Real Life Use of Bone-Targeting Agents for Bone Metastases in France: the OPTIMOS study

Confavreux C[a], Bouvard B[b], Girard N[c], Bosco-Levy P[d], Marchal C[e], Walter M[e], Lehmann E[f], Désaméricq G[f], Belhassen M[e]

[a] INSERM UMR1033 - Université Claude Bernard Lyon I - Centre Expert des Métastases Osseuses (CEMOS), Hôpital Lyon Sud, Hospices Civils de Lyon, Lyon, France; [b] Service de Rhumatologie du CHU Angers - Univ d'Angers - Nantes, Oniris, INSERM, Médecine Régénérative et Squelette, RMeS, UMR 1229, Angers, France; [c] Institut Curie, Paris - Paris Saclay, UVSQ, Versailles, France; [d] Bordeaux PharmacoEpi, INSERM CIC-P 1401, Université de Bordeaux, Bordeaux, France; [e] Pharmaco-Epidémiologie Lyon (PELyon), Lyon, France; [f] Amgen France, Boulogne Billancourt, France

INTRODUCTION

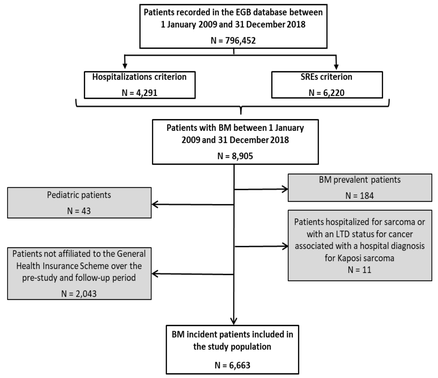
- Bone metastases (BM) are responsible for severe skeletal complications such as pathologic fractures, spinal cord compression, preventive bone surgery and severe bone pain requiring palliative radiotherapy (*Confavreux* et al, 2019). These complications are associated with altered quality of life, drug interruption and heavy costs (*Decroisette* et al. 2011).
- Bone-targeting agents (BTAs) reduce skeletal morbidity from metastatic bone disease and are used in patients with BMs across several tumor types. For most patients, whether symptomatic or not, clinical guidelines recommend starting a BTA as soon as BMs are diagnosed (*Coleman* et al. 2020).
- Progress in oncology improved survival of bone metastatic (BM) patients highlighting bone health issue.
- We aimed to describe recent use of BTA in BM patients in France.

METHODS

- We accessed EGB, a French National Health Insurance database corresponding to 1/97 of the whole population (*Bezin* et al, 2017).
- The algorithm identified adult BM patients either through BM ICD-10 hospitalization code or through the onset of a skeletal-related event (SRE): pathologic fracture, cimentoplasty, spondyloplasty, spinal cord compression, palliative radiotherapy, orthopaedic surgery and malignant hypercalcemia.
- Inclusion date corresponded to the date of the first diagnosis of BM recorded between 2009 and 2018.
- Inclusion period covered the years 2009-2018.
- Patients not affiliated to the general health system and patients with primary sarcoma or with prevalent BM during the 3 years preceding inclusion date, have been excluded.
- Dispensations of clodronate, IV bisphosphonates (zoledronate, pamidronate- IVBP) and denosumab (Dmab), the BTA marketed in France, were recorded.
- Discontinuation was defined as absence of dispensation of more than 30 days after the end of coverage period.
- Initiation of BTAs was split between early initiation (within 100 days) and late initiation (≥ 100 days) after the date of BM diagnosis.

RESULTS

Figure 1: Flowchart to identify BM incident patients



Characteristics of the overall population

- We identified 6663 new BM patients over the period.
- The median [Q1-Q3] follow-up was 1.3 yrs [0.3-3.4] mainly interrupted by death (63.5%) or end of study (35.6%).

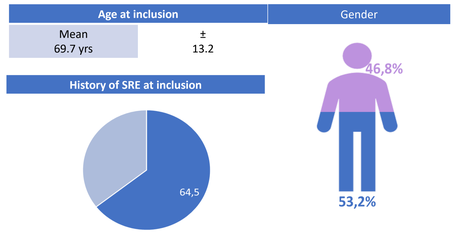


Figure 2. Repartition of the primary cancer site in the overall population (grey) and in the group of patients initiating BTA (blue).

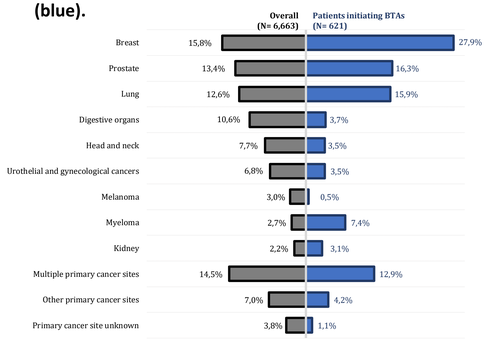


Table 1: Clinical characteristics of the patients according to the main primary cancer site

	Breast N=1,053		Lung N=839		Prostate N=890		Digestive organs N=707	
Male, n (%)	0	0%	579	69.0%	890	100%	392	55.4%
Age at inclusion date (in years)								
Median (Q1 - Q3)	69.0 (58.0-80.0)		66.0 (58.0-75.0)		75.0 (68.0-82.0)		72.0 (63.0-80.0)	
Age at inclusion date (in years), n (%)								
18 to 45	89	8.5%	20	2.4%	0	0%	20	2.8%
46 to 55	124	11.8%	116	13.8%	21	2.4%	57	8.1%
56 to 65	229	21.7%	282	33.6%	144	16.2%	156	22.1%
66 to 75	260	24.7%	221	26.3%	286	32.1%	201	28.4%
> 75	351	33.3%	200	23.8%	439	49.3%	273	38.6%
Patients with SREs, n (%)	765	72.6%	375	44.7%	647	72.7%	483	68.3%
Comorbidities at inclusion, n (%)								
Diabetes (type 1 and 2)	141	13.4%	146	17.4%	167	18.8%	123	17.4%
Cardiovascular diseases	388	36.8%	445	53.0%	450	50.6%	378	53.5%
Disabling stroke	35	3.3%	56	6.7%	49	5.5%	31	4.4%
Chronic arterial diseases	32	3.0%	146	17.4%	84	9.4%	68	9.6%
Heart failure, arrhythmias, valvular and severe congenital heart disease	132	12.5%	170	20.3%	168	18.9%	144	20.4%
Severe hypertension	301	28.6%	256	30.5%	287	32.2%	265	37.5%
Coronary heart disease	51	4.8%	115	13.7%	149	16.7%	99	14.0%
Depression	110	10.4%	85	10.1%	57	6.4%	65	9.2%
Osteoporotic fracture*	131	12.4%	42	5.0%	59	6.6%	88	12.4%

*humerus, femur, vertebra, pelvis

BTAs initiation

- After inclusion, only 621 (9.3%) patients initiated BTA (327 received Dmab)
- Median initiation delay was 99 days [37-241] similar in Dmab and IVBP.

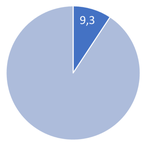


Figure 3. Median duration (Q1-Q3) of denosumab therapy (in days), by primary cancer site.

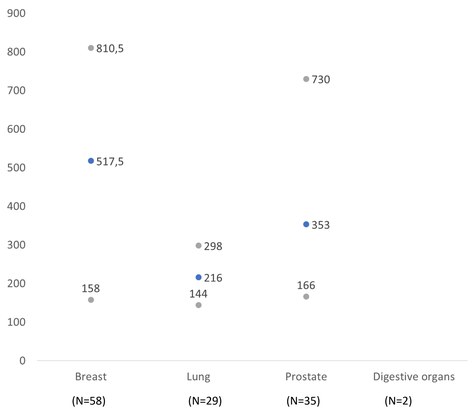
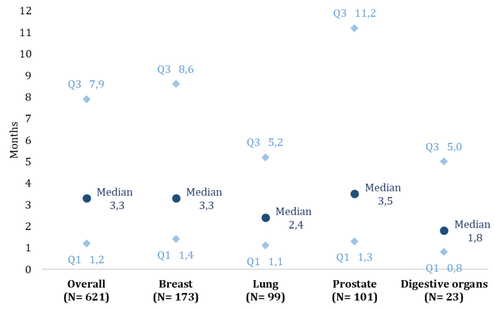


Figure 4. Median (Q1-Q3) delay between BM diagnosis and BTA initiation (in months) in the overall population and by primary cancer site

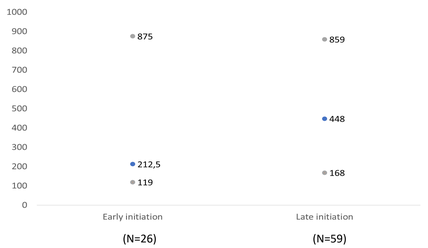


Early versus late BTAs initiation

Table 2. Incidence rate of 2nd SRE in the overall included population.

	Patients initiating BTA	
	Early initiation N=118	Late initiation N=125
Incidence rate of 2nd SRE, 100 person-years [95% CI]	12.9% [8.4% - 18.9%]	20.7% [15.7% - 26.7%]
Cumulative incidence of 2nd SRE (%), [95% CI]		
at 12 months	13.6% [8.1% - 20.4%]	21.6% [14.8% - 29.2%]
at 24 months	16.1% [10.1% - 23.4%]	34.2% [25.9% - 42.7%]
Time between 1st and 2nd event of SRE (in days)		
Number of patients with a 2nd SRE	26 (22,0%)	59 (47,2%)
Median (Q1 - Q3)	212.5 (119.0 - 875.0)	448.0 (168.0 - 859.0)

Figure 5. Median duration (Q1-Q3) between 1st and 2nd SRE event (in days) according to timing of BTA initiation.



- Among patients with only BM diagnosis at inclusion date and with at least one SRE over the follow-up period, the ones with early (<100 days) BTA initiation (N=197 vs 181) had a reduced incidence rate of 2nd SRE (16.6% pers-yrs [8.9-28.4] vs 25.4% [14.5-41,2]).

CONCLUSIONS

- These are the first real life data available in France on BM epidemiology and their BTA treatment.
- Proportion of BM patients treated with BTAs in France is low (9.3%) even in secondary prevention.
- Half of them were not treated within the recommended 3 months after diagnosis.
- Early BTA initiation is more efficient than late initiation.
- Early BTA treatment is efficient to reduce second SRE.
- Our results highlight the need for optimizing BM management in France in accordance to the ESMO guidelines (*Coleman* et al. Annals of Oncology 2020*)*.

REFERENCES

- Bone metastases from lung cancer: A paradigm for multidisciplinary onco-rheumatology management. Confavreux CB et al. Joint Bone Spine. 2019 :185-194.
- Epidemiology and treatment costs of bone metastases from lung cancer: a French prospective, observational, multicenter study (GFPC 0601). Decroisette C et al. J Thorac Oncol. 2011 :576-82
- Bone health in cancer: ESMO clinical practice guidelines. Coleman R, Hadji P, Body J-J, et al. Annals of Oncology 2020;31:1650–63.
- The national healthcare system claims databases in France, SNIIRAM and EGB: Powerful tools for pharmacoepidemiology. Bezin J et al. Pharmacoepidemiol Drug Saf. 2017 : 954-962

DISCLOSURE INFORMATION

- This study has been funded by AMGEN.
- LE and DG own shares and are full-time employees from Amgen.
- BM, MC and WM are full-time employees from PELyon.
- CC received research grant from AMGEN FOUNDATION and MSD AVENIR.

Comments on reclassification

Multiple cancers were identified from diagnoses of "malignant neoplasms of independent (primary) multiple sites" recorded in LTD status or from main, related and associated discharge diagnoses from hospital (ICD-10 code C97).
If more than one primary cancer site was identified over the pre-study period or six months after inclusion (on the same day or during two different hospitalizations), the patient was also classified in the "multiple cancers" category.
Patients presenting a lung cancer and a cancer in another site were classified according to the site of the other cancer (the assumption was that the diagnosis of lung cancer was in fact a lung metastasis).
Patients presenting a site unknown and a cancer in another site were classified according to the site of the other cancer (the assumption was that the diagnosis of unknown site was in fact a transition state before knowing the real site).