Impact of androgen pathway inhibitors on cognitive function in elderly patients with metastatic prostate cancer

FPN#1632P

results from the COG-PRO trial

Antoine Boué[a], Giulia Baciarello[b], Emmanuel Meyer[c], François Christy[d,e], Nedjla Allouache[f], Raffaele Ratta[g], Philippe Beuzeboc[g], Pierre-Emmanuel Brachet[g], Estelle Guerdoux[h], Amélie Darlix[i], Mathieu Boone[j], Sophie Gouerant[k], Alexandra Leconte[d], Justine Lequesne[d,e], Bénédicte Clarisse[d], Karim Fizazi[b], Marie Lange[a,d,e], Florence Joly[a,b,e,f,l]

[a] University of Caen Normandie, Inserm 1086 Anticipe, 14000 Caen, France. [b] Gustave Roussy, cancer medicine department, 94805 Villejuif, France. [c] François Baclesse center, radiation oncology department, 14000 Caen, France. [d] François Baclesse center, clinical research department, 14000 Caen, France. [e] University of Caen Normandie, Services unit PLATON, Cancer and cognition platform, 14000 Caen, France. [f] François Baclesse center, medical oncology department, 14000 Caen, France. [g] Foch hospital, medical oncology department, 92150 Suresnes, France. [h] Montpellier cancer institute (ICM), supportive care department, psycho-oncology unit, 34090 Montpellier, France. [i] Montpellier cancer institute (ICM), medical oncology department, 34090 Montpellier, France. [j] Amiens-Picardie university hospital center, medical oncology department, 80054 Amiens, France. [k] Henri Becquerel center, medical oncology department, 76038 Rouen, France. [l] Caen university hospital center, medical oncology department, 14000 Caen, France.

context

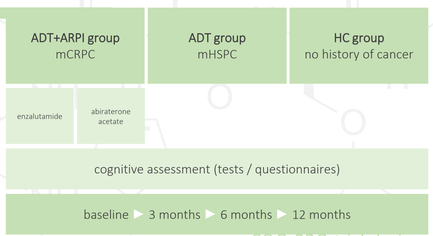
- **Androgen receptor pathway inhibitors** (ARPI) are commonly used in addition to **androgen deprivation therapy** (ADT) for metastatic prostate cancer (mPC).
- ADT and ARPI may induce cognitive impairment on:
  - objective cognitive (performance / cognitive tests)[1],
  - subjective cognition (self-reported cognitive complaints / questionnaires)[2].
- Most of the patients are **elderly**, with an **increased risk of cognitive impairment**[3], which may have potential repercussions on their autonomy and quality of life[4].
- No study has compared cognitive impact of ADT+ARPI with those of ADT alone in elderly patients.

Objective of the study

- to **estimate the frequency** of overall objective and subjective cognitive impairment before ARPI initiation and the decline during treatment in elderly mPC patients;
- to **describe differences** in objective domains and subjective cognition between patients receiving ADT+ARPI, compared to patients receiving ADT alone.

method

- COG-PRO (NCT02907372) was a prospective, multicenter, comparative trial
  - > that assessed cognition in castration resistant mPC (mCRPC) patients aged 70+ receiving **ADT+ARPI,**
  - > compared with hormone sensitive mPC (mHSPC) control patients receiving **ADT alone**, and **healthy controls** (HC).
- Cognitive assessment:
  - > **objective cognition**: six cognitive domains: Processing speed/attention, Working memory, Verbal memory, Visual memory, Visuospatial abilities, Executives functions;
  - > **subjective cognition**: PCI and PCA subscales from FACT-COG questionnaire.
- Analysis: adjusted scores + prevalence of overall and subjective cognition:
  - > **impairment** before ARPI initiation → ICCTF criterion[6] reached in 2/6 objective domains; published norms for subjective cognition
  - > **decline** after 3, 6 and 12 months → Reliable change index (RCI) ≤-1.645 in 2/6 objective domains, decrease in FACT-COG scores ≥10% since baseline.



COG-PRO trial design[5]

results

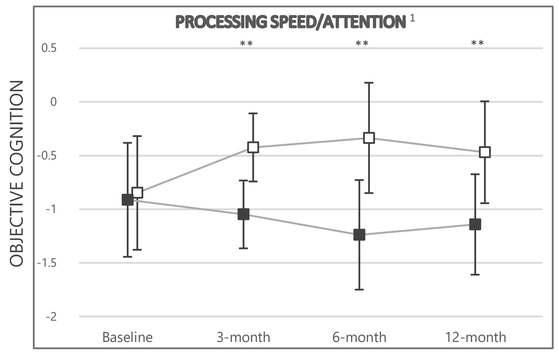
- The analysis included **74** ADT+ARPI patients, **19** ADT, and **30** HC
  → median ages: **78**, **73**, and **75**, respectively.
- At baseline:
  - > 41 (**46%**) **mPC patients** (ADT**+/-**ARPI) had **overall objective cognitive impairment,** vs. 3 (10%) HC (p<0.001),
  - > **subjective impairment** according to PCI and PCA was reported by 21 (**24%**) and 16 (**18%**) **mPC patients** (ADT**+/-**ARPI) , vs. 2 (7%) and 2 (7%) HC, respectively.
- During follow-up:
  - > **Low rates** of **overall objective cognitive decline** were observed for all patients groups (Table below), however, ADT+ARPI patients had **lower** adjusted scores compared to the ADT group at 3, 6 and 12 months in **processing speed/attention** (p≤0.010, Figure opposite).
  - > For subjective cognition, **more ADT+ARPI** patients **declined** at 6 months in PCI than ADT patient (p=0.050, Table below), and **lower adjusted scores for subjective cognition** (PCA) at 3 and 6 months (p≤0.033, Figure opposite).

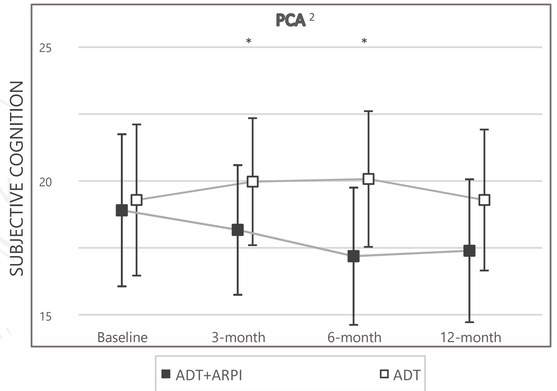
Cognitive decline during follow-up according to treatment group (unadjusted)

	ADT+ARPI	ADT	HC	p^3	
	decline % (n)	decline % (n)	decline % (n)	All patients *vs.* HC	ADT+ARPI *vs.* ADT
3-month	**N=74**	**N=19**	**N=30**		
Overall objective decline[1]	3% (2)	5% (1)	0% (0)	1.000	0.500
Subjective decline: PCI	25% (16)	11% (2)	17% (5)	0.792	0.335
Subjective decline: PCA	26% (17)	33% (6)	30% (9)	0.815	0.558
6-month	**N=54**	**N=17**	**N=28**		
Overall objective decline[1]	6% (3)	0% (0)	0% (0)	0.556	1.000
Subjective decline: PCI	34% (17)	6% (1)	32% (9)	0.628	0.050
Subjective decline: PCA	46% (23)	25% (4)	25% (7)	0.165	0.158
12-month	**N=42**	**N=13**	**N=29**		
Overall objective decline[1]	2% (1)	8% (1)	0% (0)	0.542	0.420
Subjective decline: PCI	41% (16)	17% (2)	24% (7)	0.329	0.174
Subjective decline: PCA	41% (16)	33% (4)	31% (9)	0.629	0.743

ADT: patients treated with androgen deprivation therapy. ARPI: patients treated with androgen receptor pathway inhibitors. HC: healthy controls. RCI: reliable change index. PCI: Perceived cognitive abilities. PCI: Perceived cognitive impairment. [1] Proportion of participants declining in at least two objective domains according to RCI. [2] Proportion of participants with a FACT-Cog – PCI and PCA score decreasing ≥10% from baseline. [3] Comparison of percentage of participants with cognitive decline. χ^2 or Fisher exact test. Significant difference: p<0.05

Cognitive scores during follow-up according to treatment group (adjusted)





ADT: patients treated with androgen deprivation therapy. ARPI: patients treated with androgen receptor pathway inhibitors. HC: healthy controls. Multivariable linear models, adjusted for baseline cognition, age, education and fatigue. Low scores reflect poor cognition. Significant difference: * p<0.050, ** p<0.010, *** p<0.001.
1 Adjusted composite z-scores
2 Adjusted FACT-Cog – PCI and PCA raw scores.

conclusion

Before ARPI initiation: high prevalence of objective and subjective cognitive impairment in elderly mPC patients.
During treatment with ARPI: impact of treatment on processing speed/attention domain of objective cognition, and on subjective cognition (cognitive complaints).
▶ In addition to ADT, ARPI increase cognitive complaints and decrease cognitive performance in elderly mCRPC patients.

for further information:
f.joly@baclesse.unicancer.fr
or visit us on the
Cancer&Cognition platform website

1 Ryan C, Wefel JS, Morgans AK. A review of prostate cancer treatment impact on the CNS and cognitive function. Prostate Cancer Prostatic Dis 2020;23:207–19.
2 Boué A, Joly F, Lequesne J, Lange M. Does hormone therapy impact cognition in patients with prostate cancer? A systematic review and meta-analysis. Cancer 2024.
3 Lange M, Rigal O, Clarisse B, Giffard B, Sevin E, Barillet M, et al. Cognitive dysfunctions in elderly cancer patients: a new challenge for oncologists. Cancer Treat Rev 2014;40:810–7.
4 Wefel JS, Ryan CJ, Van J, Jackson JC, Morgans AK. Assessment and Management of Cognitive Function in Patients with Prostate Cancer Treated with Second-Generation Androgen Receptor Pathway Inhibitors. CNS Drugs 2022;36:419–49.
5 Lange M, Laviec H, Castel H, Heutte N, Leconte A, Léger I, et al. Impact of new generation hormone-therapy on cognitive function in elderly patients treated for a metastatic prostate cancer: Cog-Pro trial protocol. BMC Cancer 2017;17:549.
6 Wefel JS, Vardy J, Ahles T, Schagen SB. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. Lancet Oncol 2011;12:703–8.

DOI for FJ: Amgen (invited speaker), Astellas (advisory board, research grant), AstraZeneca (advisory board, invited speaker, coordinating principal investigator), Bayer (advisory board), BMS (research grant), Chugai (travel and congress), Esai (advisory board, invited speaker, travel), GCIG (member), GSK (advisory board, invited speaker, coordinating principal investigator, travel), Ipsen (advisory board, invited speaker, travel and congress), Janssen (advisory board, invited speaker, research grant, funding), MSD (advisory board, invited speaker, travel and congress), Novartis/AAA (invited speaker), Novocure (advisory board), Pfizer (advisory board), Seagen (Advisory board), Viatris (invited speaker)
This study was supported by a public grant overseen by the French National Institute of Cancer (Institut national du cancer, INCa) as part of the program "Research in Social and Human Sciences, Epidemiology and Public Health" (SHS-E-SP-2015-9528), and by a specific donation from Astellas Pharma. The funders had no role in study design, data collection, data analysis, data interpretation or writing of the report.