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Unicancer French Breast Cancer Intergroup

Thomas Bachelot
Président

UCBG à l'ASCO 2020

FC Bidard (Institut Curie) présente une analyse exploratoire de l'étude PADA-1 lors d'un *«Clinical Science Symposium »* *: Steps Forward and Lessons Learned: Using Biomarkers to Guide Targeted Therapies in Breast Cancer*

⇒ **Impact pronostique des mutations d'*ESR1* chez les patientes présentant un cancer du sein métastatique ER+/HER2- en première ligne de traitement par Letrozol et Palbociclib**

⇒ **Abstract 1010**

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- **Etude PADA-1 (UCBG/GINECO): Première étude au monde dans ce contexte à évaluer prospectivement l'utilité de l'analyse itérative de l'adn tumoral sérique en tant que facteur pronostique et prédictif**
- **1017 patientes incluses en 2 ans (Mars 2017-Dec 2018)**
- **Le critère de jugement principal est l'intérêt du changement de traitement à l'apparition d'une mutation de résistance sur l'ADNc avant toute progression radiologique**
- **L'analyse préliminaire présenté cette année à porté sur l'impact pronostique des mutations d'*ESR1* lors du diagnostique de la maladie métastatique**

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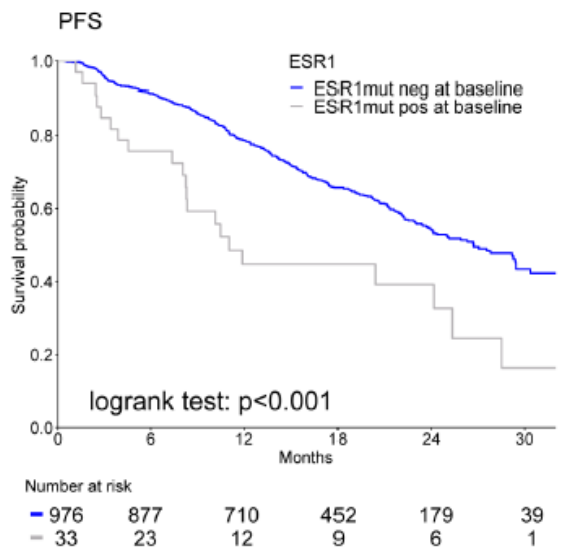
- **Seulement 33 des 1017 avaient une mutation d'*ESR1* détectable sur l'ADNc à l'inclusion (3.2%)**
- **Une petite majorité (19/33) avait reçue des anti-aromatase en adjuvant. Dans cette population, la prévalence est de 7.1%**
- **Leurs pronostique était nettement moins bon que pour les patientes sans mutation**



Median FU = 21.2 months (0-34.5)

Estimated[1] PFS:

ESR1$_{mut}$ (N=33)
Median PFS: **11.0 mo**, 95%CI=[8.3-NR]

ESR1$_{wt}$ (N=976)
Median PFS: **26.7 mo**, 95%CI=[24.1-29.4]

HR= 2.3 95%CI=[1.5;3.6]

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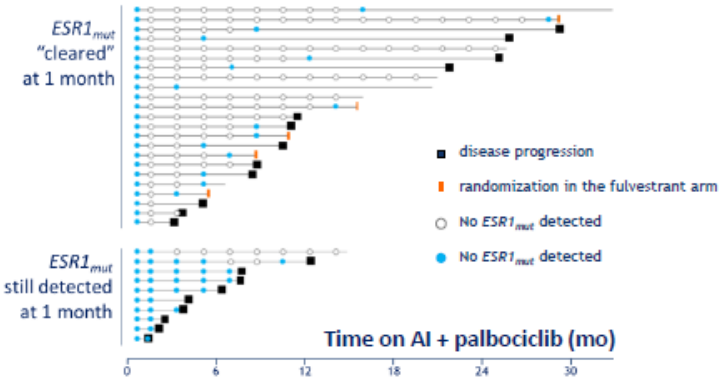
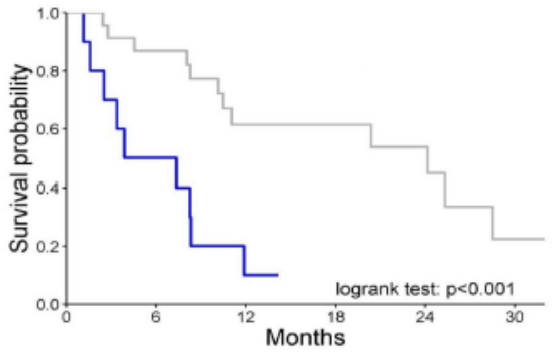
- **Malgré la présence d'une mutation « de résistance », le traitement à entrainé la disparition de l'ADNc pour 23 patientes sur 33, et c'était associée à un meilleur pronostique**

Results: Early *ESR1*$_{mut}$ clearance & outcome

Among the 33 patients with *ESR1*$_{mut}$ detected at inclusion





Early clearance (MAF <0.1%) **at 4 weeks**

Observed in 23/33 patients

Followed by a later "resurgence" of *ESR1*$_{mut}$ in 15/23 patients (at time of analysis)

PFS estimates by *ESR1*$_{mut}$ status at 1 month:

ESR1$_{mut}$ "cleared" : median **24.1 mo** [10.5-NR]

ESR1$_{mut}$ detected : median **7.4 mo** [2.5 – NR]

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1010 Clinical Science Symposium, Fri, 8:00 AM-9:30 AM

Prognostic impact of ESR1 mutations in ER+ HER2- MBC patients prior treated with first line AI and palbociclib: An exploratory analysis of the PADA-1 trial.

Francois Clement Bidard, Celine Callens, Florence Dalenc, Barbara Pistilli, Thibault De La Motte Rouge, Florian Clatot, Veronique D'hondt, Luis Teixeira, Helene Vegas, Sibille Everhard, Jerome Lemonnier, Ivan Bieche, Anne Pradines, Jean FranCois Paitel, Dominique Spaeth, Isabelle Moullet, Jean-Yves Pierga, Frederique Berger, Anne-Claire Hardy-Bessard, Thomas Bachelot; Centre René Huguenin, Saint Cloud, France; Institut Curie, Paris, France; Department of Medical Oncology, Institut Claudius Regaud–IUCT Oncopole, Toulouse, France; Gustave Roussy, Villejuif, France; Centre Eugène Marquis, Rennes, France; INSERM U1245, IRON Group, Centre Henri Becquerel, University Hospital, University of Normandy, Rouen, France; Institut du Cancer de Montpellier, Montpellier, France; Université de Paris, HIPI INSERM U976, Breast Diseases Unit, AP-HP, Hôpital Saint Louis, Paris, France; Hopital Bretonneau, Tours, France; Unicancer, Paris, France; Institut Claudius Regaud, IUCT-Oncopole, Laboratoire de Biologie Médicale Oncologique, Toulouse, France; CHI Fréjus St-Raphaël, Frejus, France; ORACLE, Centre d'Oncologie de Gentilly, Gentilly, France; Clinique de la Sauvegarde, Lyon, France; Biostatistics Unit, INSERM U900, Institut Curie, Paris, France; Medical Oncology Department, CARIO-HPCA and Cooperative Gynecological Cancer Research Group (GINECO), Plerin, France; Centre Léon Bérard, Lyon, France

Background: The question of which is the best endocrine partner to CDK4/6 inhibitors in first line for ER+ HER2- metastatic breast cancer (MBC) remains open. *ESR1* mutations might be of paramount importance, as they confer resistance to AI but not to SERD. In pts treated with first line palbociclib-AI combination (PADA-1 trial, NCT03079011), we investigated *ESR1mut* detection rate at inclusion, prior to any therapy, and their prognostic impact. **Methods:** The PADA-1 phase 3 trial (NCT03079011, UCBG-GINECO) evaluates the utility of monitoring the onset of *ESR1mut* in cell-free DNA (with a ddPCR assay [Jeannot *et al*, Oncogene 2020]) of pts receiving AI-palbociclib in first line. Included pts had no prior therapy for MBC and no overt resistance to AI. **Results:** N = 1017 ER+ HER2- MBC pts were included in 22 months from 04/2017 and had their cfDNA tested for *ESR1mut* at inclusion and during therapy. N = 33/1017 pts had a detectable circulating *ESR1mut* at inclusion (3.2%, 95%CI [2.2;4.5]), *ESR1mut* positivity being associated with a prior exposure to AI in the adjuvant setting ($p < 0.01$). N = 1 pt died after 1 month on treatment. In N = 25/32 evaluable pts (78%), *ESR1mut* became undetectable in cfDNA (AF < 0.1%) within the first 5 months on treatment, with a median time to *ESR1mut* 'clearance' of 34 days. Among these 25 pts, 14 pts (56%) had *ESR1mut* detected again during therapy; 2 pts (8%) experienced a progression with no *ESR1mut* detected; the remaining 9 patients (36%) were still both *ESR1mut*-free and progression-free at time of analysis. With a median FU time of 12.4 months (range: 0-25.3m) under AI-palbociclib, the 33 ESR1mut-positive pts had a shorter PFS (median: 17.5mo, 95%CI[10.5-NR]) than the 984 ESR1mut-negative pts (median not reached), with an estimated HR = 2.8 [1.6;5.0]. Updated data will be presented at the meeting. **Conclusions:** *ESR1mut* are rarely detected in the cfDNA of ER+ HER2- MBC patients with no overt resistance to AI. The quick 'clearance' of *ESR1mut* under treatment and the observed 17.5 months-long median PFS both suggest that the AI-palbociclib combination retain a clinical activity in this population. *ESR1mut*-positivity prior was however associated with a significantly shorter PFS, suggesting that *ESR1mut* positivity at baseline could accelerate the onset of resistance to AI-palbociclib. These findings may put into perspective the incoming results of the PARSIFAL trial. Clinical trial information: NCT03079011. Research Sponsor: Pfizer.

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Acknowledgements

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- 83 contributing centers

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ARCAGY - GINECO

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  - Institut Claudius Regaud–IUCT Oncopole Toulouse
- Funding

Pfizer

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PADA-1
THE (SUB)CLONE WARS

PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20

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