Background
Most targeted therapies in cancer have reached approval based on clinical studies performed in unselected patients. Molecular anomalies predictive of the response to targeted therapies remain largely unknown. Small subsets of patients treated with targeted therapy present exceptional and unexpected response (1-10%) which could be driven and correlated by a low level of genomic alterations in genes identified as causally implicated in cancer. Conversely, the multiplication of genomic alterations in such genes would decrease the oncogenic de-addiction process (1, 2).

Objectives
Primary objectives:
- To identify whether tumours characterised by a low level of genomic alteration in genes identified as causally implicated in cancer are associated with exceptional and unexpected response across anticancer targeted therapies.
- To compare the rate of tumours with a low level of genomic alteration in genes identified as causally implicated in cancer are associated with exceptional and unexpected response across anticancer targeted therapies.

Secondary objectives:
- To identify novel candidate somatic molecular profiles associated with exceptional response within given classes of anticancer targeted therapies.
- To identify host immunologic characteristics associated with exceptional response.
- To guide further exploratory and confirmatory studies (i.e. functional validation) based on the clinical and genomic data and biological resources raised from EXPRESS project.

Methodology
Exceptional tumour responses are naturally rare and unexpected; patients will be identified retrospectively and in a nationwide manner (figure 1). Only this exceptional response is automatically identified in patients with advanced solid cancers (breast, lung, colorectal, ovarian, kidney or melanoma) is of paramount importance as commonly driven and correlated with a low level of genomic alterations in genes identified as causally implicated in cancer. Conversely, the multiplication of genomic alterations in such genes would decrease the oncogenic de-addiction process (1, 2).

Main Inclusion Criteria
- Adult patient (≥18 years old at diagnosis).
- Patient suffering from the following tumour type - breast cancer, lung adenocarcinoma or squamous cell carcinoma, colorectal cancer, ovarian cancer, renal cell cancer, skin cutaneous melanoma.
- Metastatic or locally advanced disease.
- Exceptional and unexpected tumour response to any marketed targeted therapy alone after the agent has been stopped.
- Adverse events of severe intensity or clinically relevant progression.
- Exceptional and unexpected tumour response to any marketed targeted therapy confirmed by the college of experts.
- Availability and required quality of the tumour biopsy (FFPE or frozen sample) allowing for the whole exome sequencing analysis. Tumour biopsies obtained just before the initiation of the targeted therapy are preferred; otherwise any prior sample is possible.

Conclusion
The identification of molecular traits associated with exceptional and unexpected response might serve the development of predictive classifiers for precision medicine. This study also represents a unique opportunity to better understand cancer biology. The study is still recruiting, completion date is estimated to be in August 2019. Other tumour cases were sometimes sent and collected, and the opening of additional cohorts is under discussion.

Acknowledgment
Patients and families, Financial support of the ARC Foundation, Dr. Charles Ferté

Additional information is available on Unicancer website, including patient information and screening form: http://www.unicancer.fr/etude/express/a-bascule/bascule.html

References
1. Fu Y. Cancer Pharmacogenomics and Targeted Therapies conference 2014; Cambridge, UK

Methodology
Nationalwide Patient screening

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Methodology
Exceptional tumour responses are naturally rare and unexpected; patients will be identified retrospectively and in a nationwide manner (Figure 1). Only this approach enables the recruitment of a substantial number of exceptional responders in a relatively short period of time.

The definition of exceptional and unexpected response to an approved antineoplastic targeted therapy in patients with advanced solid cancers (breast, lung, colorectal, ovarian, kidney or melanoma) is of paramount importance and will be confirmed monthly by the Response Confirmation Committee (COREV) composed of the study coordinators and at least one expert of each organ.

We decided to apply the definition chosen by the NCI, which combines three criteria:
1. A complete response or a partial response (RECIST), and
2. Lasting more than 6 months, and
3. Not expected in more than 10% of the patients in this drug – organ type situation.

For each tumour type, we wish to test the null hypothesis H0: π = 0% against the one-sided alternative hypothesis H1: π = 0.05. For each of the six cohorts, a sample size of 44 patients is necessary to achieve 80% power at α = 0.05 with a one-sided level 5% test.

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