Next-generation androgen receptor inhibitors in non-metastatic castration-resistant prostate cancer

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***Abstract*:** Until recently, continuing androgen deprivation therapy (ADT) and closely monitoring patients until evolution towards metastatic castration-resistant prostate cancer (CRPC) were recommended in men with non-metastatic CRPC (nmCRPC). Because delaying the development of metastases and symptoms in these patients is a major issue, several trials have investigated next-generation androgen receptor (AR) axis inhibitors such as apalutamide, darolutamide, and enzalutamide in this setting. This review summarizes the recent advances in the management of nmCRPC, highlighting the favourable impact of next-generation AR inhibitors on metastases-free survival, overall survival and other clinically meaningful endpoints.

Keywords: apalutamide, castration resistance, darolutamide, enzalutamide, next generation androgen receptor inhibitors, non-metastatic setting, prostate cancer

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Introduction

Prostate cancer is the second most common cancer and the fifth leading cause of cancer-related deaths among men worldwide.[1–3] In developed countries, most patients are diagnosed with localized disease (e.g. more than 80% of prostate cancer patients in the USA[4]). Active surveillance and local treatments associated when needed with androgen deprivation therapy (ADT) are recommended therapeutic options for significant localized cancers.[5] Despite important cure rates after local treatment, a proportion of patients will relapse with rising levels of prostate-specific antigen (PSA) with no apparent metastases on conventional imaging. Although debated, salvage ADT is often part of treatment for men with recurrent non-metastatic prostate cancer after primary treatment.[5–8]

However, after initial biochemical response, the disease will progress in most of these men despite castrate levels of testosterone, defining castration-resistant prostate cancer (CRPC). Evolution towards CRPC can occur concurrently to the development of metastases (mCRPC) or before identification of any metastatic disease on conventional imaging [computed tomography (CT) scan and bone scan]. Patients without metastasis on conventional imaging are classified as having non-metastatic CRPC (nmCRPC or M0 CRPC).[9] At least one in three of these patients will thereafter develop bone metastases within 2 years.[9]

Until recently, continuing ADT and closely monitoring patients until evolution towards mCRPC were recommended in men with nmCRPC.[5] Until 2018, National Comprehensive Cancer Network guidelines also recommended hormonal manipulations such as addition or withdrawal of first-generation androgen receptor (AR) inhibitors, or the use of ketoconazole, corticosteroids, or estrogens for men with rapid PSA doubling-times (PSA-DT). However, no randomized trial ever demonstrated a clinical benefit associated with these treatments.[10] Until recently, the use of next-generation hormonal therapy was recommended only in case of established metastatic disease.[5] Additionally, optimal disease monitoring in patients with nmCRPC still

remains controversial, and is left up to the discretion of the physician, guided by the baseline PSA level, and PSA-DT which are associated with metastasis-free survival (MFS) and overall survival (OS).[9,11] In the last APCCC consensus, the majority of the expert panel voted in favour of imaging in case of rising PSA level with a PSA doubling time of 10 months and when PSA is >2 ng/ml but <10 ng/ml. Ga68-PSMA-PET was the preferred staging imaging.

Delaying the development of metastases is a major issue, as MFS has been found to be a strong surrogate for OS in localized prostate cancer and to be associated with both morbidity and prostate cancer-specific mortality. Postponing metastases delays the appearance of skeletal-related events and thus improves patients' quality of life.[12,13]

It has long been known that the AR pathway is a crucial part of the pathogenesis of prostate cancer, and as such has been the main target of prostate cancer treatment.[14] ADT has long been the mainstay of metastatic prostate cancer treatment, and the continued importance of AR in the metastatic castration-resistant stage makes it a key therapeutic target in this setting. Next-generation AR axis inhibitors such as abiraterone acetate (AA) and enzalutamide are now approved and routinely used in clinical practice in men with mCRPC before or after chemotherapy.[15–19]

These successes prompted the evaluation of these drugs also in earlier stages of the disease. AA associated with ADT has been associated with a significant OS benefit in treatment-naïve metastatic prostate cancer patients, with a 38% decrease in the risk of death compared with ADT alone.[19,20] AA is now approved for the management of metastatic castration-sensitive prostate cancer. Results of similar trials with enzalutamide or apalutamide have recently been reported with about a 35% decrease in the risk of death compared with the previous standard of care of ADT alone or in combination with docetaxel.[21,22]

Alongside *de novo* metastatic prostate cancer and mCRPC, nmCRPC represents another unique scenario of advanced prostate cancer. Whether next-generation AR axis inhibitors could also exert clinical benefit in nmCRPC has been a critical question.

This review summarizes recent advances in the management of nmCRPC, highlighting the promising results of next-generation AR inhibitors from recent clinical trials.

Continued targeting androgen receptor signalling in prostate cancer

The AR belongs to the steroid hormone receptor family of ligand-activated nuclear transcription factors. Androgens are mainly produced in testes, but also by the adrenal glands and in peripheral tissues including prostate cancer cells. AR promotes prostate cancer proliferation by modulating the expression of genes involved in growth, differentiation, and survival of tumour cells.[23] Androgens and AR signalling pathways are observed as the main oncogenic drivers in prostate carcinogenesis and represent a relevant target for prostate cancer treatment. Therapies targeting the AR, including gonadotropin-releasing hormone (GnRH) analogues and AR inhibitors, do not completely inhibit AR activity. Second-line hormonal therapy has been supported by the demonstration of sustained AR expression and intact AR signalling when the disease evolves from androgen sensitive to castration resistant.[14,24,25]

Enzalutamide (MDV3100) is an AR antagonist that binds to the AR with approximately eight-fold greater affinity compared with bicalutamide. Unlike bicalutamide, enzalutamide also inhibits AR function by blocking nuclear translocation and impairs both DNA binding to androgen response elements and recruitment of coactivators.[25] Similarly to enzalutamide, apalutamide (ARN-509) is a non-steroidal direct AR inhibitor. Its molecular structure is very close to that of enzalutamide.[26] Apalutamide binds to the ligand-binding domain of AR blocks its nuclear translocation with five-fold greater affinity than bicalutamide as well as preventing DNA binding and transcription of AR target genes. In preclinical studies, apalutamide induced partial or complete regression in both castration-sensitive and -resistant human prostate cancer xenograft models and showed maximal antitumor efficacy in these models at lower dose and approximately nine-fold lower plasma level than enzalutamide, suggestive of a higher therapeutic index.[27] Darolutamide (ODM-201, BAY-1841788) is a novel, high-affinity non-steroidal AR antagonist with a completely different chemical structure than other AR antagonists. Darolutamide and its active metabolite (keto-darolutamide) have been shown to have a higher AR-binding affinity than bicalutamide, enzalutamide, and apalutamide and to have

minimal blood–brain barrier penetration.[27] It inhibits nuclear translocation of AR in AR-overexpressing cells and significantly reduces tumour growth both *in vitro* and in the murine VCaP CRPC xenograft model.[27,28] Studies evaluated darolutamide in preclinical models, especially in enzalutamide-resistant CRPC as well as in AR mutants detected in patients after treatment with enzalutamide, abiraterone, or bicalutamide. It shows growth delays in enzalutamide-resistant prostate cancer, in particular in cells with mutated forms of the AR after previous treatment.[29]

These three promising drugs have been tested in the nmCRPC setting (Table 1).

Apalutamide

A phase II study with 51 patients with nmCRPC with a high risk for progression (PSA ⩾8 ng/ml and/or PSA-DT ⩽10 months) showed a rate of ⩾50% PSA decrease (PSA50) of 89% and a median time to PSA progression of 24 months.[30] The first study that reported efficacy in prostate cancer was the SPARTAN trial that was conducted in nmCRPC. This phase III trial enrolled 1207 patients with a PSA-DT of 10 months or less, randomized 2-to-1 to apalutamide 240 mg QD with ADT or placebo with ADT. Apalutamide showed superiority over placebo in the primary endpoint of median MFS, which was 40.5 months in the apalutamide group as compared with 16.2 months in the placebo group [hazard ratio (HR): 0.28; 95% confidence interval (CI): 0.23–0.35; $p < 0.001$]. The superiority of apalutamide was consistent across all subgroups regardless of PSA-DT (>6 months *versus* ⩽6 months), use of bone-sparing agents, and classification of local or regional nodal disease at the time of randomization. All secondary endpoints significantly favoured apalutamide. Median time to metastasis was 40.5 months in the apalutamide group *versus* 16.6 months in the placebo group, and progression-free survival (PFS) was 40.5 months with apalutamide *versus* 14.7 months.[31] The adverse events considered to be related to apalutamide were fatigue (30.4%), cutaneous rash (23.8%), falls (15.6%), fracture (11.7%), hypo-thyroidism (8.1%), and seizure (0.2%). The discontinuation rate was 10.6% in the apalutamide group and 7% in the placebo group.[31] Given the clinical benefit of apalutamide, the trial was unblinded in July 2017 and patients in the placebo group crossed-over to apalutamide. Thus, apalutamide was the first drug approved by the US Food and Drug Administration (FDA) for nmCRPC on February 2018 and then by the European Medical Agency (EMA) in November 2018. Data on PFS 2 (time from randomization to progression on next-line treatment or death) showed a 50% reduction in risk of secondary progression or death (HR 0.50; 95% CI, 0.39–0.63; $p < 0.0001$).[32,33] The last updated data on OS recently reported after 52 months of median follow-up showed a 22% significant reduction in the risk of death (95% CI: 0.64–0.96; $p = 0.0161$) with an increase of 14 months in median survival compared with placebo (59.9 months in the placebo group *versus* 73.9 months in the apalutamide group).[34] These results confirm that initiating therapy at early stage of the disease is more effective than waiting until mCRPC development.

Enzalutamide

Enzalutamide has been part of the metastatic prostate cancer therapeutic landscape for several years. Its efficacy and safety in mCRPC were evaluated in two placebo-controlled, multicentre phase III trials (AFFIRM and PREVAIL), leading to its approval for treatment of mCRPC in 2012, either upfront or after docetaxel chemotherapy.[17,18]

It was first evaluated in nmCRPC in a phase II clinical trial where patients with either metastatic ($n = 257$) or non-metastatic CRPC ($n = 139$) were randomized to receive enzalutamide or bicalutamide after progression on ADT. Encouraging results were found among nmCRPC patients treated with enzalutamide with a hazard ratio for radiological progression of 0.24 (95% CI 0.10–0.56) and a radiological PFS of 87.8% at 2 years.[35]

The PROSPER study was a randomized phase III trial conducted in 1401 nmCRPC patients with a PSA-DT of 10 months or less. Patients received enzalutamide or placebo in a 2:1 ratio. The median MFS (primary endpoint) was 36.6 months in the enzalutamide group *versus* 14.7 months in the placebo group, and enzalutamide treatment resulted in a 71% lower risk of radiographic progression or death (HR, 0.29; 95% CI, 0.24–0.35; $p < 0.001$).[36] The results of the OS presented recently showed a statistically significant 27% lower risk of death with enzalutamide when compared with placebo. The median survival was 67 months (95% CI, 64.0 to not reached) in the enzalutamide group and only 56 months (95% CI, 54.4–63.0) in the placebo group (HR for death, 0.73; 95% CI 0.61–0.89; $p = 0.001$).

Patients treated with enzalutamide have a 48-month delay in the time to the first use of a subsequent therapy compared with the placebo group and a median treatment duration more twice as long in the enzalutamide group than in placebo group.[37]

The safety profile was similar to what was known in mCRPC. The most common adverse event was fatigue (33%). Adverse events of special interest that occurred more frequently with enzalutamide were hypertension (12% *versus* 5%), major adverse cardiovascular events (5% *versus* 3%), and mental impairment disorders (5% *versus* 2%). Three patients in the enzalutamide group had convulsions and five patients developed encephalopathy. A higher percentage of patients receiving enzalutamide reported falls (11% *versus* 4%).[36]

Even if data were still too immature to identify an OS benefit in 2018, the improved MFS in the PROSPER trial led to the approval of enzalutamide by the FDA for nmCRPC with PSA-DT of 10 months or less in July 2018 and by the EMA in September 2018. Data on OS confirmed the clinically meaningful advantage to use enzalutamide in this setting.

Darolutamide

Darolutamide (ODM-201, BAY-1841788) is a novel, high-affinity non-steroidal AR antagonist with a completely different chemical structure than other AR antagonists. Darolutamide and its active metabolite (keto-darolutamide) have been shown to have a higher AR-binding affinity than bicalutamide, enzalutamide, and apalutamide and to have minimal blood–brain barrier penetration.[27] It inhibits nuclear translocation of AR in AR-overexpressing cells and significantly reduces tumour growth both *in vitro* and in the murine VCaP CRPC xenograft model.[27,28] Studies evaluated darolutamide in preclinical models, especially in enzalutamide-resistant CRPC as well as in AR mutants detected in patients after treatment with enzalutamide, abiraterone, or bicalutamide. It shows growth delays in enzalutamide-resistant prostate cancer, in particular in cells with mutated forms of the AR after previous treatment.[29]

The first phase I/II ARADES trial enrolled 136 CRPC patients (24 in the dose-escalation phase and 112 randomly assigned to receive either 200 mg, 400 mg, or 1400 mg of darolutamide). The safety profile was favourable, with only 4% of patients (5/124 patients) discontinuing darolutamide because of adverse events, which were not related to darolutamide according to the investigators. No dose reduction was required for any patient. A PSA response at 12 weeks was observed across all three doses of darolutamide: 11 (29%) patients in the 200 mg arm, 13 (33%) patients in the 400 mg arm, and 11 (33%) patients in the 1400 mg arm[38–40] Based on these encouraging findings, the ARAMIS phase III trial evaluated darolutamide at early stage of the disease, for men with nmCRPC at high risk for developing metastases, defined by PSA-DT of 10 months or less and PSA >2 ng/ml. The trial randomized 1509 patients (955 in the darolutamide group and 554 in the placebo group). The study met its primary endpoint, showing prolonged MFS with darolutamide compared with placebo: median MFS was 40.4 months in the darolutamide group, as compared with 18.4 months in the placebo group (HR 0.41; 95% CI, 0.34–0.50; $p < 0.001$). The benefit of darolutamide was observed for all secondary end points: time to pain progression was prolonged in the darolutamide group (40.3 months *versus* 25.4 months, HR, 0.65; 95% CI, 0.53–0.79; $p < 0.001$), as well as time to PSA progression (33.2 months *versus* 7.3 months; HR, 0.13; 95% CI, 0.11–0.16; $p < 0.001$), time to first cytotoxic chemotherapy and time to first symptomatic skeletal event. The safety profile of darolutamide was favourable with no detectable difference between groups regarding grade 1 or 2 adverse events (54.6% with darolutamide and 54.2% with placebo). Grade 3 or 4 adverse events occurred in 24.7% of patients treated with darolutamide and in 19.5% of those receiving placebo. The incidence of grade 5 adverse events was similar in the two groups (3.9% with darolutamide and 3.2% with placebo) as well as the incidence of seizures (0.2% in both groups). The incidence of fatigue was slightly higher with darolutamide (12.1% *versus* 8.7%), and this mild difference disappeared when adjusted for duration of use. Incidences of other adverse events of interest, including hypertension, rash, dizziness, and cognitive disorder, did not differ between the two treatment-groups.[41] Data on quality of life have been reported and darolutamide showed delay of time to pain progression (HR 0.65, $p < 0.0001$) and disease-related symptoms (HR 0.80, $p = 0.0005$) compared with placebo.[42] In May 2020 final results on OS were presented and showed a statistically significant 31% reduction in the risk of death (95% CI 0.53–0.88; $p = 0.003$), with also confirmed benefits in time to pain progression,

Table 1. Phase III trials of next-generation AR inhibitors for nonmetastatic castration-resistant prostate cancer.

Phase III trial	Enzalutamide	Apalutamide	Darolutamide
	Prosper	**Spartan**	**Aramis**
Trial design	Enzalutamide *versus* Placebo Randomization 2:1	Apalutamide *versus* Placebo Randomization 2:1	Darolutamide *versus* placebo Randomization 2/1
Pelvic nodes status	No pelvic nodes allowed	Pelvic nodes <2 cm below iliac bifurcation allowed	Pelvic nodes <2 cm below aortic bifurcation allowed
Dosage	240 mg po once daily	160 mg po once daily	600 mg po twice daily
Number (patients)	1207	1401	1509
Median time to PSA progression (months)	37.2 *versus* 3.9	NR *versus* 3.7	33.2 *versus* 7.3
>50% PSA response rate (%)	76 *versus* 2	89.7 *versus* 2.2	NA
Metastasis-free survival *versus* Placebo (months)	36.6 *versus* 14.7	40.5 *versus* 16.2	40.4 *versus* 18.5
Progression free survival (months)	Not assessed	40.5 *versus* 14.7	36.8 *versus* 14.8
Overall survival (months)	NR in both arms	NR *versus* 39	NR in both arms
Any adverse event (%)	87 *versus* 77	96.5 *versus* 93.2	83.2 *versus* 76.9
Grade 3 adverse events (%)	31 *versus* 23	45.1 *versus* 34.2	24.7 *versus* 19.5
Status	EMA approved FDA approved	EMA approved FDA approved	EMA approved FDA approved

EMA, European Medicines Agency; FDA, Food and Drug Administration; NA, not assessed; NR, not reached.

time to first cytotoxic chemotherapy, and time to first symptomatic skeletal event.[43,44]

Discussion

Until 2018, there were no approved treatments for men with nmCRPC, but three agents have recently been shown to postpone the onset of metastases and death in these patients (Table 1). Apalutamide and enzalutamide received an approval from EMA and FDA for men with nmCRPC who are at high risk of metastases (PSA-DT <10 months and PSA >2 ng/ml). Darolutamide received an approval from FDA for nmCRPC without restriction on PSA level. The final results of these studies regarding OS and clinically relevant endpoints such as the development of pain or skeletal-related events confirmed their major role in the landscape of nonmetastatic prostate cancer care. Another next-generation AR axis inhibitor, AA, has been evaluated in the nmCRPC setting for patients considered at high risk for progression to metastatic disease (PSA ⩾10 ng/ml, or PSA doubling time 10 months or less). Despite positive results on the primary endpoint of a phase II trial (86.9% of the patients achieved a 50% or greater PSA reduction, $p < 0.0001$), no randomized phase III trial testing AA has been conducted in men with nmCRPC and therefore it is not approved in this indication.[45]

The challenge of how to choose between these agents remains at this time.[46] Different variables including cost, patient preference and side effects will likely have to be taken into account for decision-making. The apparently better tolerance observed with the use of darolutamide may plead for its use, especially in elderly and frailer patients, although direct comparison will be needed to assert this.[47] However, the different incidence of side effects reported in placebo control arms in the three trials (Table 2) highlights the likely different assessments used in the trials. In this regard, studies of patient preference such as the ODENZA study (NCT03314324) and large-scale routine survey data will be useful. Another important consideration when selecting an AR-targeting therapy

Table 2. Adverse events in the three pivotal trials.

	Enzalutamide				Apalutamide				Darolutamide			
	PROSPER trial				SPARTAN trial				ARAMIS trial			
	Enzalutamide group *n* = 930		Placebo group *n* = 465		Apalutamide group *n* = 803		Placebo group *n* = 398		Darolutamide group *n* = 954		Placebo group *n* = 554	
	All grades	Grades ⩾3	All grades	Grades ⩾3	All grades	Grades ⩾3	All grades	Grades ⩾3	All grades	Grades ⩾3	All grades	Grades ⩾3
Any adverse	808 (87)	292 (31)	360 (77)	109 (23)	775 (96.5)	362 (45.1)	371 (93.2)	136	794 (83.2)	236 (24.7)	426 (76.9)	108 (19.5)
Any serious	226 (24)	–	85 (18)	–	199 (24.8)	–	92 (23.1)	–	237 (24.8)	151 (15.8)	111 (20.0)	70 (12.6)
Fatigue	303 (33)	27 (3)	64 (14)	3 (1)	244 (30.4)	7 (0.9)	84 (21.1)	1 (0.3)	115 (12.1)	4 (0.4)	48 (8.7)	5 (0.9)
Nausea	106 (11)	3 (<&°	40 (9)	0	1645 (18.1)	0	63 (15.8)	0	48 (5.0)	2 (0.2)	32 (5.8)	0
Hypertension	111 (12)	43 (5)	24 (5)	10 (2)	199 (24.8)	115 (14.3)	79 (19.8)	47 (11.8)	63 (6.6)	30 (3.1)	29 (5.2)	12 (2.2)
Falls	106 (11)	12 (1)	19 (4)	3 (1)	125 (15.6)	14 (1.7)	36 (9.0)	3 (0.8)	40 (4.2)	8 (0.8)	26 (4.7)	4 (0.7)
Arthralgia	78 (8)	1 (<1)	132 (7)	1 (<1)	128 (15.9)	0	30 (7.5)	0	77 (8.1)	3 (0.3)	51 (9.2)	2 (0.4)
Diarrhoea	91 (10)	3 (<1)	45 (10)	2 (<1)	163 (20.3)	8 (1.0)	60 (15.1)	2 (0.5)	66 (6.9)	0	31 (5.6)	1 (0.2)
Weight loss	55 (6)	2 (1)	7 (2)	0	129 (16.1)	9 (1.1)	25 (6.3)	1 (0.3)	34 (3.6)	0	12 (2.2)	0
Mental*	48 (5)	1 (<1)	9 (2)	0	41 (;&°	0	12 (3.0)	0	9 (0.9)	0	9 (1.6)	0
Seizure	3 (<1)	2 (<1)	0	0	2 (0.2)	0	0	0	2 (0.2)	0	1 (0.2)	0

*This adverse event includes cognitive disorder, memory impairment, amnesia, disturbance in attention and change in mental status.

in this population with frequent co-medications is the potential drug–drug interaction (DDI) that could lead to a lower efficacy of treatment for comorbidities, or an increased risk of their adverse events. Darolutamide has shown a favourable DDI profile,[48] whereas other AR inhibitors have large numbers of potential DDIs.[49] Whether sequential use of several AR antagonists may prove beneficial to the patient (e.g. first for nmCPRC and then for mCRPC after radiographical progression) is unlikely, given the current knowledge.[50]

Most crucial is the question of the means employed to discriminate between nmCRPC and mCRPC. In all three pivotal phase III trials of novel AR inhibitors in nmCRPC, morphological staging resorted to CT scan and conventional bone scan. Indeed, these were the universally available radiological exams for prostate cancer at the time these trials were launched. However, several novel radionuclide imaging modalities with higher sensitivity for metastasis detection, such as C11-choline positron emission tomography (PET) or Ga68-PSMA-PET, are now becoming available. A study assessing disease extent detected by PSMA-PET in 200 high-risk patients with CRPC defined as non-metastatic by conventional imaging showed a PSMA-PET imaging positive in 98% of patients: 24% of patients had disease confined to the prostate bed, 44% had disease limited to the pelvis, and 55% had M1 disease.[51] These novel PET imaging approaches will narrow down the number of patients with nmCRPC, leaving the clinician to choose between furthering imaging explorations to detect metastasis and rapidly treating classically-defined nmCRPC. This is of importance considering the still-limited access to these tests and the sometimes narrow window of opportunity to treat nmCRPC before the onset of metastases. Also, the overlapping therapeutic options between nmCRPC and mCRPC (e.g. with enzalutamide) may well render this issue questionable. In any case, it will be crucial to pay attention to the means employed to define each clinical setting in pivotal trials; then we would not prescribe 'off-label' medications with less certain benefit for the patient in the routine setting. Of importance, all three agents are approved on a basis of a negative bone scan and CT scan: this remains the case if a next-generation imaging method identifies the site of progression.

The therapeutic landscape of CRPC will probably continue to evolve rapidly as future clinical trials may change again its management. The possibility of local treatments directed against local relapse or metastatic site to treat oligo-metastatic disease remains questionable and has to be randomly investigated.[52] Genomic analysis may allow pursuing precision medicine in this heterogeneous population. Olaparib has recently shown significant benefit for men with metastatic resistant prostate cancer when harbouring alteration in genes with a role in homologous recombination repair.[53] Its clinical benefit in earlier setting for nmCRPC patients is currently unknown.

In the absence of biopsiable target in men with nmCRPC, biomarkers may be assessed on circulating tumour cells or circulating tumoir DNA to help tailor treatment according to individual characteristics of the tumour.

Conclusion

Non-metastatic CRPC is a state defined by rising PSA and no metastasis on conventional imaging. Apalutamide, darolutamide and enzalutamide have recently been shown to postpone the onset of metastases and death in these patients and have received FDA approval. Integration of novel PET imaging may redefine the management of prostate cancer in this setting of low-burden CRPC.

Conflict of interest statement

Pernelle Lavaud: Ipsen, Janssen, Astellas, Astra Zeneca, Mundi Pharma

Clément Dumont: Ipsen

ConstanceThibault: Astellas, Janssen,Pfizer, Sanofi, Ipsen, Astra Zeneca, Amgen

Laurence Albiges: Pfizer, Novartis, Merck, Astra Zeneca, MSD, Roche, Ipsen, Bristol Myer Squibb, Astellas, Exeliquis, Amgen, Peloton therapeutics, Corvus Pharmaceuticals

Giulia Baciarello: Amgen, Janssen Oncology, Sanofi, Roche, Europharma, Modra Pharmaceuticals, Astellas, Pharma, Astra Zeneca, Ipsen,

Emeline Colomba: Ipsen, BMS GSK Pfizer Sanofi

Ronan Flippot: BMS

Alina Fuerea: none

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