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The activity of crizotinib in chemo-refractory MET-amplified esogastric adenocarcinomas: Results from the AcSé-crizotinib program.

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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 tumor types

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Risk of a wide off label use of the drug

Objectives

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
- Efficacy signal force to inform pharmaceutical firms for drug development decision making

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 tumors

France organization of the 28 molecular centers for personalized medicine

Partnerships between laboratories located in University Hospitals and Cancer Centers

- Regional organization
- Cooperation between pathologists and biologists AcSé program

AcSé program

AcSé crizotinib

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 – PI : Gilles VASSAL / NCT02034981

Background

- Crizotinib is registered for treating ALK and ROS1-translocated lung cancer.
- Crizotinib is also a MET inhibitor.
- Crizotinib activity in MET-amplified (+) tumors was explored within the French National Cancer Institute (INCa) AcSé program.
- This included access to tumor molecular diagnoses and an exploratory multi-tumor 2-stage design phase II trial.

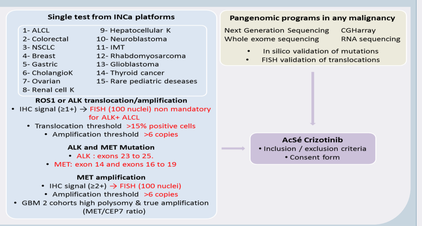
Main objective

Identification of subsets of patients that may benefit from treatment

Population

- Patients ≥1 year
- Advanced disease harboring a genomic alteration in a crizotinib target
- Patients not eligible for any other active academic or industry trial targeting the same alteration

Molecular diagnosis process



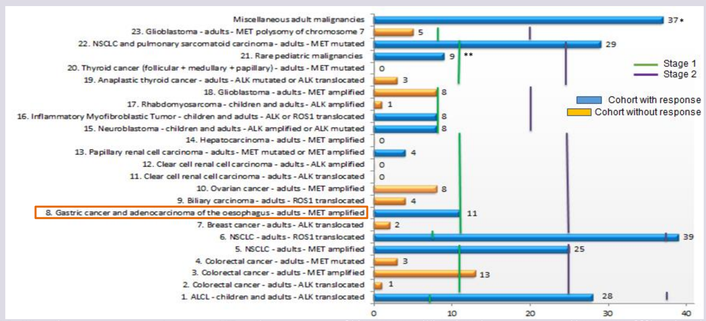
Biomarker testing

Whole screening activity (at March, 2018)	Number of positive cases	Patients included
19 764 tests (=13 179 screened patients)	611	246 (from 08/2013 to 03/2018)

Treatment plan

- Treatment pursued until progression, unacceptable toxicity, undercurrent conditions, physician decision or patient refusal
- Safety assessed continuously
- Disease response assessed every 8 weeks with CT and/or PET-CT. All imaging and response evaluation were centrally reviewed and response was evaluated according to Lugano criteria taking into account metabolic response when available or to RECIST 1.1 criteria in patients with only CT-based evaluation

Inclusions per cohorts



** 3 NSCLC – ALK amplified*
1 NSCLC – ALK mutated
1 SCLC – MET mutated + ROS1 mutated
1 urachal adenocarcinoma – MET amplified
4 cholangiocarcinoma – MET amplified
2 cholangiocarcinoma – ALK translocated
1 cholangiocarcinoma – ALK mutated
1 cholangiocarcinoma – MET mutated

*** 1 mesothelioma – ALK translocated*
1 atypical meningioma – ROS1 translocated
1 sarcoma – MET translocated

1 gallbladder – MET amplified
1 pancreas cancer – ROS1 mutated
1 pancreas cancer – ALK mutated
1 kidney cancer – ROS1 amplified
1 kidney cancer – ALK translocated
1 bladder cancer – MET translocated
1 prostate cancer – ALK translocated
1 colorectal cancer – ALK mutated

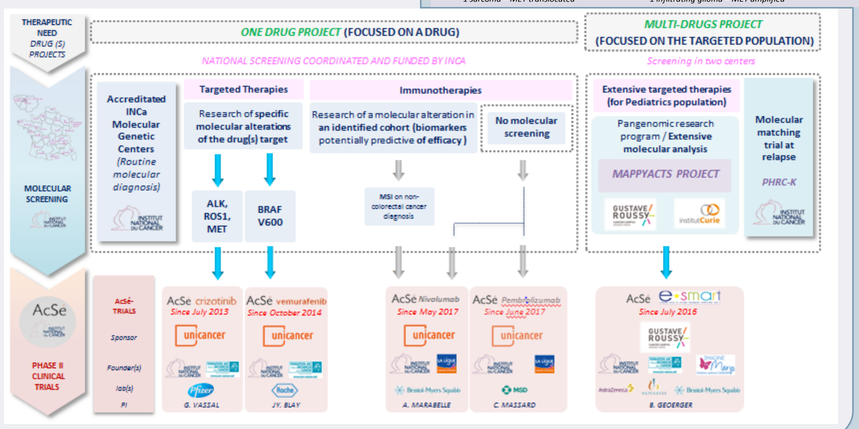
1 glioma – MET translocated
1 glioma – MET amplified
1 infiltrating glioma – MET amplified

2 leiomyosarcoma – ALK translocated
1 small intestine sarcomatoid cancer – ALK translocated
1 larynx carcinoma– MET amplified
1 neuroblastoma – ROS1 mutated
1 B large cell lymphoma – ALK translocated
1 papillary thyroid carcinoma – ALK translocated
1 ethmoid adenocarcinoma – MET amplified

1 liposarcoma – ETV6 NTRK alteration
1 medullary glioma – MET amplified and MET translocated

1 breast cancer – ROS1 translocated
1 ovarian cancer – MET mutated
1 ovarian cancer – ALK mutated
1 melanoma – ALK translocated
1 melanoma – ROS1 translocated
1 face epidermoid carcinoma – MET amplified
1 unknown primary carcinoma – ALK translocated.

1 anaplastic pleomorphic xanthoastrocytoma – MET amplified



Statistical design

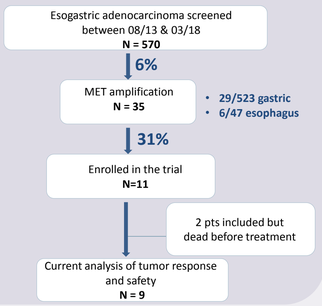
- Main endpoint: objective response (CR, PR) after 2 cycles. May be changed to the best response for cohorts that are displaying delayed responses
- 3 statistical 2-stage designs are considered for cohorts to anticipate 3 situations in terms of expected response rate and incidence. Accrual stops if 0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

Situation	Design parameters Decision rule							
	P0	P1	Alpha	Beta	N1	k1	N	k
General case	10%	30%	10%	10%	11	0	25	4
Optimistic case	20%	40%	10%	10%	7	0	37	7
Very rare disease	10%	30%	15%	15%	8	0	20	3

- Sample size estimation: 500 pts
- Centers : declared 198 - open 186 - recruiting 85

Results in patients with esogastric MET+ adenocarcinomas

Consort diagram esogastric adenocarcinoma



Patients characteristics

Disease characteristics	Frequency (%) N=9
Primary	
Gastric	6 (67%)
Esophagus	3 (33%)
Gender	
Male	8 (89%)
Age (Years)	
Median (range)	60 (45; 80)
WHO PS	
0	2 (22%)
1	5 (56%)
2	2 (22%)
Prior chemotherapy	
2 lines	3 (33%)
3 lines	3 (33%)
4 lines and more	3 (33%)

Patients under treatment

At the cut-off date (March 2018) :
- **2** still on treatment
- **7** stopped their treatment

Median treatment duration : 3,3 months
- < 1,6 months: 25% pts;
- > 6,6 months: 25% pts.

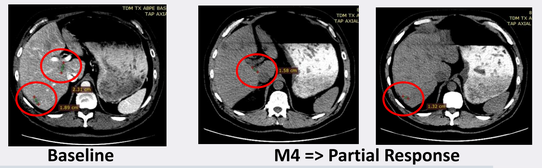
Reasons for treatment discontinuation	Frequency N = 7
Progression	5
Toxicity	2

Evaluation of response

according to RECIST 1.1 criteria (N=9)	CR	PR	SD	PD
Response at 8 weeks	0	3	3	3*
Best response during the whole treatment duration	0	5	1	3*

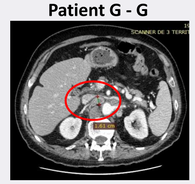
* 1 early clinical progression before the first RECIST evaluation at 2 cycles

Patient R - P

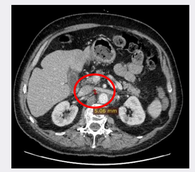


Baseline M4 => Partial Response

Patient G - G

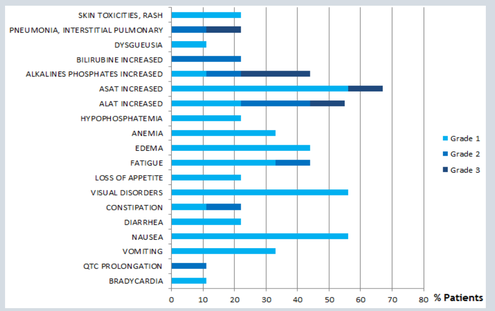


Baseline



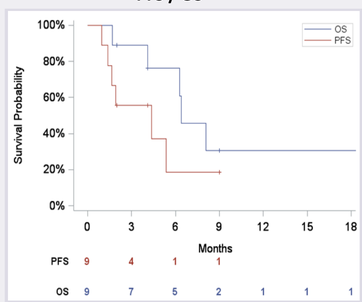
M2 => Partial Response

Related toxicities (N= 9)



Adverse events classified as related to study treatment in esogastric patients

PFS / OS



Median PFS
4,4 months; CI 95% [0,95 ; NA], 6 events
Median OS
6,4 months; CI 95% [1,7 ; 30,5], 6 deaths.

Outcome

- Overall response rate at 8 weeks in 9 evaluable patients: 33% [7 - 70], 3 partial responses, 3 stabilizations and 3 progressions.
- Disease control rate at 16 weeks in 6 evaluable patients: 33%. CI 95% [6-76%].
- 7 grade ≥ 3 adverse events : 2 alkalines phosphates increases, 2 ALAT increases, 1 ASAT increase, 1 Bilirubin increase and 1 pneumonia.
- All grade most common adverse events: ASAT increase (67%), nausea - visual disorders - ALAT increase (56% for each), edema – fatigue – alkaline phosphate increase (44% for each), vomiting – anemia (33%).

CONCLUSION

- **National biomarker-driven access to crizotinib for MET+ esogastric adenocarcinoma patients is feasible.**
- **MET amplification was observed in around 5,5% of gastric adenocarcinoma and 12,7% of the oesophagus adenocarcinoma.**
- **Preliminary results show crizotinib activity, with partial response and stabilisation, in MET+ esogastric adenocarcinoma.**

Thanks

Patients & families

Study support
- financial support from INCa, the ARC Foundation, the Unicancer's partner for Personalized Medicine research
- institutional support of Pfizer

Collaborative groups
- **French Digestive Cancers Groups (UCGI / FFCD / GERCOR)**
- French Society of Pediatric Oncology (SFCE)
- French thoracic oncology Intergroup (IFCT)
- Francophone Neuro-Oncologist Association (ANOCEF)
- French Cooperative Gynecological Cancer Research Group (ARCAGY-GINECO)
- French Genito-Unirary Cancer Cooperative Groups (GETUG / AFU)
- French Breast Cancer Intergroup - UNICANCER (UCBG)
- French Sarcoma Group - Bone Tumor Group (GSF-GETO)
- French Thyroid Cancer Network (TUTHYREF)
- Lymphoma Study Association (LYSA)

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Results of other malignancies (#2504) presented orally at session "Developmental Therapeutics — Clinical Pharmacology and Experimental Therapeutics" (June 1, 2018, 2:45 PM).