ALpha-T: a Pre-Pandemic Decentralized Trial in Oncology

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On behalf of the ALpha-T study team

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OUTLINE

1. ALpha-T study design
   ○ Rare disease, precision enrollment and home-based assessments
2. Extensive Collaborations: Patients’ Identification and Enrollment
3. ALpha-T Operational Workflow in the US vs EU
4. Patients’ safety
5. Data collection and data quality
6. Regulatory landscape
7. Advantages of a decentralised clinical trial
ALpha-T (Alectinib to Patients at Home in Agnostic Tumors)

**Ph2 open-label, single-arm trial with decentralized home-based approach**

**Primary endpoint**

Confirmed ORR in ALK fusion-positive patients
determined by the investigator using RECIST v1.1

**Key secondary and exploratory endpoints**

- ORR by IRF
- PFS
- DoR
- CNS –ORR –DoR –PFS
- OS
- Safety

**Statistical considerations**

- Target ORR 46%
- With N=50, lower 95%CI is 32% (clopper-pearson) which is considered clinically meaningful in this population

**Locally-advanced or metastatic ALK fusion or mutation† solid tumours**

- No available treat. options
- ECOG PS 0–2

**Alectinib 600mg orally BID**

**Home-based assessments every 4 weeks**

**Radiological progression (RECIST v1.1), death or withdrawal of consent**

**Further treatments and survival follow-up**

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**Tumour assessments every 8 weeks at local facilities**

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Kurzrock, et al. Presented at ASCO 2021 (Abs TPS3155)

*Excluding lung cancer; †ALK-positive tumor as per tissue or blood-based FMI NGS; NGS = Next Generation Sequencing; ORR = Objective Response Rate; IRF = Independent Review Facility; PFS = Progression-Free Survival; DoR = Duration of Response; CNS = Central Nervous System; OS = Overall Survival; CI = Confidence Interval
Rare disease, precision enrollment and home-based assessments

- Non-NSCLC tumours with ALK-fusions -> \textbf{0.2\% prevalence} (Ross et al, The Oncologist. 2017)

- With traditional recruitment approaches, estimated to require \textit{screening of more than 25,000 patients} in order to enroll \textbf{50 potentially eligible patients}

- Drug development for patients with rare cancers pose \textit{recruitment challenges} due to \textit{low prevalence}
  - \textbf{very difficult to open clinical trial sites in advance} (no prediction of where potentially eligible patients may be located)
  - \textbf{inappropriate to activate site once an eligible patient is identified} (significant delays to the start of treatment)

- Centralised Foundation Medicine inc. (FMI)’s \textit{precision enrollment approach}
  - FMI analyzes thousands of samples from patients, potentially eligible for our trial based on biomarker
  - FMI can reach out to physicians who asked for the test, who can then \textit{inform the patient}

- Without traditional sites, patients’ consent and visits will be home-based, ALPHA-T is a decentralized trial that brings the “\textit{Trial to the Patient}”
Collaboration: Patients’ enrollment into the study

1. Following testing of sample, FMI informs ordering physician of the study and establishes connection to Science 37
2. “Three-party” TC between FMI, Science 37 (including Study Investigator) and the Local Oncologist
3. Ordering Physician informs the patient of the possibility to participate in the study and obtains agreement to move forward
4. Science 37 contacts patient and ordering physician to initiate enrolment procedures and the Ordering physician releases the patient’s medical records to Science 37
5. If the patient is considered potentially eligible, the Study Investigator (S37) obtains the Informed Consent Form (ICF) from the patient to start screening procedures
ALpha-T Operational Workflow in the US

In the EU:
- One physical hospital site per country versus one virtual site in the US
- Remote investigator and research coordinator must be working at the hospital versus for virtual site in the US
- May be central or local lab
- IMP depot is at the hospital pharmacy versus central pharmacy in the US
Patients’ safety in ALpha-T

Mostly similar oversight to traditional clinical trial

- Safety of Alecensa is **well-established**
- Oral drug, administered at home, **IMP accountability** performed by a mobile nurse
- **Eligibility criteria** have been designed to exclude patients at higher risk for toxicities
- **Safety monitoring** of the patients during study via an Internal Monitoring Committee (IMC)
- The investigator and mobile nurse or clinical research coordinator are responsible for ensuring that all **adverse events** are recorded and reported to the Sponsor

- Investigator does not see the patient in person (telemedicine). Mobile nurse is at home with the patient. Local physician provides continuity of care
- Protocol provides guidelines for managing adverse events, dosage modification and treatment interruption or discontinuation
  - e.g. eliciting adverse event information and causal attribution guidance

**IMP** = investigational medicinal product
Data collection in ALpha-T

Data integration
to de-risk the data integrity elements of the study
(GCP compliant)

- eCRF data is collected in Science 37 Platform (NORA) which mimics RAVE eCRF’s
- **Real time** eCRF data integration from Science 37 Platform to RAVE
- **Process in RAVE is as per usual clinical trial for:**
  - Data Management and Science data review and query
  - Coding
  - Serious Adverse Events (SAE) reporting and reconciliation

Note: In the EU, data will be entered directly into the clinical database

GCP = Good Clinical Practice; Nora = Network Oriented Research Assistant
Data quality in a DCT

➢ Good first DCT in oncology to learn from
  ○ rare disease, unmet need, randomised (RCT)/ real world (RWE) not feasible
  ○ single arm study, simplified with respect to randomization, blinding
  ○ small sample size with 50 patients

➢ Potential impact on the variability of the data?
  ○ Local vs central labs assessments:
    ■ Already accepted in trials if patients are unable to go to central lab
  ○ Imaging assessments: possibility for a local and/or central facility for a given patient
    ■ Need to ensure the local radiology facility is performing scans to the quality required and follows target lesions consistently with the central site assessments (training, list of trial-related tasks)
  ○ Use of telemedicine instead of clinic visits:
    ■ Nurse at home with the patient and investigator always online (qualified, clinical trials standards)

➢ Potential impact on the integrity of the data?
  ○ (?) more diverse trial population
  ○ (?) increased patient retention into the study
  ○ (?) missing visits, out of window (flexibility of phone call vs clinic visit)
  ○ (?) dose modification / AE-SAE rates
  ○ (?) NORA as both source and CRF in the US
## Regulatory landscape

*Health Authority interactions: key milestones for ALpha-T*

<table>
<thead>
<tr>
<th>2020</th>
<th>2021</th>
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<tbody>
<tr>
<td>Sep</td>
<td>Oct</td>
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<tr>
<td>ALPHA-T IND clearance (1st Sept)</td>
<td>EMA ITF Meeting (15 Oct.)</td>
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<tr>
<td>FDA OCE Meeting (26 Oct.)</td>
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**IND** = Investigational New Drug; **ITF** = Innovation Task Force; **OCE** = Oncology Center of Excellence; **DIA** = Drug Information Association; **DCT** = Decentralised Trial
Thinking is still evolving
(EMA ITF and FDA OCE)

- Application of decentralized trials must be considered on a case-by-case basis (decentralized approach for a molecule with a well-established safety profile would be more likely to be acceptable).

- No systematic approach can be employed yet and level of decentralisation may vary across country due to legal or healthcare operating model constraints.

- However both EU and US Health Authorities demonstrated a high interest and willingness to remove or minimise obstacles and to find ways to be more flexible!

Key topic discussed: Principal Investigator (PI)/Local oncologist relationship, telemedicine/mobile nurse, digital tool (e.g. eICF), Data Source, Monitoring, local imaging center

- Remote vs local activities: ensuring that roles and responsibilities are clear as well as ensuring a two way data exchange between the different stakeholders is paramount
- Adequate data audit trail is needed as multiple data source will be employed + Patient data protection needs to be ensured
- Activities performed remotely should stay as close as possible to standard practice
- Ensure good drug distribution practice are in place (i.e. right medication to the right patient, enough drug shipped in the event of delay in visit, check damage and label)
### Regulatory landscape

#### Health Authority interactions: summary

Overview of HA acceptance on key topics

<table>
<thead>
<tr>
<th>Country</th>
<th>Telemedicine / Mobile nurse</th>
<th>Informed Consent Form (ICF) e-signature</th>
<th>Drug shipment at home</th>
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</thead>
<tbody>
<tr>
<td>Spain</td>
<td>✅</td>
<td>✅ during pandemic</td>
<td>✅</td>
</tr>
<tr>
<td>Sweden</td>
<td>❌ (Medical doctor needed)</td>
<td>✅</td>
<td>✅ but via Pharmacist or Principal Investigator</td>
</tr>
<tr>
<td>Denmark</td>
<td>❌ (Medical doctor needed)</td>
<td>✅ if accepted by the ethics committee</td>
<td>✅</td>
</tr>
<tr>
<td>UK</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Switzerland</td>
<td>✅</td>
<td>❌ (alternative remote paper sig.)</td>
<td>Depend on the canton</td>
</tr>
<tr>
<td>FDA</td>
<td>✅</td>
<td>✅</td>
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Advantages of a decentralised clinical trial

- Performed at or close to the patient’s home and fits around their day to day life
- Allows access to the patient, irrespective of where they live
- Allows continued connection to the medical team that the patient is already familiar with
- More diverse & representative patient population
Doing now what patients need next