3902

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Vemurafenib in patients (pts) harboring BRAF V600 mutation. Results of non-small cell lung cancer (NSCLC) cohort from the AcSé trial.

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Abstract #5138

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

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

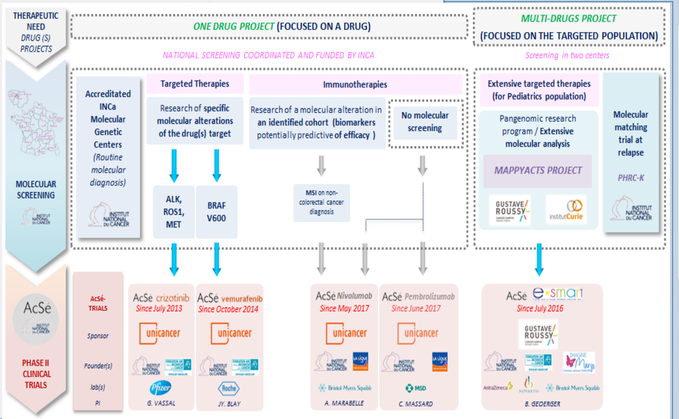
- Provide nationwide molecular tumor diagnosis for all patients through INCa molecular genetic centers
- Whatever the healthcare institution status (public hospitals, private hospitals…)
- Perform high quality tests
- Hemopathies, solid tumors

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 Vemurafenib

Phase 2 clinical trial: Secured Access to Vemurafenib for patients with tumours harbouring BRAF genomic alterations – PI : Jean-Yves BLAY / NCT02304809

Background

- Vemurafenib is registered as a monotherapy for the treatment of adult patients with BRAF V600 mutation unresectable or metastatic melanoma
- Responses were observed in other tumour types

Main objective

Identification of subsets of patients that may benefit from treatment

Population

- Patients ≥18 years with advanced disease harbouring BRAF genomic alterations (except colorectal cancer and V600 BRAF mutated melanoma) and not eligible for any other active trial targeting the same alteration.

Molecular diagnosis process

Screening for BRAF mutation

Single test from INCa platforms

- Non small cell lung cancer - NSCLC
- Ovarian cancer
- Cholangiocarcinoma
- Thyroid cancer
- Prostatic cancer
- Bladder cancer
- Sarcoma/GIST
- Multiple myeloma
- Chronic Lymphocytic Leukemia (CLL)
- Hairy cell leukaemia (HCL)

Molecular pangenomic programs

AcSé vemurafenib

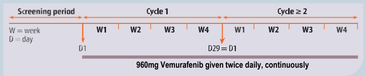
- Inclusion/Exclusion criteria
- Consent form

Accrual

BRAF V600 screening activity* (At February 28, 2018)	Number of positive cases	Patients included (from October 1, 2014 to September 29, 2018)
2037	89	198**

** : except NSCLC, colorectal and melanoma, tests performed for diagnosis*
*** : whose 118 NSCLC + 50 pts from molecular pangenomic programs or other circuits.*

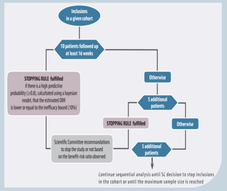
Treatment scheme



- Disease response assessed every 8 weeks
- Safety assessed continuously
- Treatment pursued until progression, unacceptable toxicity, undercurrent conditions, or patient refusal
  For HCL and CLL, Vemurafenib is prescribed for 2 cycles and possibly for 2 additional cycles if CR is not achieved. Treatment is stopped at day 112 max whatever the response.

Statistical design

- Endpoint : Objective Response Rate (ORR) evaluated in each cohort
- Bayesian sequential design
- 100 patients/cohort maximum
- New data could lead to open additional cohorts
- Up to 200 investigating centres

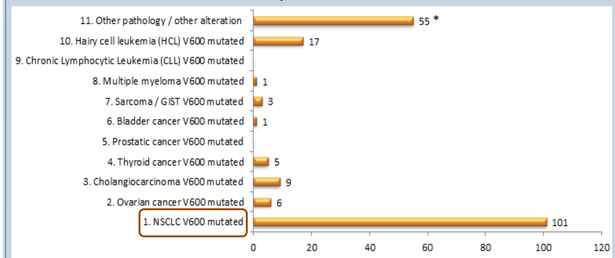


Dermatological monitoring

A regular dermatological monitoring has been set up. Indeed, all patients are referred to a dermatologist prior to first intake, after 28 days of Vemurafenib and then every 3 months. An initial dermatologic history, including photo type, history of sun / UV exposure, previous skin cancers and immunosuppression is completed. Suspicious skin lesions are biopsied or excised. Melanoma and squamous cell carcinoma lesions are submitted for central dermatopathology review.

Furthermore, specialists have been appointed for the management of BRAF inhibitors specific skin toxicities.

Inclusions per cohorts



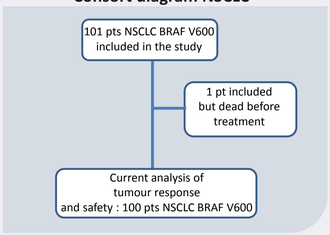
* : 1 NSCLC – BRAF G466A MUT, 3 NSCLC – BRAF G466V MUT, 3 NSCLC – BRAF G469A MUT, 1 NSCLC – BRAF G469V MUT, 1 NSCLC – BRAF G596R MUT, 3 NSCLC – BRAF K601E MUT, 2 NSCLC – BRAF K601N MUT, 3 NSCLC – BRAF N581S MUT

8 HISTIOCYTOSIS - BRAF V600E MUT, 1 ASTROCYTOMA - BRAF V600E MUT, 3 XANTHO ASTROCYTOMA - BRAF V600E MUT, 2 GLIOMA - BRAF V600E MUT, 4 GANGLIOGLIOMA - BRAF V600E MUT, 6 GLIOBLASTOMA - BRAF V600E MUT, 1 NEPHROBLASTOMA - BRAF V600E MUT, 1 LYMPHOMA - BRAF V600E MUT, 1 CANCER OF APPENDIX - BRAF V600E MUT, 1 UNKNOWN PRIMARY CANCER - MUTATION BRAF V600E

1 MÉLANOME - BRAF K601E MUT, 1 MÉLANOMA - BRAF G596K MUT, 1 MÉLANOMA - BRAF L597S MUT, 1 MÉLANOMA - BRAF V600INS THR MUT, 1 CARCINOMA OF MAXILLARY SINUS - BRAF G469E MUT, 1 BLADDER CANCER - BRAF G469E MUT, 1 PROSTATIC CANCER - BRAF L613S MUT, 1 PROSTATIC CANCER - BRAF K601E MUT, 1 BREAST CANCER - BRAF G466A MUT, 1 SPLENIC LYMPHOMA - BRAF G600INS TAC MUT

Focus on non-small cell lung cancers with BRAF V600 mutation

Consort diagram NSCLC

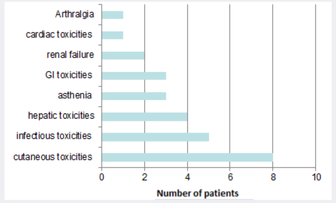


Patients characteristics

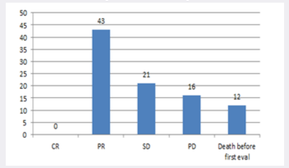
Disease characteristic	Frequency (%) N= 100
Sex	
Male	51 (50.5%)
Female	50 (49,5%)
Age (Years)	
Median [range]	68 [41 ; 85]
Number of previous line of chemo	80 (79,3%)
1	50 (49,5%)
2	24 (23,8%)
3 or more	6 (6,0%)
Tobacco*	
Smokers/ex-Smokers	58 (69%)
WHO PS	
0	27 (27%)
1	54 (54%)
2	19 (19%)

** 17 missing data.*

Causes of treatment cessation for toxicities



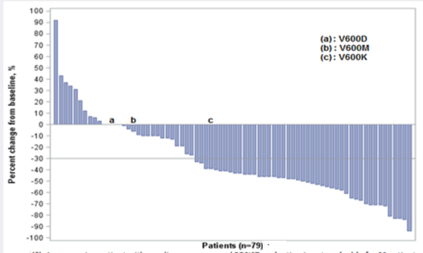
Efficacy - Best response



Objective Response Rate (CR + PR)

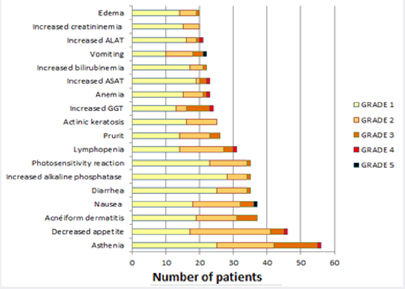
- Mean Bayesian Estimated Success rate : 44.9% credibility 95%CI : [35.2;54.8]
- Prob ORR > efficacy bound (30%): 99.9%
- Median response duration: 6.4 months

Waterfall plot of best reduction in tumour measurement from baseline

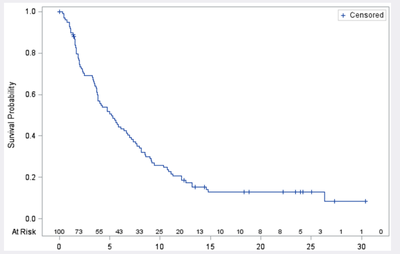


(*): 1 progressive patient with pending measures and RECIST evaluation is not evaluable for 20 patients : 12 deaths before first evaluation, 7 treatment stop before first evaluation, 1 clinic progression.

Related toxicities (n=100)

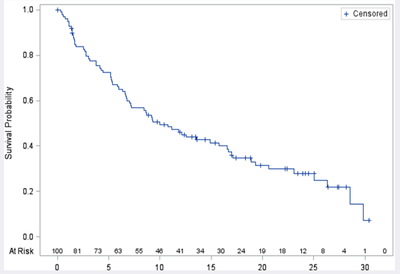


PFS



Median PFS: 5.2 months [3.8;6.9]

OS



Median OS: 9.3 months [6.8;14.9]

Conclusion

- **Vemurafenib provided reasonable response rate and extended PFS in pretreated NSCLC patients with BRAF V600 mutations**
- **Tolerance was manageable**
- **These results emphasize the need of integrating BRAF V600 in routine biomarkers screening.**
- **Vemurafenib has comparable efficacy to dabrafenib monotherapy even if the combination of dabrafenib and trametinib remains the standard of care.**

Acknowledgements

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Collaborative groups

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- French Cooperative Gynecological Cancer Research Group (ARCAGY Gineco)
- French genito-urinary cancer cooperative groups (GETUG/AFU)
- French Sarcoma Group (GSF-GETO)
- French Gastro Institutional Groups (UCGI)
- French thyroid cancer network (TUTHYREF)
- French Innovative Leukemia Organization (FILO)
- French of myeloma intergroup (IFM)
- Skin Cancer Group (GCC) from the French Society of Dermatology (SFD)

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