td></td>
</tr>
<tr>
<td>ECOG PS, %</td>
<td>0</td>
<td>43 (21–63)</td>
</tr>
<tr>
<td>1</td>
<td>46</td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Prior lines of systemic therapy, %</td>
<td>0</td>
<td>37 (21–63)</td>
</tr>
<tr>
<td>1</td>
<td>20</td>
<td>43</td>
</tr>
<tr>
<td>Prior treatment, %</td>
<td>Chemotherapy</td>
<td>85</td>
</tr>
<tr>
<td>Targeted therapy</td>
<td>24</td>
<td>17</td>
</tr>
<tr>
<td>Hormonal therapy</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>CNS metastases at baseline, %</td>
<td>Yes</td>
<td>22 (21–63)</td>
</tr>
<tr>
<td>Tumor category, %</td>
<td>Sarcoma</td>
<td>24</td>
</tr>
<tr>
<td>NSCLC</td>
<td>18</td>
<td>100</td>
</tr>
<tr>
<td>MASC (salivary)</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Pancreatic</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Gynecologic</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

*Includes previous treatment with tyrosine kinase inhibitors; does not include targeted treatment with TRK or ROS1 inhibitors. *CNS disease at baseline determined by investigator.
ECOG PS, Eastern Cooperative Oncology Group performance status; MASC, mammary analogue secretory carcinoma.

Figure 1. Waterfall plot of change in tumor size (NTRK+ solid tumor)

Figure 2. Waterfall plot of change in tumor size (ROS1+ NSCLC)

*Best change at any single timepoint. SLD, sum of longest diameter.
Study Design – Prospective / Retrospective Cohort

<table>
<thead>
<tr>
<th>Retrospective cohort</th>
<th>Prospective cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Retrospective registration of patients</td>
<td>• Patients currently seen in routine hospital visits</td>
</tr>
<tr>
<td>• General broad consent, for secondary use</td>
<td>• Informed consent to NIS</td>
</tr>
<tr>
<td>• Complete data set available at registration</td>
<td>• FU data will be collected every 6 months at usual care visit, from registration until death, loss to FU, any other censoring event, or 18 months from the time of registration, whichever is the longer period.</td>
</tr>
<tr>
<td>• Patient Survival Status Information</td>
<td>• Quality of Life questionnaire 4x (not mandatory)</td>
</tr>
</tbody>
</table>
ESMO recommendations on NTRK testing

Sample to be investigated for the presence of NTRK rearrangements

As a confirmatory technique, use FISH, RT-PCR or targeted RNA NGS assays with specific probes for the rearrangement involving the known NTRK gene.

Is the histologic tumor type known to harbor highly recurrent NTRK rearrangements?

Is there a sequencing platform available?

NO

Use IHC as a screening tool

IHC to confirm protein expression in positive cases

NO TRK expression

Detection of TRK expression

Use front line NGS reliably detecting NTRK fusions, preferably including RNA testing when possible

YES

Core Inclusion Criteria

- NTRK or ROS1 (NSCLC only) fusion
- Histological diagnosis of either;
  - NSCLC, non-squamous, locally advanced stage, IIIB, IIIC, IV
  - TNBC, secretory, early to late stage
  - STS, including CFS, locally advanced or metastatic

- Prospective cohort: Written Informed Consent for NIS
- Retrospective cohort: General broad consent for secondary use.

- Availability of clinical and demographic data, information on treatment and clinical outcome
- Male or female patients, all ages
Study Design – NTRK, ROS1 Testing Requirements

**Procedure a.**
NCSLC, TNBC/SBC, STS/CFS if local NGS test for NTRK/ROS1 available

- **Local NGS Testing**
  - Registration
  - ETOP data / medical review
  - Tumour Tissue Submission optional
  - Accepted

**Procedure b.**
NCSLC, TNBC/SBC, STS/CFS other local tests for NTRK/ROS1 available

- **Local 2-step Method**
  - NTRK: RT-PCR/ FISH/ NanoString/Other
  - ROS1: FISH

- Registration
- ETOP data / medical review
- Tumour Tissue Submission required
- Accepted
- Central confirmation by NGS

**Procedure c.**
TNBC/SBC no local tests for NTRK available

- **Central Testing by IHC**
  - Registration
  - ETOP data / medical review
  - Tumour Tissue Submission required
  - Accepted
  - Central NTRK confirmation by NGS
Study Design – Retrospective Cohort

Positive NTRK (ROS1) testing results

A. Local NGS

B. Local 2-step method + tissue submission

C. Central testing (TNBC/SCB)

Case registration in NIS

1yr

2yr

3yr

Confirmation of prior broad consent

Local data entry + (tissue submission)

Patient Survival Status Information

Central NGS for confirmation

Central data management/ medical review

Patient Survival Status Information

Information
Study Design – Prospective Cohort

Positive NTRK (ROS1) testing results

A. Local NGS

B. Local 2-step method + tissue submission

C. Central testing (TNBC/SCB)

Case registration in NIS

1yr 2yr 3yr

QoL QoL QoL

Explicit Patient Consent

Local data entry + (tissue submission)

Central NGS for confirmation
Central data management/ medical review

FU data entry

FU data entry

FU data entry

FU data entry

FU data entry

FU data entry
## Mandatory Data Collection

**Patient data**
- Year of birth
- Gender
- Ethnicity
- Family history of cancer
- Smoking history
- HRT therapy (breast)
- History of previous malignancy

**Disease data**
- Diagnosis date
- Histology
- Type of sample
- Primary tumour/metastatic site
- Localisation of primary tumour
- Disease stage at diagnosis (TNM)
- Presence of CNS disease (Y/N)
- Diagnosis date of CNS disease
- Localisation of recurrence/progression

**Molecular pathology data**
- Testing method
- Date of testing
- Genotyping (NGS/other)
- IHC done/not done & date
- Molecular confirmation (date, type)
- NTRK diagnostic codes available
- NTRK subtype gene fusion (1/2/3)

**Treatment data**
- Current/prior treatment
  - type & line of treatment
  - start/stop date
- Surgical procedures
- Radiotherapy
- Other medications

**Additional data**
- Follow-up data (date of last FU, patient status, clinical outcome)
- Death (date, cause)
A descriptive statistical analysis will be performed, in patient cohorts with NTRK/ROS1 fusion positive cancers.

- Summary of patient & tumor baseline characteristics
- Treatment patterns
- Exploration of molecular/biomarker alterations in NTRK or ROS1 fusion-positive cohorts
- Time-to-event endpoints/clinical outcome
- QoL assessment
- Subgroup analysis
Timelines and Status Study Development

- Recruiting Phase 3 yrs
- 18 months Follow-up

<table>
<thead>
<tr>
<th>Year</th>
<th>Patients Registered</th>
</tr>
</thead>
<tbody>
<tr>
<td>2019</td>
<td>Protocol Release Dec 2019</td>
</tr>
<tr>
<td>2020</td>
<td>35 STS / CFS NTRK</td>
</tr>
<tr>
<td>2021</td>
<td>125 NSCLC (35 NTRK / 90 ROS1)</td>
</tr>
<tr>
<td>2022</td>
<td>25 TNBC/ SBC NTRK</td>
</tr>
<tr>
<td>2023</td>
<td></td>
</tr>
<tr>
<td>2024</td>
<td></td>
</tr>
</tbody>
</table>

Descriptive Statistical Analysis
Center Selection

Planned are 50 sites in 10 countries

France, Germany, Italy, Spain, United Kingdom, Switzerland, Belgium, Ireland, Netherlands, Poland

Centres are asked to contribute to *all* cohorts:

- Lung
- Breast and Paediatric
- Sarcoma and Paediatric
Non-Interventional Study NTRK, ROS1 – an Intergroup Collaboration

• Unique opportunity to collaborate between established cancer research networks to achieve this NIS for the rare cancer subtypes.

• Resulting in one of the largest NIS assessing the natural history of the disease in NTRK/ROS1 rearranged patients.

• This inter-group collaboration builds on past achievements.
Study Organization

Chair
Dr. Rosario García Campelo

Co-Chair Breast Track
Dr. Manuela Rabaglio

Co-Chair Lung Track
Dr. Nuria Nely Mederos-Alfonso

Co-Chair Sarcoma Track
Dr. Christian Britschgi

Molecular Pathologist Co-Chair
Prof. Giuseppe Viale, Central Testing Lab IHC, NGS

Molecular Pathologist Co-Chair
Prof. Stephen Finn, Central Confirmation NGS

Pharma Partner
Roche

ETOP Coordinating Office, Bern:
Study Coordination, Regulatory, Data Management, Medical Review, Monitoring

ETOP Statistical Office, Athens:
Statistical Analysis
ETOP 16-19 NIS – Patient Fee

- Patient fee upon registration: 2000 €
- Quality of Life completed questionnaires: 400 €
- FFPE Tumor Tissue upon submission: 250 €
Contact Information

For more information or interest in participation please email ETOP:

NIS_NTRK_ROS1@etop-eu.org
Thank you for listening!
Study Duration – Maturity of Data

- The study duration allows maturity of OS data for NSCLC late stage, and STS metastatic or advanced.

- The larger retrospective TNBC cohort will ensure that a certain number of cases have an extended follow up.

- Secretory BC has a very high prevalence for NTRK fusion of 95%, and have a good outcome. Therefore some early stage are expected without OS data.

- This is not an event-driven study. The sample size is not chosen so that a test has adequate power to detect a difference, i.e. specific number of events is not a prerequisite.
Limitations of the Study

• Limited number of tumor types (generalization question)
• Potential bias from sites selection (performing NGS)
• Likely heterogeneity in SoC
• Combining retrospective and prospective part
Study Design – NTRK /ROS1 Testing

NSCLC:

A: Local routine testing by NGS for ROS1 and NTRK followed by central confirmation if tissue is available

B: Local 2-Step Method requires submission of tissue
   1) Local testing (NTRK: RT-PCR/ FISH/ NanoString/Other or ROS: FISH)
   2) Followed by central NGS confirmation at the ETOP Central Laboratory, CPL St James Hospital, Dublin, Ireland
Study Design – NTRK Testing

TNBC / SBC:

A: Local routine testing by NGS for ROS1 and NTRK followed by central confirmation if tissue is available

B: Local 2-Step Method requires submission of tissue
   1) Local testing by NTRK: RT-PCR/ FISH/ NanoString/Other
   2) Followed by central NGS confirmation

C: Central testing by, followed by central confirmation by NGS at IBCSG Central Pathology Office and Laboratory, IEO, Milan
Study Design – NTRK Testing

STS / CFS:

A: Local routine testing by NGS for ROS1 and NTRK followed by central confirmation if tissue is available

B: Local 2-Step Method requires submission of tissue
   1) Local testing (NTRK: RT-PCR/ FISH/ NanoString/Other or ROS: FISH)
   2) Followed by central NGS confirmation at the ETOP Central Laboratory, CPL St James Hospital, Dublin, Ireland