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MASITINIB IN PANCREATIC CANCER

11 December 2020

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Presenting KOL

Julien Taieb, MD, PhD

Juline Taieb is Head of the Gastroenterology and Gastrointestinal Oncology Department at the Georges Pompidou European Hospital, Sorbonne Paris-Cité, Université Paris-Descartes. He is a regular reviewer for *Lancet Oncology*, *Journal of Clinical Oncology*, *Annals of Oncology*, and the *European Journal of Cancer*. Professor Taieb is a member of the European Society for Medical Oncology (ESMO), the American Society of Clinical Oncology, and a number of French gastrointestinal cooperative groups and societies. He has a position in the administrative council or the scientific committee of ESMO, FFCD and SNFGE. He is a member of ESMO nomination Committee since 2018. His main research topics are non-metastatic and metastatic colon cancer and pancreatic cancer. Particularly involved in clinical trials and translational research, Prof Taieb has led more than 10 national and international phase II and III studies and has authored 3 educational books, more than 200 peer reviewed publications and 500 meeting abstracts.

Oliver HERMINE, MD, PhD

Olivier Hermine is Professor of Hematology at Paris V-René Descartes University, Chief of adults Hematology staff at Hospital Necker (Paris), member of the French *Académie des Sciences* and author of over 700 international publications. He is founder and coordinator of the reference center of mastocytosis (CEREMAST). Olivier Hermine is also co-founder of AB Science and head of its scientific committee.

Scientific Rationale

Innate immune cells, in particular mast cells and macrophages, are critical components of the tumor microenvironment, promoting angiogenesis and tumor growth, and also contributing to tumorigenesis by suppression of the immune response

- **There is a compelling body of evidence implicating mast cells in the orchestration of tumor microenvironment remodeling and specifically pancreatic cancer cell proliferation, invasion, and metastasis.**
- **An intense crosstalk between mast cells and pancreatic cancer cells contributes to the pancreatic ductal adenocarcinoma progression. Mast cells contribute to the aggressiveness of the pancreatic ductal carcinoma enhancing the expression of several pro-angiogenic factors [1].**
- **Mast cell activity within the tumor microenvironment promotes disease progression via release of numerous pro-tumoral factors [2–7].**
- **Increased mast cell infiltration into the tumor is known to promote disease progression and is a prognostic factor for poor survival in pancreatic ductal adenocarcinoma patients [8–15].**
- **Mast cells down-regulate the immune response to tumors and skew polarization of tumor-associated macrophages (TAM) towards a pro-tumoral macrophage type-2 (M2) [16–21].**
- **Masitinib's highly selective inhibition of mast cell survival and activation modulates mast cell related remodeling of the tumor microenvironment, thereby inhibiting tumor growth and also redirects the immune system toward an anti-tumoral TH1-type response**

References
[1] Longo V, et al. Clin Exp Med. 2018 Aug;18(3):319-323; [2] Komi DEA, et al. Clin Rev Allergy Immunol. 2020;58(3):313-325; [3] Aponte-López A, et al. Adv Exp Med Biol. 2020;1273:159-173; [4] Liu CY, et al. Lab Invest. Jul 2013;93(7):844-854; [5] Dyduch G, et al. Pol J Pathol. Mar 2012;63(1):1-7; [6] Khazaie K, et al. Cancer Metastasis Rev. Mar 2011;30(1):45-60; [7] Theoharides TC. N Engl J Med. Apr 24 2008;358(17):1860-1861; [8] Ammendola M, et al. Oncotarget. 2017;8(41):70463-70471; [9] Protti MP, et al. Front Physiol. 2013;4:210; [10] Ma Y, et al. Cancer Res. Jul 1 2013;73(13):3927-3937; [11] Cai SW, et al. Surgery. Apr 2011;149(4):576-584; [12] Chang DZ, et al. Clin Cancer Res. Nov 15 2011;17(22):7015-7023;13(10):1211-1218. [13] Strouch MJ, et al. Clin Cancer Res. Apr 15 2010;16(8):2257-2265; [14] Soucek L, et al. Nat Med. Oct 2007; [15] Ribatti D, et al. Br J Haematol. Dec 2001;115(3):514-521; [16] Padoan et al. Int J Mol Sci. 2019 Feb 5;20(3):676; [17] Vilalou et al. Cytokine Growth Factor Rev. 2018;39:46-61; [18] Evans A, et al. Front Physiol. 2012;3:270; [19] Dyduch G, et al. Pol J Pathol. Mar 2012;63(1):1-7.26; [20] Maltby S, et al. Biochim Biophys Acta. Aug 2009;1796(1):19-26; [21] Christy AL, et al. J Immunol. Sep 1 2007;179(5):2673-2679.

Scientific Rationale

The presence of pain in pancreatic cancer is thought to flag an increased mast cell activity within the tumor microenvironment, which in turn promotes disease progression. Pain therefore effectively identifies those patients with a pro-tumoral immune response

- **There is evidence that mast cell degranulation mediates cancer-induced pain and that pain is a clinical predictor of poor prognosis in pancreatic cancer.**
- **Mast cell infiltration is strongly implicated with development of neuropathic pain in pancreatic ductal adenocarcinoma patients [1].**
- **Mast cells contribute to pancreatic carcinoma-induced visceral hypersensitivity through enrichment and degranulation in pericarcinoma tissues [2].**
- **Mast cells within the cancer microenvironment potentiate and prolong protease-induced cancer pain [3].**
- **Considerable neural remodeling of intrapancreatic nerves is observed in pancreatic ductal adenocarcinoma patients experiencing pain and perineural invasion has also detected in the early stages of pancreatic cancer, which is associated with pain, increased tumor recurrence and diminished overall survival [4,5].**
- **Pain intensity correlates to disease progression and significantly poorer survival rate in pancreatic cancer [5-10]**

References
[1] Demir IE, et al. PLoS One. 2013;8(3):e60529; [2] Yu D, et al. J Mol Neurosci. 2019;69(2):235-245. [3] Lam DK, et al. Pain. 2010;149(2):263-272; [4] Gasparini G, et al. Cancers (Basel). 2019;11(7):893; [5] Ceyhan GO, et al. Gastroenterology. 2009;136(1):177-186.e1; [6] Morizane C, et al. Pancreas. Apr 2012;40(3):415-421; [7] Vickers MM, et al. Eur J Cancer. Jul 2012;48(10):1434-1442; [8] Watanabe I, et al. Pancreas. Mar 2004;28(2):160-165; [9] Okusaka T, et al. Pancreas. Apr 2001;22(3):279-284; [10] Lindsay TH, et al. Pain. Dec 15 2005;119(1-3):233-246.

Masitinib Profile and Mechanism of Action

Orally-administered kinase inhibitor selectively targeting mast cells and macrophages

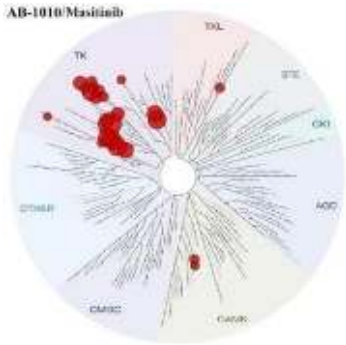
Masitinib targets mast cells

- Masitinib is a potent and selective inhibitor of c-Kit, Lyn, and Fyn kinases. These kinases play critical roles in the activation of mast cells
- Mast cells are a target in neurodegenerative diseases, inflammatory diseases and in oncology

Masitinib targets macrophages/microglia

- Masitinib is a potent and selective inhibitor of MCSFR-1
- Macrophages are a target in oncology. Microglia are a target in amyotrophic lateral sclerosis and Alzheimer's disease.

Kinase inhibition profile of masitinib			
Cellular Target	Molecular Target	IC_{50} [nM]	Kd [µM]
Mast cells	KIT wild-type (WT)	20	0.008
	FYN	240	0.14
	LYN	225	0.061
Macrophages / Microglia	MCSFR-1	90	0.0076

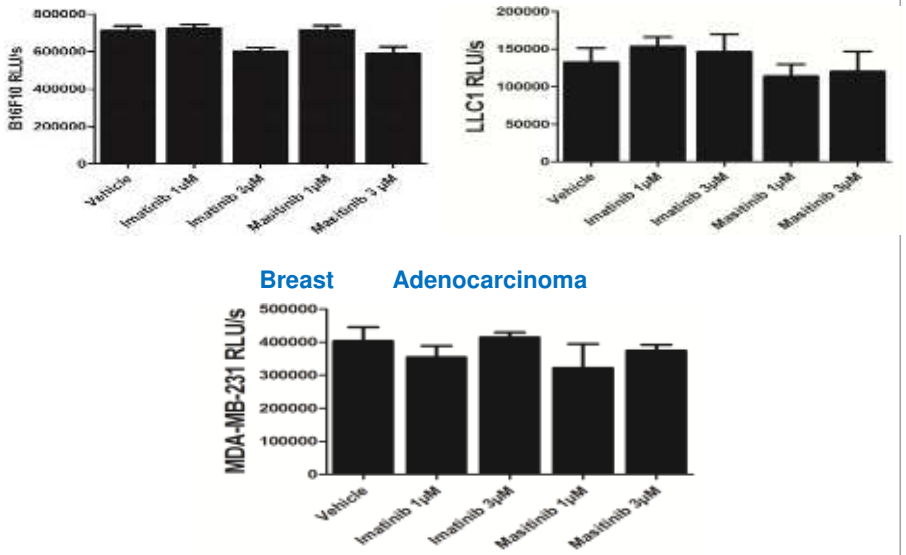


Dubreuil 2009, PLoSONE.4(9):e7258; AB Science. Davis 2011, Nat Biotechnol; 29(11):1046

Pharmacology Data - Masitinib targets tumor microenvronment

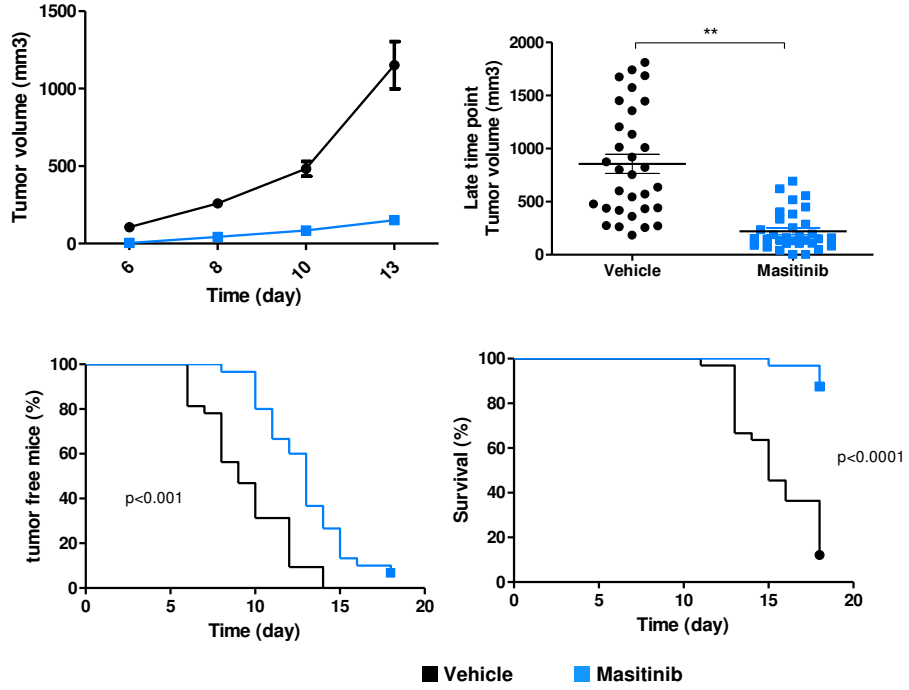
Masitinib has no direct “tumor killer” general activity but has shown efficacy on tumor proliferation in vivo, mediated through the tumor micro-environment

No direct effect on tumor cells *in vitro…*



In vitro, in tumors which are not driven by c -kit or other relevant kinases tyrosine kinase, inhibition by masitinib did not have any direct effect on tumor proliferation

…but decreases tumor volume growth *in vivo*



In vivo, the observed anti-tumor activity is therefore mediated through the tumor micro-environment.

ClinicalTrials.gov Identifier: Pancreatic cancer NCT00789633 & NCT03766295

Masitinib Clinical Development Plan in Pancreatic Cancer

The development program in pancreatic cancer is comprised of one proof of concept study *(published)*, one hypothesis generating study *(published)* and one pivotal study

Phase	Study code	Design	Population	Masitinib Dosing	Primary endpoint	Patient target	Related publications
2	AB05034	Open-label, single arm study	Patients with advanced pancreatic cancer	9.0 mg/kg/day	Time to Tumor Progression (TTP)	22	Mitry, 2010
2/3	AB07012 (NCT00789633)	Prospective, double-blind, placebo-controlled, 2-parallel groups study	Patients with advanced/metastatic pancreatic cancer	9.0 mg/kg/day	Overall survival (OS)	348	Hammel, 2015
3	AB12005 (NCT03766295)	Prospective, double-blind, placebo-controlled, 2-parallel groups study	Patients with non resectable locally advanced or metastatic pancreatic cancer	6.0 mg/kg/day	Overall survival (OS)	377	-

AB07012 Hypothesis generating study

Masitinib did not demonstrate significant overall survival improvement in the overall study population, but demonstrated significant overall survival improvement in patients with pain (marker of mast cell activation) at baseline

	N	Median OS [95% CI] (months)	[a]Median OS Gain (months)	HR [95% CI]	*P*-value
Overall (mITT)	348				
P + G	175	7.0 [6.1;10.6]	+0.7	0.89 [0.70;1.13]	0.695
M + G	173	7.7 [6.1;10.6]			
'Pain' subgroup	137				
P + G	73	5.4 [4.5;8.0]	+2.6	0.62 [0.43;0.89]	0.012
M + G	64	8.0 [5.8;11.5]			

- **Pain decreases survival** : 7.0 months OS in overall population receiving gemcitabine alone, versus 5.4 months in subgroup with pain
- **Masitinib reverses this negative factor :** 7.7 months OS in overall population receiving masitinib, versus 8.0 months in subgroup with pain

Publication:

P Hammel. A randomized, placebo-controlled phase III trial of masitinib plus gemcitabine in the treatment of advanced pancreatic cancer. Ann Oncol. 2015 Jun;26(6):1194-1200.

AB12005 – Study Design

Study AB12005 evaluated masitinib 6.0mg/kg/day in first line pancreatic cancer patients with pain

Design

Design:

Double-blind, 2-parallel Groups, Phase 3 Study to Compare as First Line Therapy Efficacy and Safety of Masitinib in Combination With Gemcitabine, to Gemcitabine in Combination With Placebo, in the Treatment of Patients With Non Resectable Locally Advanced or Metastatic Pancreatic Cancer

Randomisation: 2:1

Planned Enrolment : 377 patients

Primary endpoint: Overall Survival

Secondary endpoints:

- Progression Free Survival according to central RECIST criteria
- Quality of Life
- Pain

Main inclusion criteria

1) Histologically or cytologically confirmed adenocarcinoma of the pancreas, non resectable locally advanced or metastatic stage

2) Patient with pain related to the disease:

- Pain defined as clinical and documented evaluation by the investigator during physical examinations.
- Pain, as assessed by the patient is defined as Visual Analogue Scale > 20mm

OR

- Patient treated with opioid analgesics at a dose ≥ 1 mg/kg/day (morphinic equivalent).

3) Chemotherapy naïve patient for the advanced/metastatic disease

AB12005 – Study Design

The primary analysis was prespecified in both the overall population and locally advanced tumors each tested at 2.5% level of significance

Pre-specified Analysis Plan

Statistical analysis: Alpha spending split between the overall population (2.5%) and locally advanced subgroup (2.5%).

Stratification factors

- Patients with locally advanced pancreatic cancer versus patients with metastatic pancreatic cancer (only for the overall population)
- ECOG grade 0 versus grade 1 versus grade 2
- Country

Populations analysed

- Primary analysis : mITT

  The mITT population will include all ITT patients with pancreatic cancer satisfying the pain criteria (VAS > 20 and/or patients treated with opioid analgesics' dose ≥ 1 mg/kg/day at baseline) who took at least one dose of study treatment (masitinib/placebo)

Patient disposition (57 sites in 12 countries, incl. 6 EU countries)

Analysis Population	Overall Population	Locally advanced
ITT Population	383	92
One patient without study treatment excluded		
Safety Population	382	92
Three patients without pain excluded		
Modified Intention to Treatment(mITT)	379	92

AB12005 – Baseline Characteristics

Overall Population

	Masitinib (N = 246) n (%)	Placebo (N = 137) n (%)
Age (Years)		
Mean (std)	61.5 (8.95)	61.9 (8.44)
Median	62.0	62.0
Sex [n (%)]		
Male	132 (53.7)	76 (55.5)
Female	114 (46.3)	61 (44.5)
ECOG		
0	26 (10.6)	15 (10.9)
1	211 (85.8)	118 (86.1)
2	9 (3.7)	4 (2.9)
CA19-9		
Mean (std)	12 033 (67320)	4181.0 (11 699)
Median	413.7	275.8
Albumin		
Mean (std)	41.3 (4.64)	42.2 (5.38)
Median	41.8	43.0

Locally advanced

	Masitinib (N = 62) n (%)	Placebo (N = 30) n (%)
Age (Years)		
Mean (std)	61.2 (8.51)	63.4 (10.65)
Median	61.5	66.5
Sex [n (%)]		
Male	28 (45.2)	15 (50.0)
Female	34 (54.8)	15 (50.0)
ECOG		
0	8 (12.9)	1 (3.3)
1	52 (83.9)	29 (96.7)
2	2 (3.2)	
CA19-9		
Mean (std)	686 (1263)	871 (1386)
Median	194.0	258.0
Albumin		
Mean (std)	42.1 (3.63)	43.6 (3.99)
Median	42.4	43.8

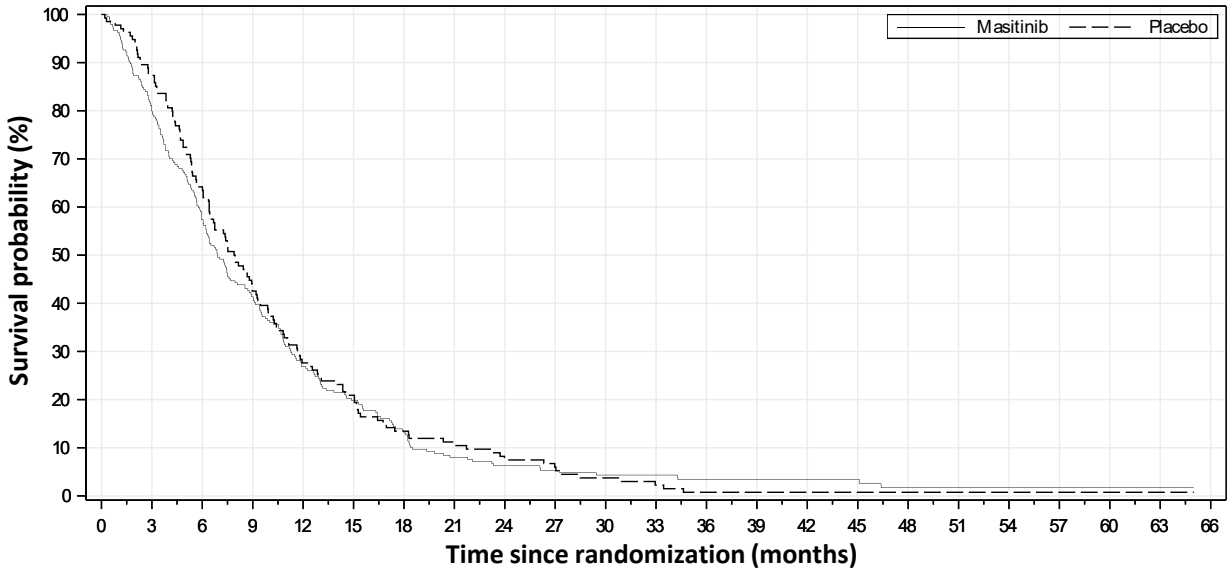
AB12005 – Overall Survival

There was no benefit in the overall population, yet the study met its primary endpoint with significant OS increase (+1.8 months median, p=0.007, below 2.5%) in population with locally advanced tumors

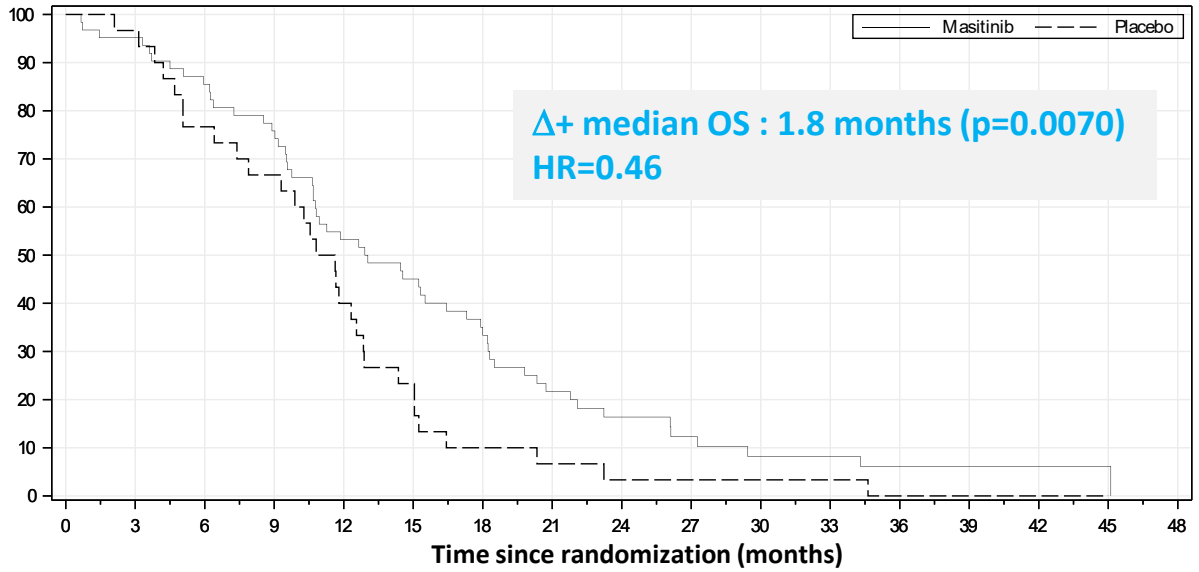
No benefit on survival in the Overall Population

54% risk reduction of time to death in locally advanced

Overall Population – KM Analysis of Overall Survival - mITT



Locally advanced – KM Analysis of Overall Survival



					p-value	Hazard	
Treatment group	Total	No. of Events	% censored	Median 97.5% CI	Log Rank	Ratio (97.5 CI)	p-Value
Masitinib	244	235	3.69	6.9 [6.1;8.1]	0.4614	1.16 (0.9,1.4)	0.1844
Placebo	135	133	1.48	8.0 [6.4;9.2]			

					p-value	Hazard	
Treatment group	Total	No. of Events	% censored	Median 97.5% CI	Log Rank	Ratio (97.5 CI)	p-Value
Masitinib	62	57	8.06	13.0 [11; 18]	0.0070	0.46 (0. .2,0.9)	0.0047
Placebo	30	30	0.00	11.2 [7.4; 13]			

AB12005 – Survival rate

18-month survival rates was 33.9% with masitinib versus 10.0% with the control arm, and 2-year survival rate was 14.5% with masitinib versus 3.3% with the control arm in population, with locally advanced tumors

4.4 fold increase in 2-year survival rate in locally advanced

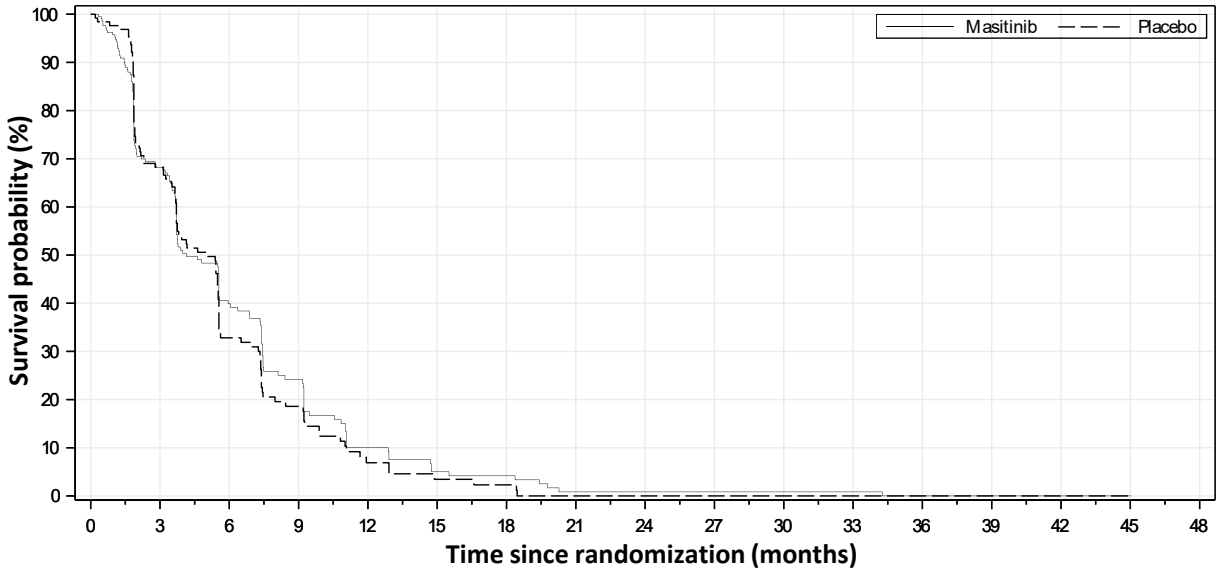
Survival rate	Masitinib	Placebo	Ratio of improvement
6 months	85.5	76.7	**1.1**
12 months	53.2	40.0	**1.3**
18 months	33.9	10.0	**3.4**
24 months	14.5	3.3	**4.4**

AB12005 – Progression Free Survival

PFS was consistent with survival results, with significant PFS increase (+1.8 months, p=0.0391) in the pre-specified population with locally advanced tumors and no benefit in overall population

No benefit on PFS in the Overall Population

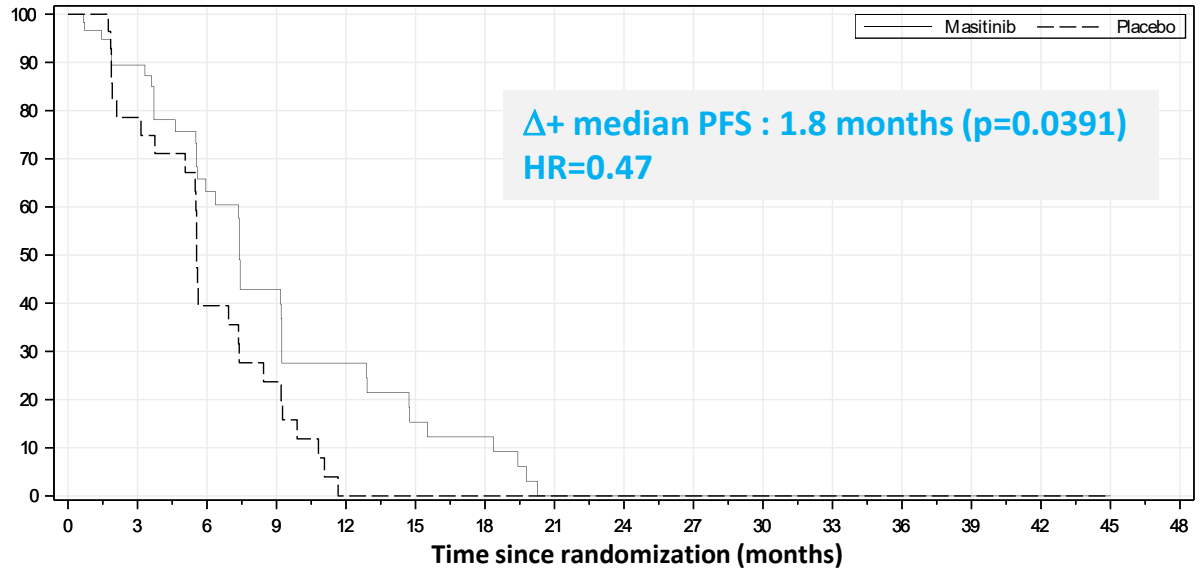
Overall Population – KM Analysis of PFS - mITT



					p-value	Hazard	
Treatment group	Total	No. of Events	% censored	Median 95% CI	Log Rank	Ratio (CI)	p-Value
Masitinib	244	157	35.66	4.1 [3.7;5.6]	0.9604	1.00 (0.8,1.3)	0.9788
Placebo	135	113	16.30	5.1 [3.7;5.5]			

53% risk reduction of time to progression in locally advanced

Locally advanced – KM Analysis of PFS



					p-value	Hazard	
Treatment group	Total	No. of Events	% censored	Median 95% CI	Log Rank	Ratio (CI)	p-Value
Masitinib	62	38	38.71	7.4 [5.6;9.2]	0.0391	0.47 (0.3,0.9)	0.0136
Placebo	30	26	13.33	5.6 [5.1;7.4]			

AB12005 – Response rate

Response rate was in favor of masitinib and consistent with PFS and survival results

1 complete response in the Overall population, ORR 8.2% (M) vs 5.9% (P)

Best Response	Masitinib	Placebo
Complete Response	**1 (0.41%)**	-
Partial Response	**20 (8.20%)**	**8 (5.93%)**
Stable Disease	129 (52.9%)	81 (60.0%)
Progressive Disease	35 (14.3%)	29 (21.5%)
No post-baseline	59 (24.2%)	17 (12.6%)

ORR 14.5% (M) vs 3.3% (P) in locally advanced

Best Response	Masitinib	Placebo
Complete Response	-	-
Partial Response	**9 (14.5%)**	**1 (3.33%)**
Stable Disease	43 (69.4%)	21 (70.0%)
Progressive Disease	3 (4.84%)	6 (20.0%)
No post-baseline	7 (11.3%)	2 (6.67%)

ORR : Objective Response rate

CR : Complete response

PR : Partial response

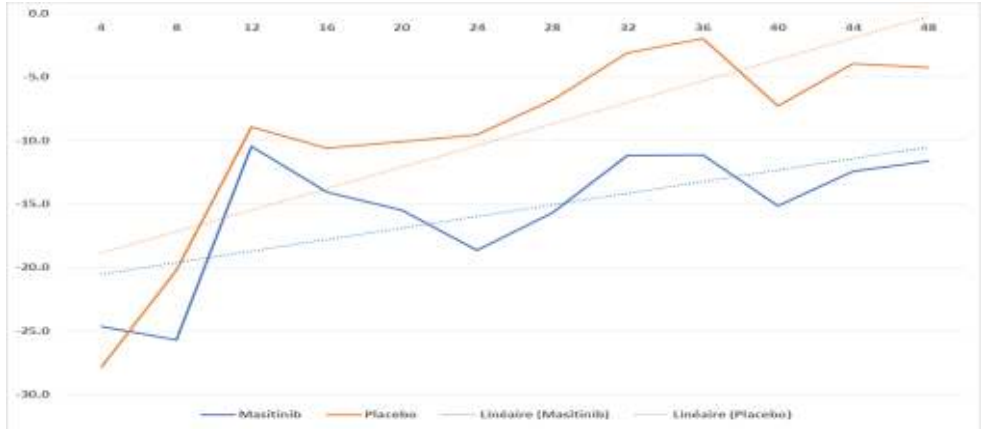
ORR = CR + PR

AB12005 – Pain

Masitinib reduced pain in patients with locally advanced tumors, supporting the rationale for targeting this population having pain at baseline

Numerical improvement vs control in pain in overall population

Overall Population – Change from baseline in VAS (LS Mean) - mITT

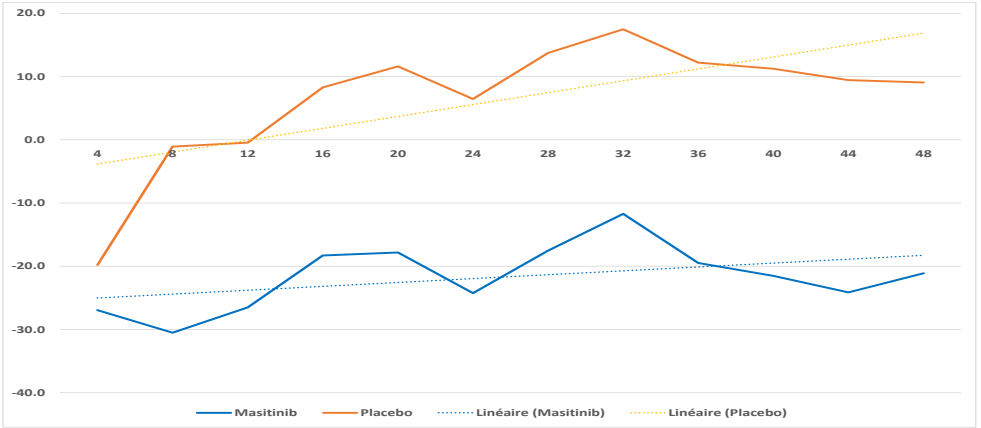


VISIT	4	8	12	16	20	24
Masitinib	-24.6	-25.7	-10.5	-14.0	-15.5	-18.6
Placebo	-27.8	-20.2	-8.9	-10.6	-10.1	-9.5
M-P	3.2	-5.5	-1.5	-3.5	-5.4	-9.1
p-Value	0.477	0.379	0.827	0.596	0.402	0.167
Std Error (CI)	4.5 (-5.6, 12.0)	6.2 (-17.8, 6.8)	7.01 (-15.4, 12.3)	6.50 (-16.3, 9.3)	6.5 (-18.1, 7.3)	6.6 (-22.0, 3.8)

VISIT	28	32	36	40	44	48
Masitinib	-15.7	-11.2	-11.1	-15.2	-12.4	-11.6
Placebo	-6.8	-3.1	-2.0	-7.3	-3.9	-4.2
M-P	-8.9	-8.1	-9.2	-7.9	-8.5	-7.4
p-Value	0.179	0.224	0.176	0.238	0.210	0.273
Std Error (CI)	6.6 (-21.9, 4.1)	6.6 (-21.1, 5.0)	6.74 (-22.4, 4.1)	6.7 (-21.0, 5.2)	6.8 (-21.8, 4.8)	6.72 (-20.6, 5.8)

Significant improvement vs control in pain in locally advanced

Locally advanced – Change from baseline in VAS (LS Mean)



VISIT	4	8	12	16	20	24
Masitinib	-26.9	-30.5	-26.5	-18.3	-17.8	-24.3
Placebo	-19.8	-1.1	-0.5	8.3	11.6	6.5
M-P	-7.2	-29.4	-26.1	-26.6	-29.4	-30.7
p-Value	0.453	0.060	0.090	0.093	0.059	0.051
Std Error (CI)	9.7 (-26.1, 11.7)	15.4 (-60.2, 1.3)	15.2 (-56.3, 4.2)	15.6 (-57.7, 4.6)	15.3 (-60.0, 1.1)	15.5 (-61.6, 0.2)

VISIT	28	32	36	40	44	48
Masitinib	-17.5	-11.7	-19.5	-21.5	-24.1	-21.1
Placebo	13.7	17.5	12.2	11.2	9.4	9.1
M-P	-31.3	-29.2	-31.7	-32.8	-33.6	-30.2
p-Value	0.047	0.069	0.050	0.046	0.042	0.062
Std Error (CI)	15.4 (-62.1, -.5)	15.8 (-60.7, 2.3)	15.9 (-63.4, -.0)	16.1 (-64.9, -.6)	16.2 (-65.9, -1.2)	**15.93 (-62.0, 1.6)**

AB12005 – Safety

There were fewer AEs, SAEs and severe AEs in the masitinib arm as compared with the control arm

Summary of Adverse Events – Safety population

	Masitinib (N = 246) n (%)	Placebo (N = 136) n (%)
At least one AE	237 (96.3)	135 (99.3)
Fatal AE	46 (18.7)	26 (19.1)
At least one serious AE (non-fatal)	47 (19.1)	29 (21.3)
At least one AE with Grade 3 or 4	184 (74.8)	113 (83.1)
At least one AE leading to study treatment permanent discontinuation (excluding fatal AE)	49 (19.9)	20 (14.7)
At least one AE leading to study treatment temporarily interruption	116 (47.2)	72 (52.9)
At least one AE leading to study treatment dose reduction	55 (22.4)	36 (26.5)

Discussion - Efficacy

Overall Survival (OS) benefit reported in AB12005 study is not biased

- OS increase of +1.8 month is associated with PFS increase of +1.8 month, unlikely to be due to potential second line of treatment
- Median OS of observed in AB12005 control arm is consistent
  - Median OS of 11.2 months observed in AB12005 study for patients receiving gemcitabine alone
  - Median OS in patient with LAPC (not restricted to pain) treated with single agent gemcitabine ranges from 9.2 to 13.6 months

	Prospective, randomized study	Population analyzed	Median OS (months)
Tada et al (2008)	No	45	11.6
Poplin et al (2009)	Yes	27	9.2
Kindler et al (2010)	Yes	45	9.9
Loehrer et al (2011)	Yes	37	9.2
Hammel (2016) - LAP07 Randomized Clinical Trial	Yes	223	13.6

- Pain is a poor prognosis factor and likely to reduce survival

Discussion - Positioning

Masitinib has a different positioning from treatments currently in use

- **Positioning in patients with pain**
  - Difficult to compare AB12005 with other studies
  - Pain is a prognosis factor associated with shorter survival
- **Positioning in unresectable locally advanced pancreatic cancer (LAPC)**
  - Abraxane is registered only in metastatic pancreatic cancer
  - Folfirinox is recommended in metastatic pancreatic cancer, supported by academic data and not registered
  - Gemcitabine remains the only drug with a label for LAPC
- **Positioning vs Folfirinox**
  - One third of patients with LAPC are unfit to receive Folfirinox, mainly aged > 70 years
  - Patients older than 70 are eligible to masitinib
- **Positioning vs Abraxane**
  - In Europe, abraxane is not reimbursed and therefore not frequently used
- **Favorable safety profile**
  - Safety of Masitinib + Gemcitabine combination compared favorably vs Gemcitabine alone
  - Masitinib is not a chemotherapy, unlike Abraxane and Folfirinox, which generate hemato-toxicity, peripheral neuropathy, alopecia, mucosisitis, as reported in the labelling information

Discussion – Next steps

Discussion with health authorities for marketing authorization application

Enough evidence to support filling

- Confirmatory study: Second randomized controlled study of masitinib in pancreatic cancer
- Efficacy assessment based on 92 patients in the claim can be mitigated
  - Prospective study, pre-specified claim
  - Strong statistical significance ($p<0.01$) on primary analysis
  - Medically relevant result with 54% risk reduction of time to death
  - Efficacy endpoint based on survival, which is the gold standard
  - Consistency of results on OS / PFS / Response rate
  - LAPC is still one of the worst prognosis
  - Orphan drug status granted to masitinib in pancreatic cancer
- Safety assessment supported by a large safety database with over 7000 patients enrolled in masitinib clinical program

Favorable Benefit risk

- Significant OS and PFS benefit vs Gemcitabine alone in LAPC
- Safety of Masitinib + Gemcitabine combination compares favorably vs Gemcitabine alone
- High medical need, in particular for patients unfit for combination of chemotherapies

Market potential

Indication	Prevalance	Estimated number of patients with LAPC and pain		Annual cost of drugs registered in similar indication (USD)
		USA	EU Patients	
Pancreatic Cancer	21 / 100,000 [1]	12,000	16,500	Abraxane (240,000) Tarceva (27,000) Erlotinib (6,500)
LAPC *	35% [2;3]			
Pain *	50% [4;5]			

* : expressed as percentage of pancreatic cancer

Source :
Population : https://data.worldbank.org/indicator/SP.POP.TOTL and https://ec.europa.eu/eurostat/web/population-demography-migration-projections/population-data/main-tables

1. National Cancer Institute, Pancreatic Cancer statistics, 2015
2. Suker M, Nuyttens JJ, Eskens FALM, et al. Efficacy and feasibility of stereotactic radiotherapy after folfirinox in patients with locally advanced pancreatic cancer (LAPC-1 trial). EClinicalMedicine. 2019;17:100200. Published 2019 Nov 19. doi:10.1016/j.eclinm.2019.10.013
   <<At the time of diagnosis, approximately 15% of patients have (borderline) resectable disease (stage I or II), while 35% and 50% of patients present with irresectable locally advanced pancreatic cancer (LAPC, stage III) or metastatic disease (stage IV), respectively>>
3. Goto Y, Nakamura A, Ashida R, et al. Clinical evaluation of intensity-modulated radiotherapy for locally advanced pancreatic cancer. Radiat Oncol. 2018;13(1):118. Published 2018 Jun 25. doi:10.1186/s13014-018-1063-5
   <<Approximately 35% of patients with pancreatic cancer have unresectable locally advanced pancreatic cancer (LAPC), and the treatment for them is chemotherapy with or without radiotherapy>>
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