Biomarker-driven access to crizotinib in ALK, MET or ROS1 positive malignancies in adults and children: feasibility of the French National AcSé Program

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#535647 2014 ASCO conference, Chicago

AcSé Program: secured access program to innovative cancer drugs

Background
- When a marketed targeted therapy exists in a molecularly defined subgroup of patients
- When the same alteration is found in other tumour types

Objective 1
Promote a secured access for all patients with an advanced refractory malignancy and no therapeutical alternative through an academic phase II clinical trial.
- One trial for each targeted treatment selected
- Withdrawal if high toxicity or no efficacy in a predefined number of patients with the same tumor type
- If efficacy coding signal: drug development by the pharmaceutical firm

Objective 2
Ensuring equity of access to innovation
- Provide nationwide molecular tumor diagnosis for all patients through INCa molecular genetic centers
- Whatever the healthcare institution status (public hospitals, private hospitals…)
- Perform high quality tests
- Hemopathies, solid tumours

France organisation of molecular centres for personalized medicine: 28 regional centres
Partnerships between several laboratories located in University Hospitals and Cancer Centres
- Regional organization
- Cooperation between pathologists and biologists

AcSé program

Principles

Drug X* Project

Molecular diagnosis of drug X targets

INCa molecular genetic centers

Molecular testing task force

IDMC

AcSé Crizotinib project

AcSé drug project

Validated projects

Crizotinib Project

Drug Y Project

Approved by pharmaceutical firms

Risk of a wide off label use of the drug

Phase 2 clinical trial: secured access to crizotinib for patients with tumors harboring a genomic alteration on one of the biological targets of the drug

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Background
- Crizotinib is registered only for the treatment of patients with ALK+ lung cancer
- Crizotinib targets, ALK, MET and ROS1, are also altered in a wide range of malignancies in adult and children
- Pediatric dose (Mosse et al, Lancet Oncol 2013) and oral formulation available

Main objective: identification of subsets of patients that may benefit from treatment

Population
- Patients ≥ 1 year
- Advanced disease harboring a genomic alteration in a crizotinib target

Molecular diagnosis process

Pathologies diagnosed by INCa molecular genetic centers


Molecular genetic profiles

- Molecular and pathological profiles
- Genetic and clinical expertise

Cohorts

A/ Pathology cohorts « one pathology, one target alteration » diagnosed by INCa molecular genetic centers
1. ALC, children and adults, ALK-translocated
2. Colorectal cancer, adults, ALK-translocated
3. Colorectal cancer, adults, MET amplified
4. Colorectal cancer, adults, MET mutated
5. NSCLC, adults, MET amplified
6. NSCLC, adults, ROS1-translocated
7. Breast cancer, adults, ALK-translocated
8. Gastric cancer, adults, MET amplified
9. Cholangiocarcinoma, adults, ROS1-translocated
10. Ovarian cancer, adults, MET amplified
11. Clear cell renal cell carcinoma, adults, ALK-translocated
12. Clear cell renal cell carcinoma, adults, ALK-amplified
13. Papillary renal cell carcinoma, adults, MET mutated (+ MET amplified)
14. Hepatocellular carcinoma, adults, MET amplified
15. Neuroblastoma, children and adults, ALK amplified
16. INT, children and adults, ALK-translocated
17. Rhabdomyosarcoma (alveolar and embryonal), children and adults, ALK-translocated
18. Glioblastoma, adults, MET amplified

B/ Rare pediatric malignancies cohort
- Diagnosed by INCa molecular genetic centers: hepatoblastoma MET amplified or mutated, renal medullary carcinoma ALK-translocated, anaplastic medullary thyroid carcinoma MET amplified or mutated, HGG or DIPG MET amplified
- Any other pathology with an altered crizotinib target evidenced through genomic profiling

C/ Miscellaneous adult malignancies
- Any other pathology with an altered crizotinib target evidenced through genomic profiling

AcSé crizotinib

Treatment scheme
- Cycles are defined in 28-day periods
- Disease response assessed every 8 weeks
- Safety assessed continuously
- Treatment pursued until disease progression, unacceptable toxicity, intercurrent conditions that preclude continuation of treatment, or patient refusal
- Adult: 250 mg x 2; child: 280 mg/m² x 2

Statistical design
- Main endpoint: objective response (CR, PR) after 2 cycles. May be changed to the best response for cohorts that are displaying delayed responses
- Three statistical 2-stage designs are considered for cohorts to anticipate 3 situations in terms of expected response rate and incidence. Accrual stops if 0 response / N1 pts; else additional pts are recruited up to N
  - General case: most of the cohorts
  - Optimistic design: NSCLC with ROS1 translocation and ALCL
  - Rare diseases: IMT, neuroblastoma, glioblastoma, RMS, cohorts identified from the pangenomic programs

Screening period

W = week
D = day
Cycle 1
Cycle 2

W1 W2 W3 W4 W5 W1 W2 W3 W4
N = neut D0 W1 W2 W3 W4 W5 D0 D1

Statistical analysis

- Sample size estimation: 500 pts
- Investigating centers: up to 250

Inclusions per cohorts

- 49 Patients included

Cohorts

Study support

- Study receives:
  - Financial support from INCa
  - Financial support from the ARC Foundation, the UNICANCER’s partner for Personalized Medicine research

Collaborative groups

- French Pediatric Society (SFCE)
- French Genito-Urinary Cancer Cooperative Groups (GETUG / GERCOR)
- French Cooperative Gynecological Cancer Research Group (ARCAGY - Franchophone Neuro-Oncologist Association (ANOCEF)
- French Hemato-Oncology Cancer Cooperative Groups (FFHOC)
- French Thyroid Cancer Network (TUTHYREF)
- French Digestive Cancers Groups (UCGI / FFCD) / GERCOR)
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