Corporate Presentation

January 2022

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Experienced Management Team

ALAIN MOUSSY

Co-founder and CEO

Former strategic consultant at Booz, Allen & Hamilton and former Head of Corporate Development at Carrefour.
President of AFIRMM, association of mastocytosis patients.

CHRISTIAN FASSOTTE

Global Chief Medical Officer

Medical Doctor. 30 years of experience, including executive position at Sanofi for Medical, Regulatory Affairs and R&D.

OLIVIER HERMINE, MD, PHD

Chairman of Scientific Committee

Member of the French Académie des Sciences and author of 700 international publications

LAURENT GUY

Chief Financial Officer

Former positions in the banking industry (Société Générale and Paribas) and strategy consulting (Accenture).

Investment Highlights

Portfolio based on Diversified and Multiple Late-Stage Programs

Breakthrough mechanism of action

- Lead compound: Masitinib, kinase inhibitor selectively targeting **mast cells and macrophages/microglia**
- New opportunity in viral diseases as masitinib is broad coronavirus 3CL non-peptitomitetic inhibitor that blocks replication of SARS-CoV-2 (*Science. 2021*).
- New compound: AB8939, next generation, synthetic microtubule destabilizer not binding to PgP

Late stage pipeline with Eight positive Phase 2B/3 read outs

CNS Diseases

- Amyotrophic lateral sclerosis (ALS)
- Alzheimer's Disease (AD)
- Multiple sclerosis (primary progressive and secondary progressive)

Inflammatory Diseases

- Mastocytosis (ISM)
- Severe asthma uncontrolled by oral corticosteroids
- Severe asthma uncontrolled by inhaled corticosteroids

Oncology

- Locally advanced pancreatic cancer (LAPC)
- Metastatic prostate cancer (mCRPC)

Strong IP position

- **IP 100% owned** by AB Science

Pipeline

Diversified portfolio with eight positive phase 2B/3 trials

Compound	Therapeutic area	Indication	Preclinical	Phase 1	Phase 2	Phase 2B/3	Confirmatory Phase 3
Masitinib	Neurology Diseases	Amyotrophic Lateral Sclerosis*				First phase 2B/3 completed; 394 patients enrolled. On-going confirmatory study	★
		Alzheimer's Disease*				First phase 2B/3 completed; 720 patients enrolled	
		Progressive forms of Multiple Sclerosis*				First phase 2B/3 completed; 656 patients enrolled	
	Inflammatory Diseases	Indolent Systemic Mastocytosis*				First phase 3 completed; 135 patients enrolled. On-going confirmatory study	★
		MCAS (mast cell activation syndrome)			Authorized phase 2 ★		
		Severe Asthma Uncontrolled with OCS*				First phase 3 completed; 419 patients enrolled	
		Severe Asthma Uncontrolled with ICS*				First phase 3 completed; 347 patients enrolled	
	Oncology	Pancreatic Cancer*				First phase 3 completed; 383 patients enrolled	
		Metastatic Prostate Cancer *				First phase 3 completed; 580 patients enrolled	
	Viral Diseases	Moderate and severe COVID-19 *(anti-inflammatory)*			On-going phase 2 ★		
		Mild and moderate COVID-19 *(anti-viral)*			Authorized phase 2 ★		
AB8939	Oncology	Acute Myeloid Leukemia			Authorized phase 1/2 ★		

** Positive Results Reported* ★ *Active programme (enrolment on-going or study authorized with patient recruitment to be initiated*

MASITINIB

Masitinib Profile and Mechanism of Action

Orally-administered kinase inhibitor selectively targeting mast cells and macrophages

Masitinib targets mast cells

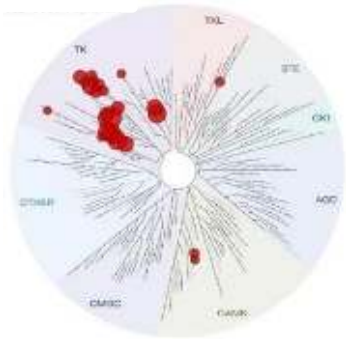
- Masitinib is a potent and selective inhibitor of c-Kit, Lyn, and Fyn kinases. These kinases play critical roles in the activation of mast cells
- Mast cells are a target in neurodegenerative diseases, inflammatory diseases and in oncology

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.

Masitinib is orally administered

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

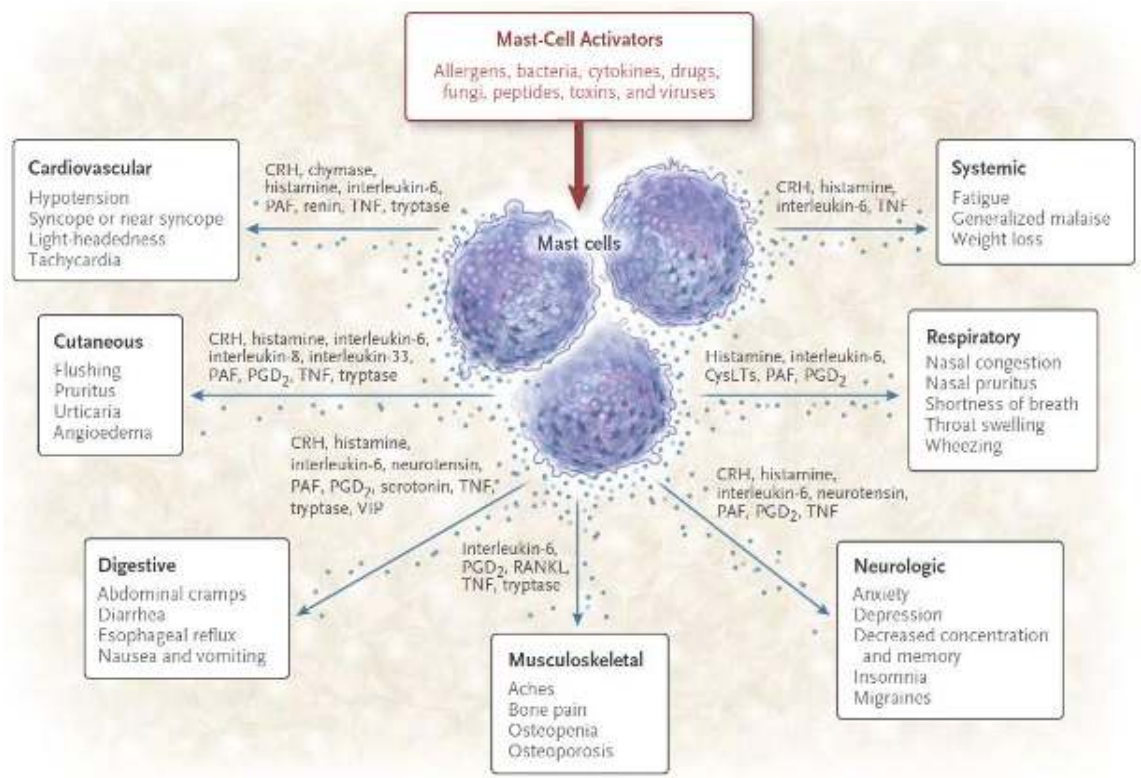


Dubreuil 2009, PLoSONE.4(9):e7258; AB Science. Davis 2011, Nat Biotechnol; 29(11):1046

Critical Role of Mast Cells & Macrophages / Microglia

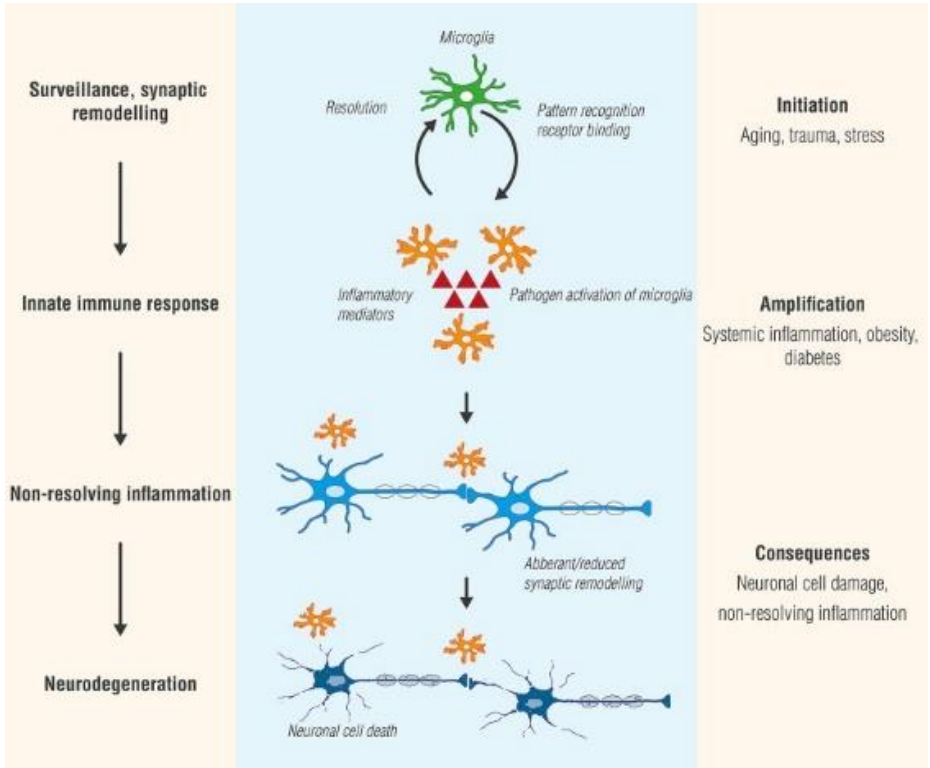
Mast cells and microglia contribute to neuro-inflammation, which is strongly influenced by their potential for mutual interaction and exacerbation of pathology

Activation of mast cells leads to degranulation and secretion of numerous mediators that are thought to contribute to the multiple symptoms observed in patients



Theoharides T., Valent P., Akin C., NEJM 2015. Mast Cells, Mastocytosis, and Related Disorders

Non-resolving neuroinflammation can lead to neuronal cell death



Stephen D. Skaper, Laura Facci, Morena Zusso, and Pietro Giusti. Front Cell Neurosci. 2018; 12: 72. An Inflammation-Centric View of Neurological Disease: Beyond the Neuron

Rationale

The clinical development is primarily based on the targeting of Mast Cells & Macrophages/Microglia

Compound	Therapeutic area	Indication	**Cellular** (Molectular) **Target**
Masitinib	Neurology Diseases	Amyotrophic Lateral Sclerosis	▪ **Mast Cells** (c-Kit, Lyn, Fyn kinases) ▪ **Microglia** (MCSFR-1 kinase)
		Progressive forms of Multiple Sclerosis	
		Alzheimer's Disease	
	Inflammatory Diseases	Indolent Systemic Mastocytosis	▪ **Mast Cells** (c-Kit, Lyn, Fyn kinases)
		Mast Cell Activation Syndrome	
		Severe Asthma Uncontrolled with OCS	
		Severe Asthma Uncontrolled with ICS	
	Oncology	Pancreatic Cancer	▪ **Mast Cells** (c-Kit, Lyn, Fyn kinases) ▪ **Macrophages** (MCSFR-1 kinase)
		Metastatic Prostate Cancer	
	Viral Diseases	Moderate and severe COVID-19 *(anti-inflammatory)*	▪ **Mast Cells** (c-Kit, Lyn, Fyn kinases) ▪ **Macrophages** (MCSFR-1 kinase)
		Mild and moderate COVID-19 *(anti-viral)*	▪ (3CL protease)
AB8939	Oncology	Acute Myeloid Leukemia	▪ (microtubules)

Masitinib Safety Database Across Indications

Well established safety profile with long-term exposure

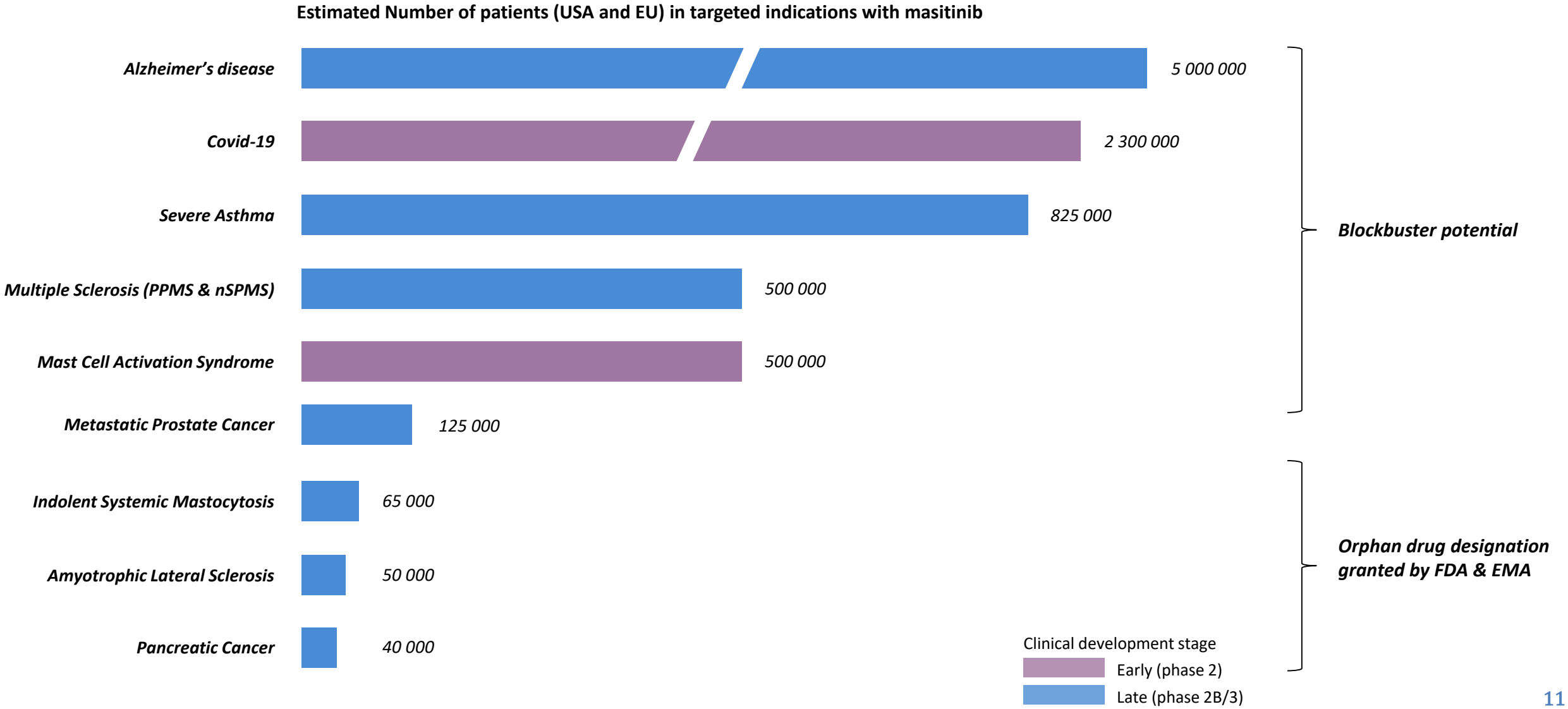
	Safety population	Patients exposed for at least			
	All	≥ 6 months	≥ 12 months	≥ 2 years	≥ 5 years
Healthy Volunteers subjects	114	0	0	0	0
Non Oncology subjects	3,338	2,124	1,519	665	50
Oncology subjects	3,333	1,191	574	221	51
Total	**6,785**	**3,315**	**2,093**	**886**	**101**

Safety profile

- AEs are primarily mild to moderate
- Most common AEs are periorbital edema, anemia, diarrhea, nausea, and vomiting
- AEs primarily occurs in the first 3 months and are usually manageable with dose titration
- Masitinib is suitable for long-term administration, because it is not immunosuppressive

Market Potential

Blockbuster potential but also addressing orphan diseases



Masitinib in Neurology Diseases

Amyotrophic Lateral Sclerosis (ALS)

Alzheimer's Disease (AD)

Multiple Sclerosis (PPMS and nSPMS)

Amyotrophic Lateral Sclerosis (ALS)

Study AB10015 evaluated two masitinib doses in patients with ALS.

Design

Design

Prospective, multicenter, randomized, double blind, placebo-controlled, phase 2/3 study

Groups

- Masitinib 4.5mg/kg/day + riluzole
- Masitinib 3 mg/kg/day + riluzole
- Placebo + riluzole

Enrolment: 394 patients

Duration: 48 weeks

Primary endpoint: Change from baseline in ALSFRS-R score

Secondary endpoint

- PFS, Progression Free Survival: ALSFRS-R deterioration ≥ 9 points, or death

Main inclusion criteria

1) Patients with probable, or definite ALS, sporadic or familial ALS

2) Patients on stable dose of riluzole for at least 30 days prior to screening

3) Patients with disease duration ≤ 36 months and FVC ≥ 60%

Pre-specified Analysis Plan

Two distinct populations were differentiated:

- 'Normal Progressors': rate <1.1 points/month
- 'Faster Progressors': rate ≥ 1.1 points/month
- Rate of ALSFRS-R progression from first symptom to randomization (points/month):

Efficacy analyses were conducted in a stepwise manner

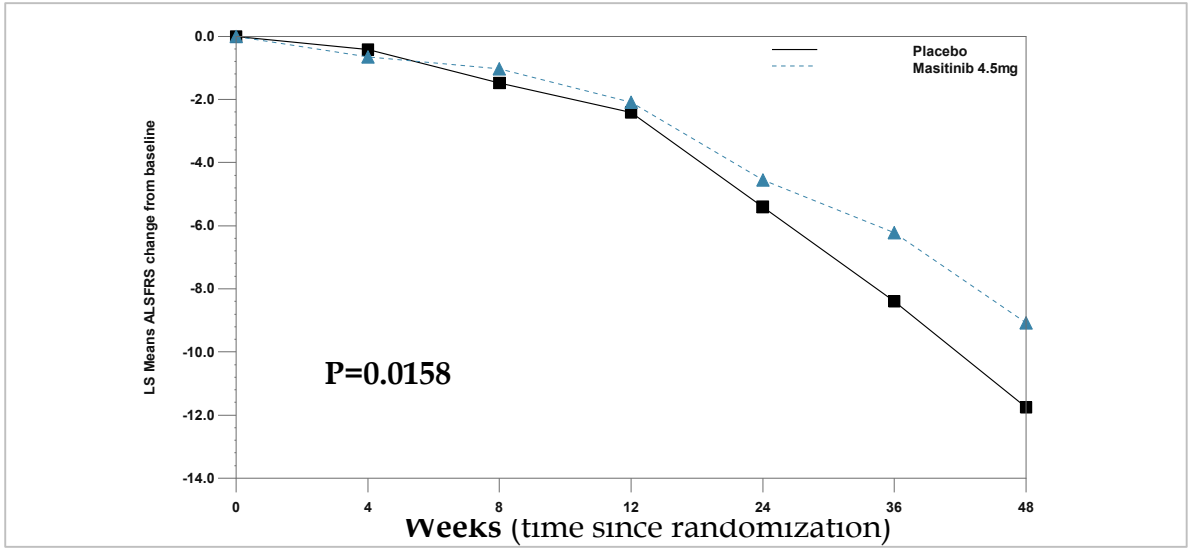
- Fixed sequence method, to control the global family-wise error rate at the 0.05 level for the primary analysis for each dose.

STEP	POPULATION
1	Normal Masitinib 4.5 mg
2	Normal Masitinib 3.0 mg
3	Normal + Faster Masitinib 4.5 mg
4	Normal + Faster Masitinib 3.0 mg

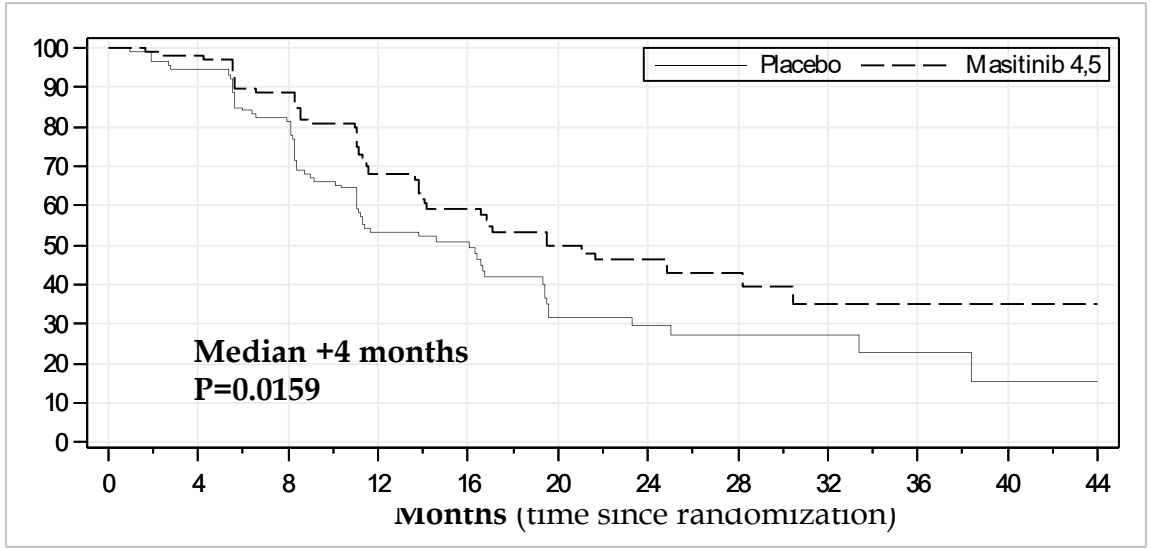
Amyotrophic Lateral Sclerosis (ALS)

Phase 2B/3 demonstrated significant delay in disease progression in “Normal” progressors with masitinib 4.5 mg/kg/day

27% slowing of functional deterioration (Primary Endpoint)



25% delay in disease progression (PFS)



Effectiveness supported by validated mechanism of action

- Schwann Cells Orchestrate Peripheral Nerve Inflammation Through the Expression of CSF1, IL-34, and SCF in Amyotrophic Lateral Sclerosis. Glia 2020
- Mast cells and neutrophils mediate peripheral motor pathway degeneration in ALS. JCI Insight. 2018.
- Evidence for mast cells contributing to neuromuscular pathology in an inherited model of ALS. JCI Insight, 2017. .
- Post-paralysis tyrosine kinase inhibition with masitinib abrogates neuroinflammation and slows disease progression in inherited amyotrophic lateral sclerosis. J Neuroinflammation, 2016.

Amyotroph Lateral Scler Frontotemporal Degener. 2020 Feb;21(1-2):5-14.

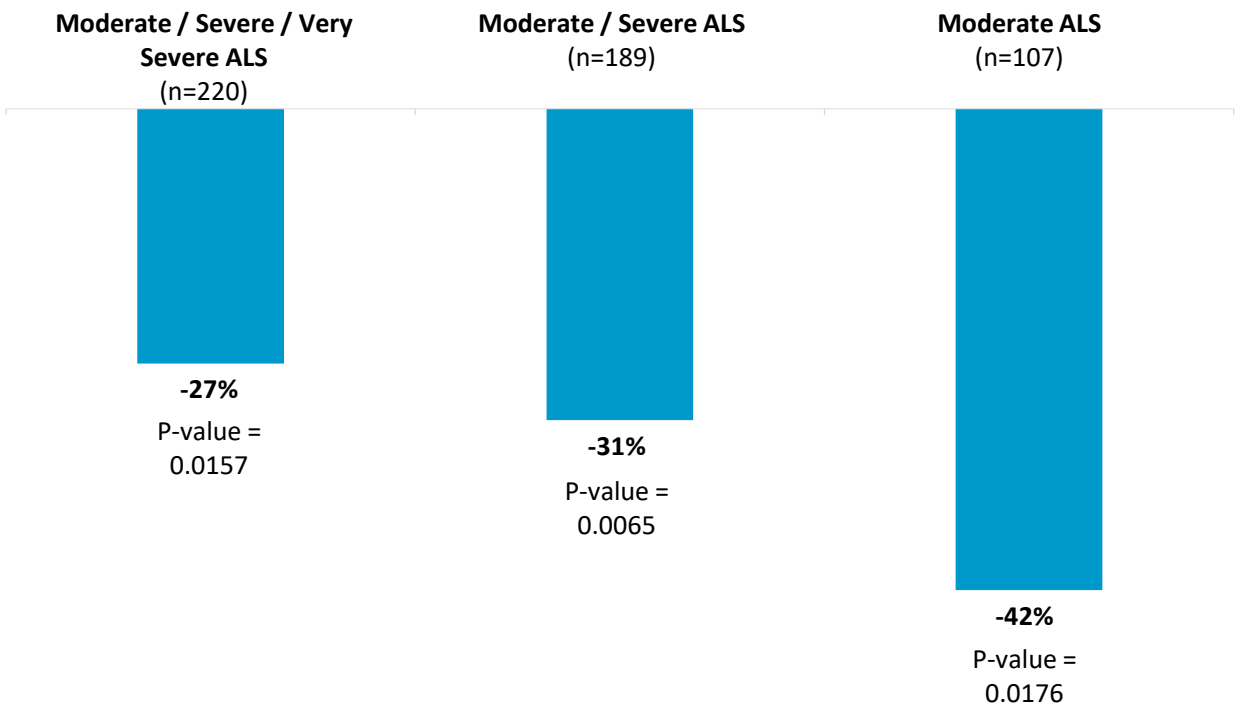
ClinicalTrials.gov Identifier: NCT02588677

Amyotrophic Lateral Sclerosis (ALS)

Clinical benefit further enhanced when treatment initiated early

42% slowing of functional deterioration (vs 27%)

% reduction in change in ALSFRS (primary endpoint – Normal progressors)
Masitinib 4.5mg/kg/day



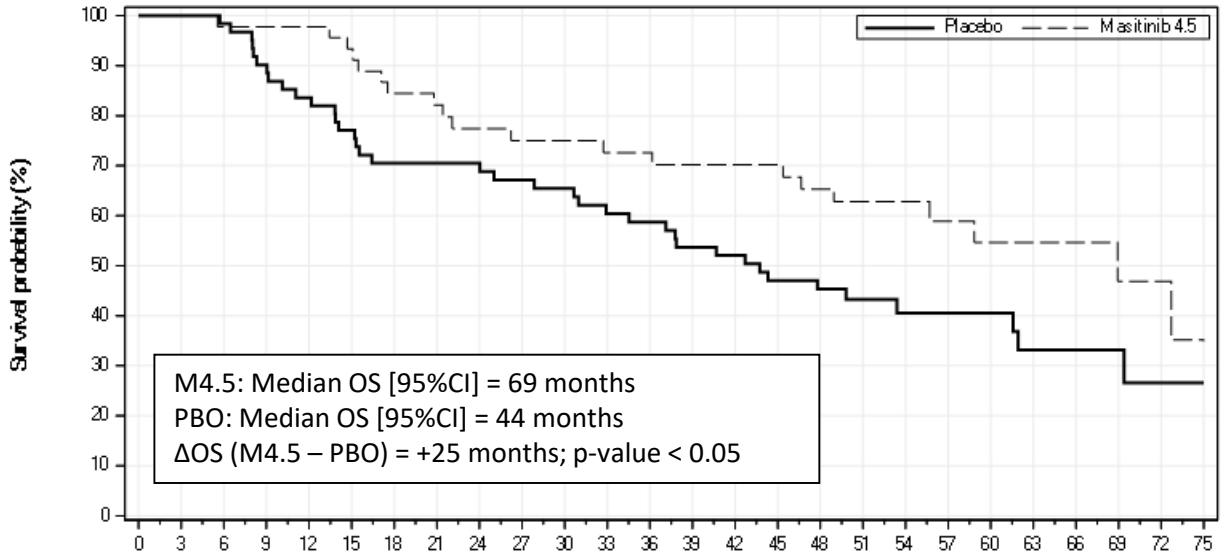
Moderate / Severe / Very Severe ALS : Primary Analysis (Any baseline ALSFRS-R score; ΔFS<1.1)
Moderate / Severe ALS : (≥1 each baseline ALSFRS-R item; ; ΔFS<1.1)
Moderate ALS : (≥2 each baseline ALSFRS-R item; ; ΔFS<1.1)

Amyotrophic Lateral Sclerosis (ALS)

Long-term survival follow-up showed a significant survival benefit of +25 months when treatment was initiated early

+ 25 months in median Overall Survival in patients with moderate ALS

Kaplan–Meier survival curves from masitinib study AB10015 long-term survival analysis progressors - Masitinib 4.5mg/kg/day



Moderate ALS (≥2 each baseline ALSFRS-R item; ; ΔFS<1.1)

Amyotrophic Lateral Sclerosis (ALS)

On-going confirmatory phase 3 study, with design validated by health authorities through Scientific Advise

Confirmatory phase 3 design

Design: Double blind, placebo controlled, randomized 1:1:1:1, comparing masitinib titration up to 6.0 mg/kg/day with placebo and masitinib titration up to 4.5 mg/kg/day with placebo

Main inclusion criteria:

- Disease duration ≤ 24 months,
- Moderate ALS (Baseline functional score ≥ 2 on each ALSFRS-R items
- Exclusion of slow progressors (less than a 1-point decline over 3 months prior to randomization), and fast progressors (more than a 4-point decline over 3 months prior to randomization).
- 50 fast progressors included for exploratory analysis

Enrolment: 550 patients

Duration: 48 weeks

Primary endpoint: Change in the ALSFRS-R score

Optimizations from previous phase 3

Enriched inclusion criteria

- Previous study had broad inclusion criteria, with 20% having a loss of function at baseline (i.e. sore of 0 on at least 1 item of ALSFRS score)
- In new study, patients are less advanced in their disease and a doubling of the treatment effect is expected

Testing of a higher dose of 6.0 mg/kg/day

- In previous study, only 3.0 or 4.5 mg/kg/day were tested and a dose effect was observed. Greater efficacy is expected with the dose of 6.0 mg/kg/day

Dose titration

- With dose titration from 3.0 to 4.5 and then 6.0 mg over a 2-month period, marginal discontinuation rate is expected

Status
Actively recruiting patients

ClinicalTrials.gov Identifier: NCT04333108

Alzheimer's disease (AD)

Masitinib is positioned in patients with mild and moderate dementia, which is different from other compounds

Disease severity	MMSE Score (mini mental state examination)
Prodromal	> 25
Mild	[21 – 25]
Moderate	[12 – 20]
Severe	< 12

Aducanumab	Masitinib
Prodromal AD > 22 / > 24	**Mild & Moderate AD [12 – 25]**

Alzheimer's disease (AD)

Study AB09004 evaluated in patients with mild and moderate AD, three doses of masitinib, each dose having its own placebo control

Design

Design

Prospective, multicenter, randomized, double blind, placebo-controlled, phase 3 study

Groups

- Masitinib 3 mg/kg/day (stopped early based on IDMC recommendation)
- Masitinib 4.5 mg/kg/day, randomisation 1:1
- Masitinib titration 4.5 to 6.0 mg/kg/day, randomisation 2:1

Enrolment: 718 patients

Duration: 24 weeks

Primary endpoint:

- Change in ADAS-Cog
- Change in ADCS-ADL

Main inclusion criteria

1) Patient with dementia of Alzheimer's type, according to the Diagnostic and Statistical Manual of Mental Disorders criteria (DSM-IV)
2) Patient with probable Alzheimer' disease according to the NINCDS-ADRDA criteria (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association)
3) Patient with MMSE ≥ 12 and ≤ 25 at baseline
4) Patient treated for a minimum of 6 months with a stable dose of cholinesterase inhibitors and/or a stable dose of memantine, with no changes foreseen in therapy throughout the study.

Pre-specified Analysis Plan

Statistical analysis:

- Statistical risk Alpha (chance finding) splited between ADAS-COG (2.5%) or ADCS-ADL (2.5%).
- Study is successful if the treatment effect is established in at least one of the two primary endpoints

Stratification factors

- MMSE score at baseline
- Age at baseline
- ADCS-ADL total score at baseline
- ADAS-COG total score at baseline

Alzheimer's disease (AD)

The Phase 2B/3 study demonstrated a statistically significant reduction in Cognitive impairment based on ADAS-COG (p=0.0003) and improvement on daily activity based on ADCS-ADL (p=0.0381) with masitinib 4.5 mg/kg/day

Significant effect on cognitive function after 24 weeks of treatment

Change in ADAS-Cog - ANCOVA Analysis (Full Analysis Set) - M4.5 vs Placebo

	Descriptive Statistics		Model Summary - LSM		Difference		
Treatment	n	Mean (SD)	LS Mean	95% CI	LS Mean (SE)	97.51% CI	p-value
Masitinib 4.5 mg/kg/day + SoC	182	-1.51 (5.81)	-1.46	(-2.46, -0.45)	-2.15 (0.59)	(-3.48, -0.81)	0.0003
Placebo + SoC	176	0.63 (5.35)	0.69	(-0.36, 1.75)			

Significant effect on daily activity after 24 weeks of treatment

Change in ADCS-Adl - ANCOVA Analysis (Full Analysis Set) - M4.5 vs Placebo

	Descriptive Statistics		Model Summary - LSM		Difference		
Treatment	n	Mean (SD)	LS Mean	95% CI	LS Mean (SE)	97.51% CI	p-value
Masitinib 4.5 mg/kg/day + SoC	182	0.51 (7.78)	1.01	(-0.48, 2.50)	1.82 (0.87)	(-0.15, 3.79)	0.0381
Placebo + SoC	176	-1.09 (9.17)	-0.81	(-2.36, 0.74)			

Alzheimer's disease (AD)

There were significantly fewer patients reaching severe dementia stage (MMSE<10) and a significant decrease in time to severe dementia with masitinib 4.5 mg/kg/day compared with the pooled placebo arms

Significant effect on severe dementia (MMSE<10) with masitinib 4.5 versus combined placebo

Dementia- M4.5 vs Placebo Pooled (FAS)

							p-value		Hazard	
Treatment group	Total	No. of Events	Percentage Events	No. Censored	Percentage censored	Median [95% CI]	KM p-Value	Log Rank	Ratio (95% CI)	p-Value
Masitinib 4.5 mg/kg/day	182	2	1.10	180	98.90	Not reached [;]	0.0446	0.0403	0.19 (0.0,0.8)	0.0276
Pooled Placebo	267	15	5.62	252	94.38	6.3 [5.9;6.3]				

Baseline MMSE (FAS)	Masitinib + SoC (N = 182)	Pooled Placebo + SoC (N =267)
< 14	18 (9.9)	30 (11.2)
< 17	54 (29.7)	81 (30.3)

Multiple Sclerosis

Tremendous unmet need, with no approved drugs for non-active SPMS and only one for PPMS

	Manufacturer	Masitinib Positioning Label				First approved
		Primary Progressive MS	Non-active Secondary Progressive MS*	Active Secondary Progressive MS	Relapsing Remitting MS	
Distribution of patients *(Estimated Nbr of patients Europe + USA)*		**15%** *(~ 150 000)*	**35%** *(~ 350 000)*	**10%** *(~ 90 000)*	**40%** *(~ 400 000)*	
Total number of drugs registered		**1**	**0**	**16**	**16**	
Zeposia (ozanimod)	BMS			X	X	2020
Mayzent (siponimod)	Novartis			X	X	2019
Vumerity (diroximel fumarate)	Alkermes / Biogen			X	X	2019
Ocrevus (ocrelizumab)	Roche / Genentech	X		X	X	2017
Mavenclad (cladribine)	EMD Serono / Merck			X	X	2017
Plegridy (peginterferon beta-1a)	Biogen			X	X	2014
Tecfidera (dimethyl fumarate)	Biogen			X	X	2013
Aubagio (Teriflunomide)	Sanofi-Aventis			X	X	2012
Gilenya (fingolimod)	Novartis			X	X	2010
Extavia (interferon beta-1b)	Novartis			X	X	2008
Tysabri (natalizumab)	Biogen			X	X	2004
Lemtrada (alemtuzumab)	Sanofi / Genzyme			X	X	2001
Rebif (interferon beta-1b)	Serono			X	X	1998
Avonex (interferon beta-1a)	Biogen			X	X	1996
Copaxone (glatiramer acetate)	Teva Pharms			X	X	1996
Betaferon / Betaseron (interferon beta-1b)	Bayer Healthcare			X	X	1993

**: Non-active SPMS is a stage of MS that follows relapsing-remitting multiple sclerosis and that is characterized with an EDSS score progression ≥ 1 point without any relapse in the last 2 years.*

Multiple Sclerosis

Study AB7002 evaluated two masitinib doses in patients with PPMS and non-active SPMS.

Design

Design

Prospective, multicenter, randomized, double blind, placebo-controlled, phase 3 study

Groups

- Masitinib 4.5 mg/kg/day versus its own placebo
- Masitinib titration 4.5 to 6.0 mg/kg/day versus its own placebo
- Randomisation 2:1

Enrolment: 611 patients*

Duration: 96 weeks

Primary endpoint: Change from baseline in absolute EDSS value averaged over the two-year study

Main inclusion criteria

1) Patient with Primary Progressive (PPMS) or Non-active secondary progressive multiple sclerosis (nSPMS) defined as:
   - No relapse (measured by EDSS progression, not by imaging) within 2 years before inclusion according to the revised McDonald's criteria
   - EDSS score progression ≥ 1 point within 2 years before inclusion
2) Must be EDSS and age requirements
   - EDSS score of [2.0 to 6.0] inclusive at baseline
   - Age 18 to 75 years old

Pre-specified Analysis Plan

Statistical analysis:

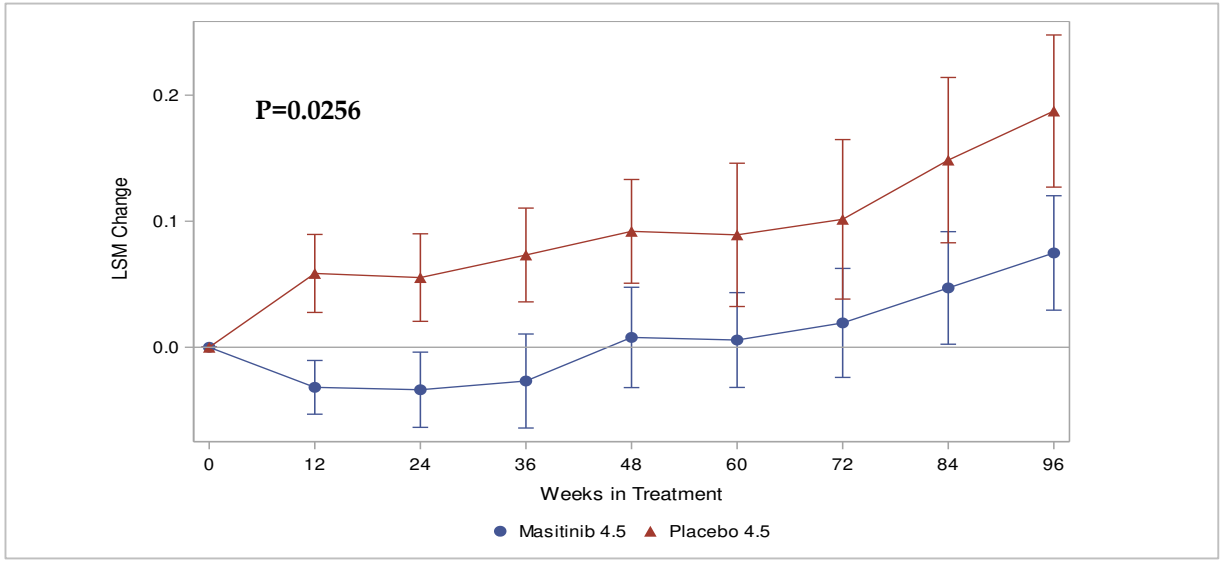
- Study AB7002 is treated as two independent sub-studies under a common study identifier, with alpha control set at 5% for each dose

** + 45 patients in 6mg flat dose arm, stopped early in the study by Sponsor decision*

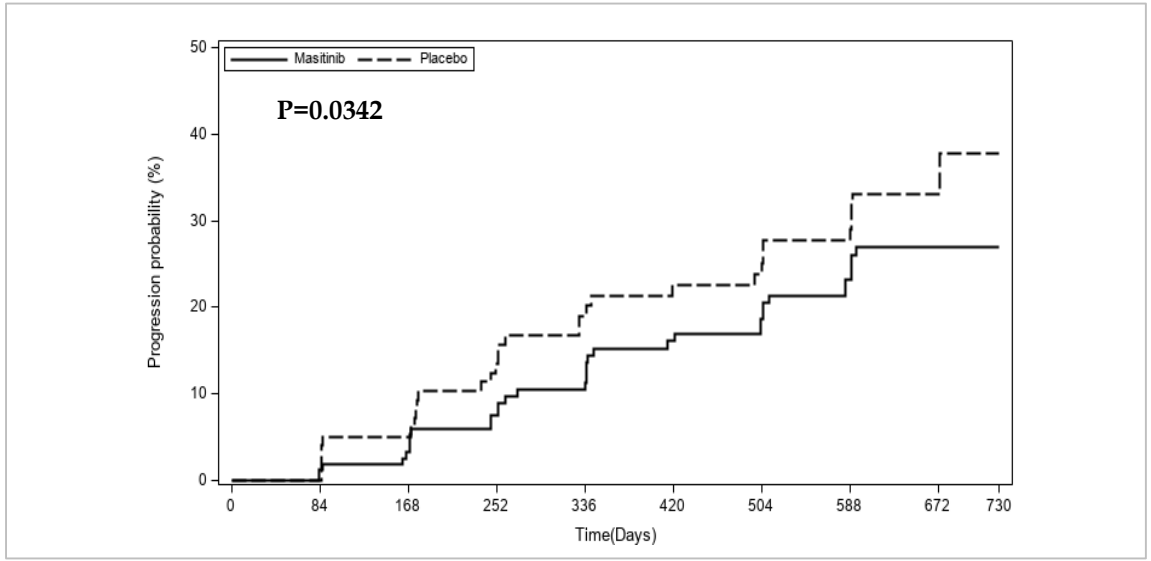
Multiple Sclerosis

Phase 2B/3 demonstrated significant benefit on disability progression with masitinib 4.5 mg/kg/day

Significant reduction in progression on EDSS (Primary Endpoint)



42% risk reduction of time to disability progression



Patients were enrolled at advanced disease stage

- Median age (years) : 50.0 (both masitinib and placebo)
- Media Duration of First MS Symptom to Randomization (years) : 12.4 masitinib and 12.2 placebo
- Median EDSS Score : 5.5 (both masitinib and placebo)
- % of patients with EDSS score of 6 : 49.0% masitinib and 47.5% placebo

Neurology

Blockbuster Opportunity across three indications

Indication	Phase of Development	Annual cost of registered Drugs (USD)	No US Patients	No EU Patients	Penetration	Market Opportunity US (M€)	Market Opportunity EU (M€)
ALS	Positive phase 2/3 study Launch of confirmatory phase 3 study	• Radicava (145,000)	20,000[2]	30,000[2]	50%	800 *(based on a 80,000€ annual price)*	1,200 *(based on a 80,000€ annual price)*
MS	Positive phase 2/3 study	• Ocrevus (65,000) • Rebif (61,800) • Extavia (61,848) • Lemtrada (158,000) • Copaxone (66,000)	200,000[1]	300,000[1]	33%	4,000 *(based on a 60,000€ annual price)*	6,000 *(based on a 60,000€ annual price)*
Alzheimer's	Positive phase 2/3 interim analysis	• No branded drug	2,000,000[3]	3,000,000[3]	25%	15,000 *(based on a 30,000€ annual price)*	22,000 *(based on a 30,000€ annual price)*

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 : Antel J, Antel S, Caramanos Z, Arnold DL, Kuhlmann T. Primary progressive multiple sclerosis: part of the MS disease spectrum or separate disease entity? Acta Neuropathol. 2012 May;123(5):627-38.
Paz Soldán MM, et al. Relapses and disability accumulation in progressive multiple sclerosis. Neurology. 2015 Jan 6;84(1):81-8

2 : Meta-analysis from 7 studies
(1) Logroscino G *et al*. EURALS. Incidence of amyotrophic lateral sclerosis in Europe. *J Neurol Neurosurg Psychiatry*. 2010; 81:385-90
(2) Huisman MH *et al*. Population based epidemiology of amyotrophic lateral sclerosis using capture-recapture methodology. *J Neurol Neurosurg Psychiatry.* 2011; 82:1165-70
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Masitinib in Neurology Inflammatory Diseases

Indolent Systemic Mastocytosis (ISM)

Mast Cell Activation Syndrome (MCAS)

Severe Asthma

Indolent Systemic Mastocytosis (ISM)

Study AB06006 evaluated masitinib versus placebo in 135 patients with ISM and severe symptoms at baseline.

Design

Design

Prospective, multicenter, randomized, double blind, placebo-controlled, phase 3 study

Groups

- Masitinib 6 mg/kg/day versus its own placebo
- Randomisation 1:1

Enrolment: 135 patients with ISM

Duration: 24 weeks

Primary endpoint:

- Number of cumulative responses on 4 severe symptoms from week 8 to week 24
- Severe symptoms are Pruritus, flushes, depression, and asthenia

Main inclusion criteria

1) Patient with one of the following documented mastocytosis as per WHO classification:
   - Smouldering Systemic Mastocytosis
   - Indolent Systemic Mastocytosis
2) Patient unresponsive to optimal symptomatic treatment
3) At least one severe symptom (handicap) at baseline. A handicap was defined as a baseline symptom above predefined severity threshold
   - Pruritus score : ≥ 9
   - Number of flushes per week : ≥ 8
   - Depression (HAMD-17) score : ≥ 19
   - Asthenia (FIS) total score :≥ 75

Pre-specified Analysis Plan

Response :

- Decrease of ≥75% in any 4 handicap
- 5 assessments at w8, w12, w16, w20, w24

Calculation

- Patients can have between 1 and 4 handicaps at baseline
- Therefore a patient can score for 1 to 4 responses at each timepoint

The primary endpoint presented for each treatment arm the number of actual responses divided by the total of theoretical responses

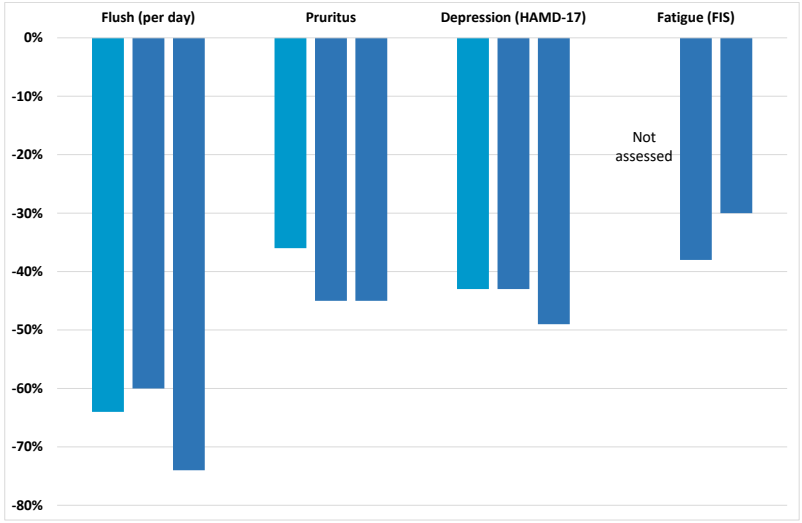
Statistical calculation of the p-value is based on the GEE (generalized estimating equation) model that takes into consideration correlation across variables and across time so that valid inferences can be assured. Missing data = failure

Indolent Systemic Mastocytosis

Phase 2 showed masitinib is effective on key disease symptoms, regardless of c-Kit mutation status, and efficacy is sustainable

Improvement in disease symptoms

% Change from baseline at week 12

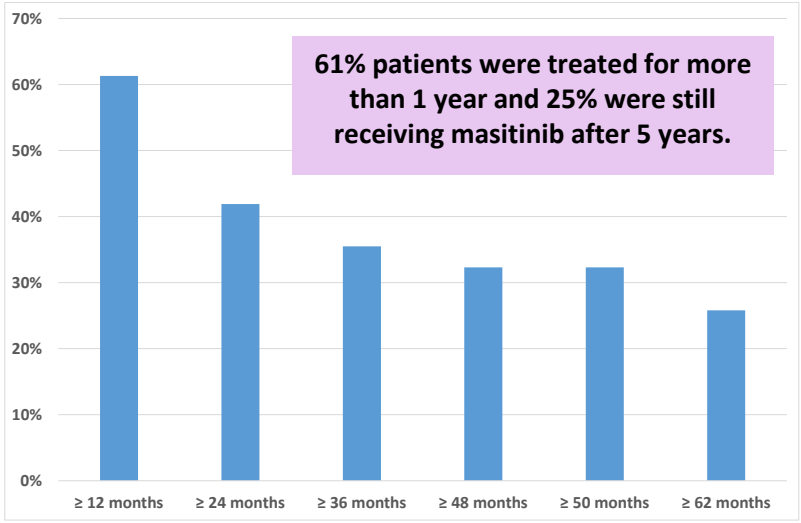


Phase 2 **with c-Kit D816 mutation** (n=21,single arm)

Phase 2 **without c-Kit D816V** (n=25,single arm)
(Middle columns represents patients with moderate baseline symptoms and right column represents patient with severe baseline symptoms)

Sustained efficacy

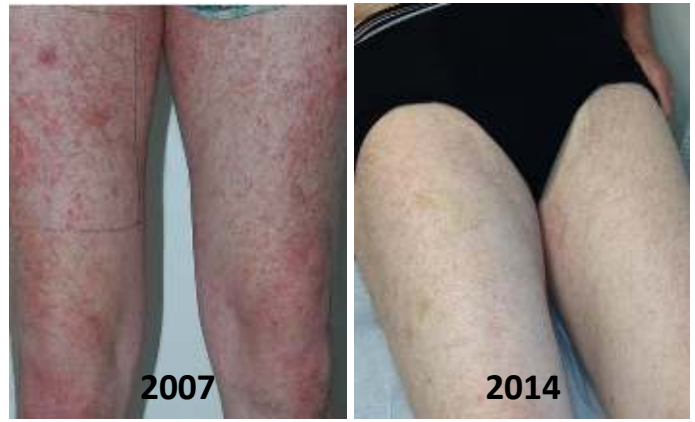
% of patients still under treatment



61% patients were treated for more than 1 year and 25% were still receiving masitinib after 5 years.

Pooled phase 2 (n=46,single arm)

Reduction in urticaria pigmentosa



Masitinib inhibits mast cells, regardless of c-Kit mutation status, through c-Kit, Lyn and Fyn kinases

ClinicalTrials.gov Identifier: NCT01266369 & NCT00831974

Indolent Systemic Mastocytosis

Phase 3 demonstrates significant reduction in symptoms with masitinib 6.0 mg/kg/day

3.6 fold improvement in most prevalent symptoms

		Masitinib	Placebo	p-value	Odds ratio
Primary Analysis	**4H75% pruritus, flushes, depression, asthenia**	18.7%	7.4%	0.0076	**3.63**
Secondary Analyses	**3H75% pruritus, flushes, depression**	24.7%	9.8%	0.0071	**3.06**
	2H75% pruritus or flushes	27.2%	10.7%	0.038	**2.63**
	Pruritus 75% pruritus	22.0%	7.3%	0.032	**3.13**

Improvement in objective markers of the disease

	Masitinib	Placebo	p-value
Tryptase - Patients with baseline tryptase ≥20 µg/L	46	44	0.0001
Average relative change from baseline Mean±SD	-18.0 ± 21.4	2.2 ± 26.9	
Urticaria Pigmentosa (UP) - Patients with baseline UP	33	36	0.0210
Average relative change from baseline in the Body Surface Area (BSA) covered by UP (Wallace correction)	-12.34 ± 26.41	15.91 ± 59.79	
Darier's sign – Number of patients (baseline)	37	37	0.0187
Response rate for Darier's sign disappearance (Yes/No) in patients with "Darier's sign" at baseline	18.92%	2.70%	

Cumulative response based on the generalized estimating equation model with missing data considered as failure. Longitudinal analysis with respect to symptoms as opposed to patient response rate at a single point in time.
Response rates expressed as ratio of sum of actual responses between weeks 8 and 24 divided by the total number of possible responses over the same treatment period.
Respose = 75% reduction from baseline in symptoms severity
4H75% = cumulative response in severe symptoms present at baseline among the four :pruritus, flushes, depression, asthenia.
3H75% = cumulative response in severe symptoms present at baseline among the three: pruritus, flushes, depression.
2H75% = cumulative response in severe symptoms present at baseline among the two: pruritus, flushes.
NOTE that in *Lancet* article these endpoints use the nomenclature 4R75% etc, R standing for 'response', a term preferred over 'Handicap'.

Lancet 2017 Feb 11;389(10069):612-620. doi: 10.1016/S0140-6736(16)31403-9. Epub 2017 Jan 7

ClinicalTrials.gov Identifier: NCT00814073

Indolent Systemic Mastocytosis

On-going confirmatory phase 3 study, with design validated by key health authorities

Confirmatory phase 3 design

Design: Double blind, placebo controlled, randomized 1:1, comparing masitinib titration up to 6.0 mg/kg/day with placebo

Main inclusion criteria: Smouldering or Indolent Mastocytosis, with severe symptoms at baseline (Pruritus score ≥ 9 and/or Flushes per week ≥ 8 and/or HAMD-score ≥ 19) and in failure to optimal symptomatic treatment

Enrolment: 140 patients

Duration: 24 weeks

Primary endpoint: Cumulative 75% response rate on baseline severe symptoms/handicaps among (pruritus, flush, depression). Response on a handicap is defined as an improvement ≥ 75% for pruritus, flushes and depression.

Optimizations from previous phase 3

Dose Titration

- In previous study, starting dose of 6 mg/kg/day without titration
- This led to 20% treatment discontinuation, with discontinuation equal to treatment failure in the analysis
- With dose titration from 3.0 to 4.5 and then 6.0 mg over two months period, marginal discontinuation rate

Run-in period

- In previous study, there was no run-in to ensure that patients were taking optimal symptomatic treatment at screening
- In new study, one-month run-in period to control failure to symptomatic treatment

Status
Actively recruiting patients

ClinicalTrials.gov Identifier: NCT04333108

MCAS (Mast Cell Activation Syndrome)

MCAS is a disease caused by activation of mast cells

Disease Features

- **MCAS is a common disease associated with numerous symptoms.**
  - Symptoms are similar to mastocytosis ones and include
    - Fatigue,
    - Neurologic/psychiatric symptoms,
    - Pain
    - Pruritus,
    - Nausea, abdominal cramping and diarrhea,
    - Anaphylaxis, hypotension, tachycardia or unexplained arrhythmias,
  - But affects around 5 to 10% of general population
  - MCAS can be diagnosed by specific markers of mast cell hyperactivity:
    - Elevated blood levels of mast cell-specific mediators (tryptase, histamine, and heparin)
    - Elevated level of histamine into the urine
    - No urticaria pigmentosa unlike mastocytosis
    - Clonal like mastocytosis or not remains to be explored
- **MCAS can be severe**
  - As for systemic mastocytosis, MCAS symptoms can be mild, moderate, or severe
  - Proportion of severe forms is unknown
  - Could include part of multiple sclerosis, Crohn's disease, inflammatory bowel disease, Duchenne muscular dystrophy, chronic fatigue syndrome

Treatment Objectives

As for severe systemic mastocytosis, the objective in severe MCAS in adults is to reduce symptoms and improve impaired quality of life

MCAS (Mast Cell Activation Syndrome)

Study AB20006 is a phase 2 evaluating ascending doses of masitinib

Design

Design:

Randomized, double-blind, placebo-controlled, parallel-group, multicenter comparative study with ascending dose titrations of masitinib and matching placebo

Randomisation: 2:1

Planned Enrolment : 60 patients

Duration: 24 weeks

Primary endpoint: Cumulative response at 50% on 3 handicaps (pruritus, flush, depression) from W8 to W24.

Main inclusion criteria

1) Patient with severe Mast cell activation syndrome (MCAS) diagnosed based on both clinical and biomarker criteria

2) Patient with documented symptomatic treatment failure

3) Patients treated with stable dose of Anti-H1

Status
Authorized ; Patients recruitment to be initiated

Severe Asthma Uncontrolled with Oral Corticosteroids

Study AB07015 evaluated masitinib 6.0 mg/kg/day in patients with severe asthma uncontrolled by OCS

Design

Design

Prospective, multicenter, randomized, double blind, placebo-controlled, phase 3 study

Groups

- Masitinib 6 mg/kg/day versus its own placebo
- Randomisation 2:1

Enrolment:

- 409 patients randomized
- 355 patients with severe asthma (OCS ≥ 7.5 mg)
- 268 patients with severe asthma and eosinophils ≥ 150K/uL

Duration: 36 weeks + blinded extension

Primary endpoint: Number of severe asthma exacerbations divided by the time under treatment for the overall protocol period

Main inclusion criteria

1) Oral corticosteroids (OCS) dose ≥ 7.5 mg daily for at least 3 months prior to screening visit.

2) Patient with history of severe asthma ≥ 1 year
   - baseline FEV1 ≥35 to <80% of the predicted normal value
   - at least 2 asthma exacerbations within one year prior to screening visit

3) Both high (≥ 150K/uL) and low (<150K/uL) eosinophils.

Pre-specified Analysis Plan

Primary analysis :

- Study powered to detect 33% reduction on severe asthma exacerbation in severe asthma population (OCS dose ≥ 7.5 mg))

Definition

- Severe asthma exacerbation rate defined as asthma worsening that requires an increase from stable maintenance dose of corticosteroids for at least three days and /or hospitalization because of Asthma

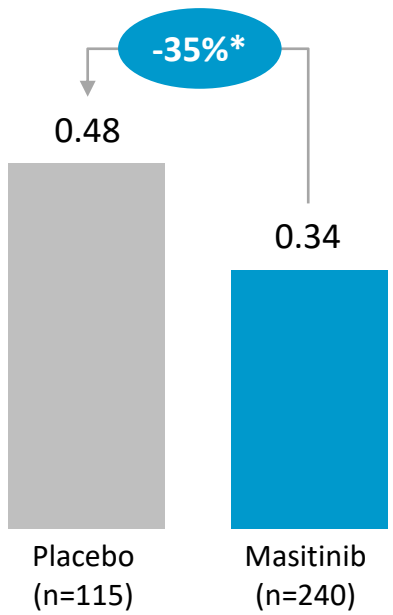
ClinicalTrials.gov Identifier: NCT01449162

Severe Asthma Uncontrolled with Oral Corticosteroids

Significant decreases in asthma exacerbations regardless of eosinophil level

Annualized severe asthma exacerbation rate

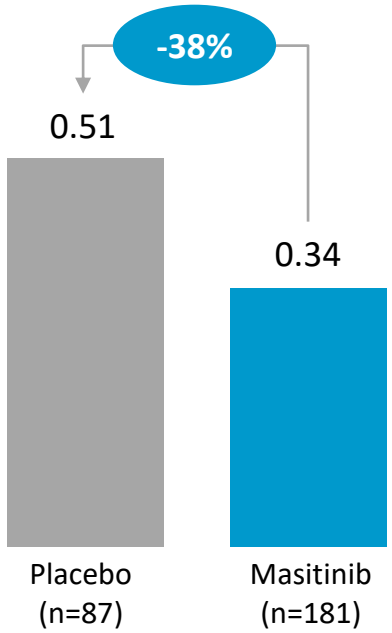
Primary Analysis



Relative risk reduction = 0.65
95% CI: 0.47, 0.90. p-value < 0.0103

* ITT analysis : -33%, p=0.0156

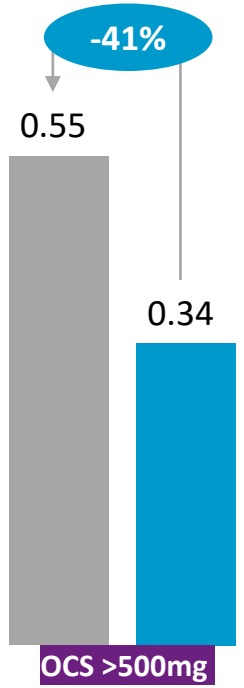
Sequential Analysis patients with eosinophils>150



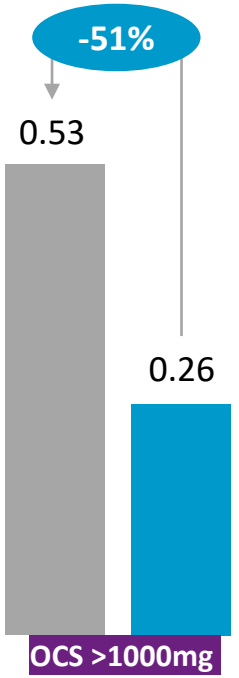
Relative risk reduction = 0.62
95% CI: 0.42, 0.91. p-value < 0.0156

Greater benefit in patients with higher cumulative OCS (>500mg or >1000mg)

Sensitivity Analysis

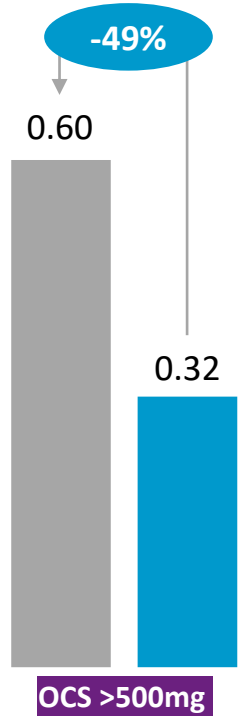


P-value = 0.0092

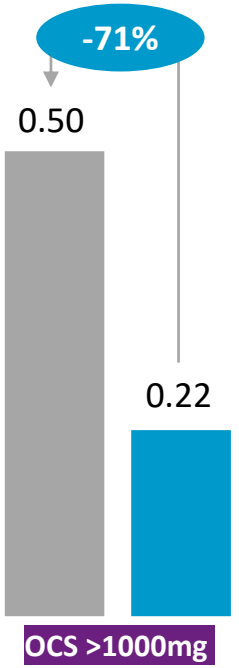


P-value = 0.0060

Sensitivity Analysis patients with eosinophils>150



P-value = 0.0049



P-value = 0.0003

Higher cumulative OCS is indicative of more severe asthma

Severe Asthma Uncontrolled with Inhaled Corticosteroïds

Study AB14001 evaluated masitinib titration up to 6.0 mg/kg/day in patients with severe asthma uncontrolled by ICS and with elevated eosinophil levels

Design

Design

Prospective, multicenter, randomized, double blind, placebo-controlled, phase 3 study

Groups

- Masitinib titration 3.0 to 4.5 to 6.0 mg/kg/day versus its own placebo
- Randomisation 2:1

Enrolment:

- 347 patients randomized
- 295 patient in claim (Exclusion of patients with eosinophils <150K/uL)

Duration: 36 weeks + blinded extension

Primary endpoint: Number of severe asthma exacerbations divided by the time under treatment for the overall protocol period

Main inclusion criteria

1) Patient with history of severe asthma ≥ 1 year partially controlled or uncontrolled on ICS/LABA combination therapy
   - baseline FEV1 ≥35 to <80% of the predicted normal value
   - at least 2 severe asthma exacerbations within one year prior to screening visit
3) Eosinophils ≥ 150K/uL

Pre-specified Analysis Plan

Primary analysis :

- Study powered to detect 33% reduction on severe asthma exacerbation in severe asthma population with eosinophils ≥ 150K/uL (Claim)

Definition

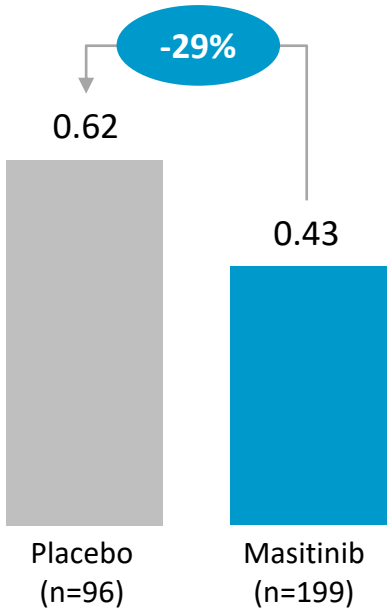
- Severe asthma exacerbation rate defined as asthma worsening that requires an increase from stable maintenance dose of corticosteroids for at least three days and /or hospitalization because of Asthma

Severe Asthma Uncontrolled with Inhaled Corticosteroïds

Phase 3 AB14001 in severe asthma uncontrolled by high-dose inhaled corticosteroids (ICS) and with high eosinophil level also met its primary endpoint

Annualized severe asthma exacerbation rate

Primary Analysis



Relative risk reduction = 0.71
95% CI: 0.53, 0.95. p-value = 0.0217

Significant improvement in quality of life

- Δ ACQ = -0.2085 (p=0.039)
- Δ AQLQ = 0.2741 (p=0.0177)

ClinicalTrials.gov Identifier: NCT03771040

Inflammatory Diseases

Strong market potential across three indications

Indication	Phase of Development	Annual cost of drugs registered in similar indication (USD)	No US Patients	No EU Patients	Penetration	Market Opportunity US (M€)	Market Opportunity EU (M€)
ISM	Launch of confirmatory phase 2/3 study	No registered drug	25,000[3]	40,000[3]	50%	500 *(based on a 40,000€ annual price)*	800 *(based on a 40,000€ annual price)*
Severe Asthma	Positive phase 2/3 study	• Nucala (35,000) • Cinqair (31,000) • Fasenra (31,000) • Dupixent (31,000) • Gleevec (32,000) • Xolair (13,000)	275,000[4]	550,000[4]	33%	3,000 *(based on a 30,000€ annual price)*	5,500 *(based on a 30,000€ annual price)*
MCAS	Launch of a Phase 2 study	No registered drug	200,000[5]	300,000[5]	50%	4,000 *(based on a 40,000€ annual price)*	6,000 *(based on a 40,000€ annual price)*

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

3 : Cohen SS, Skovbo S, Vestergaard H, et al. Epidemiology of systemic mastocytosis in Denmark. Br J Haematol 2014; 166: 521-8.
Population Division, U.S. Census Bureau.
Theoharides T., Valent P., Akin C., NEJM 2015. Mast Cells, Mastocytosis, and Related Disorders

4 : Respir Med. 2006 Jul;100(7):1139-51. Epub 2006 May 18.
J Investig Allergol Clin Immunol 2012; Vol. 22(7): 460-475
Data from study AB07015 for the proportion of patients with oesinophil level between 150 and 300 and above 300

5 : Molderings GJ, Haenisch B, Bogdanow M, Fimmers R, Nöthen MM. Familial Occurrence of Systemic Mast Cell Activation Disease. PLoS One. 2013;8:e76241.
Haenisch B, Nöthen MM, Molderings GJ. Systemic mast cell activation disease: the role of molecular genetic alterations in pathogenesis, heritability and diagnostics. Immunol. 2012; 137:197–205.
Severe MCAS accounting for 5% of MCAS patients (Company's estimation)

Masitinib in Oncology

First Line Non Resectable Locally Advanced Pancreatic Cancer (LAPC)

First Line Metastatic Castrate Resistant Prostate Cancer (mCRPC)

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 contribute 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.

Pain in cancer

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

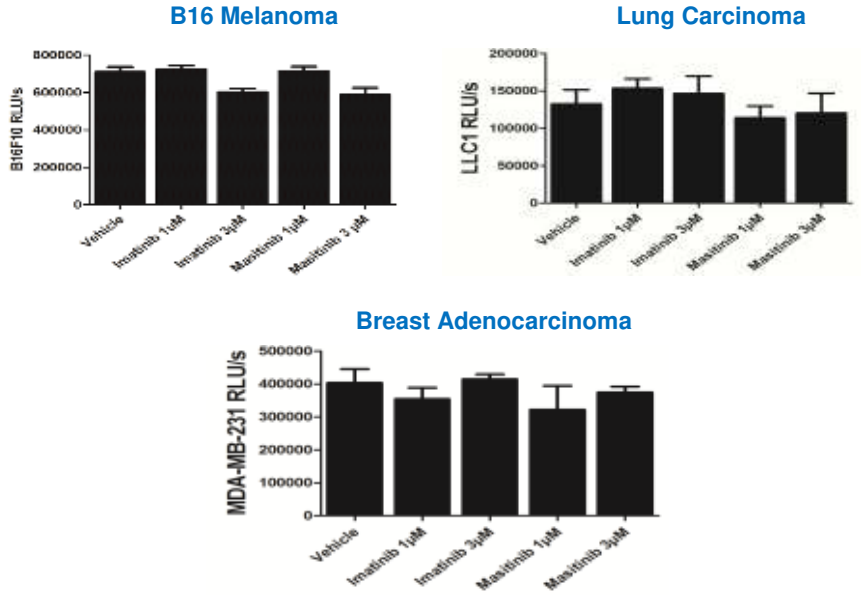
- **There is evidence that mast cell degranulation mediates cancer-induced pain and that pain is a clinical predictor of poor prognosis in pancreatic cancer.**
- **Mast cell infiltration is strongly implicated with development of neuropathic pain in pancreatic ductal adenocarcinoma patients [1].**
- **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.

Pharmacology Data - Masitinib targets tumor microenvronment

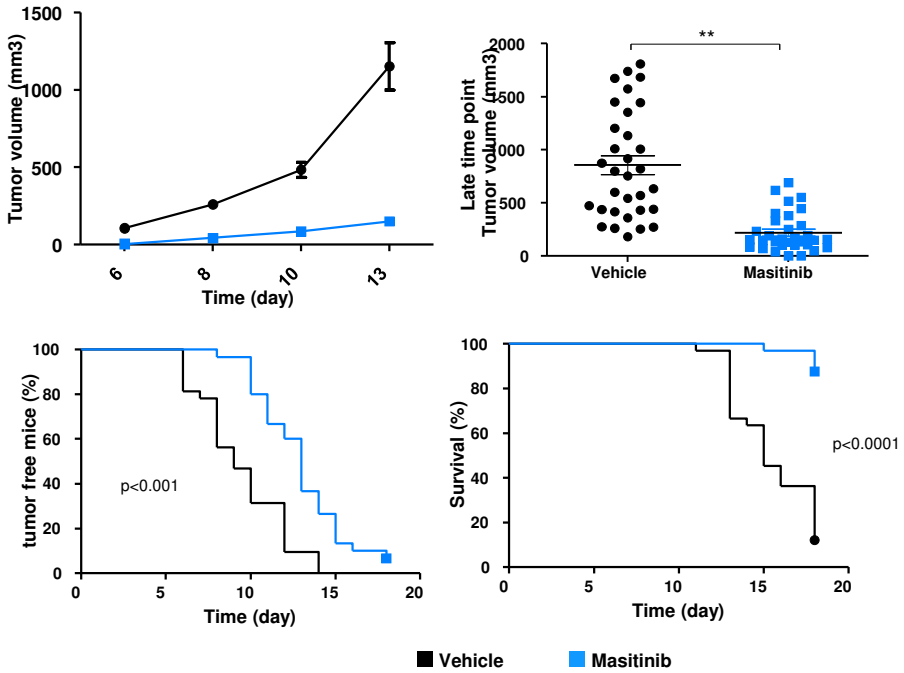
Masitinib has no direct "tumor killer" general activity but has shown efficacy on tumor proliferation *in vivo*, mediated through the tumor micro-environment

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

Based on this mechanism of action targeting the tumor micro-environment and not distant metastasis, **masitinib is expected to be effective at the early stage of metastatic process, flagged by Alkaline phosphatase in prostate cancer**

Pancreatic cancer with pain

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

Design

Design

Prospective, multicenter, randomized, double blind, placebo-controlled, 2-parallel groups, phase 3 study

Groups

- Masitinib 6.0 mg/kg/day + gemcitabine versus Placebo + gemcitabine
- Randomisation: 2:1

Enrolment

- 92 patients locally advanced pancreatic cancer (LAPC)
- 383 patients in the overall population (metastatic and LAPC)

Primary endpoint: Overall Survival

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) First line of treatment (Chemotherapy naïve patient for the advanced/metastatic disease)

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

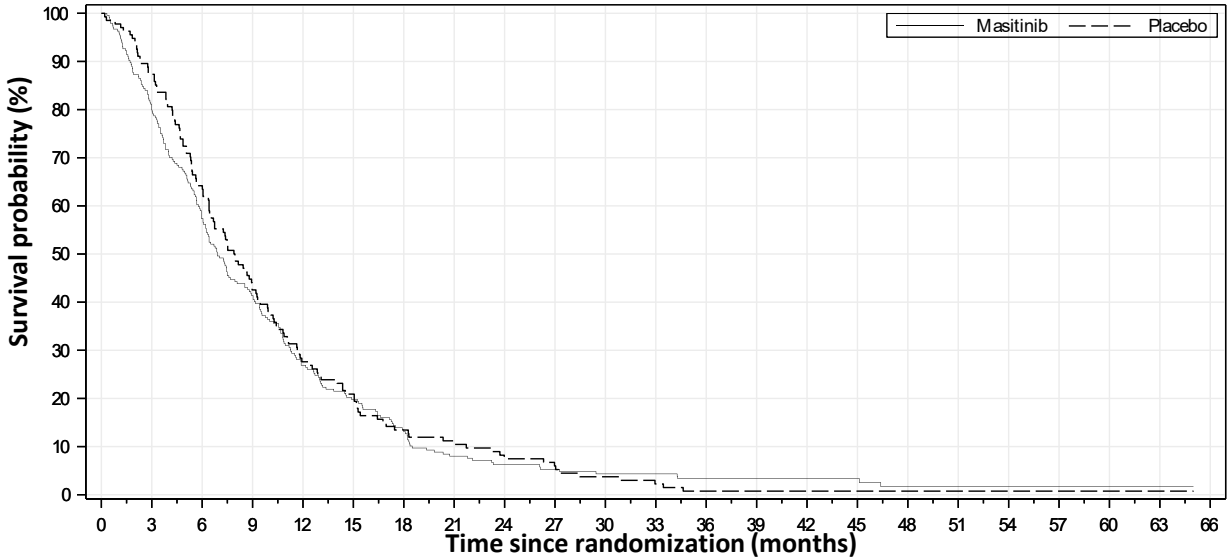
Pancreatic cancer with pain

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

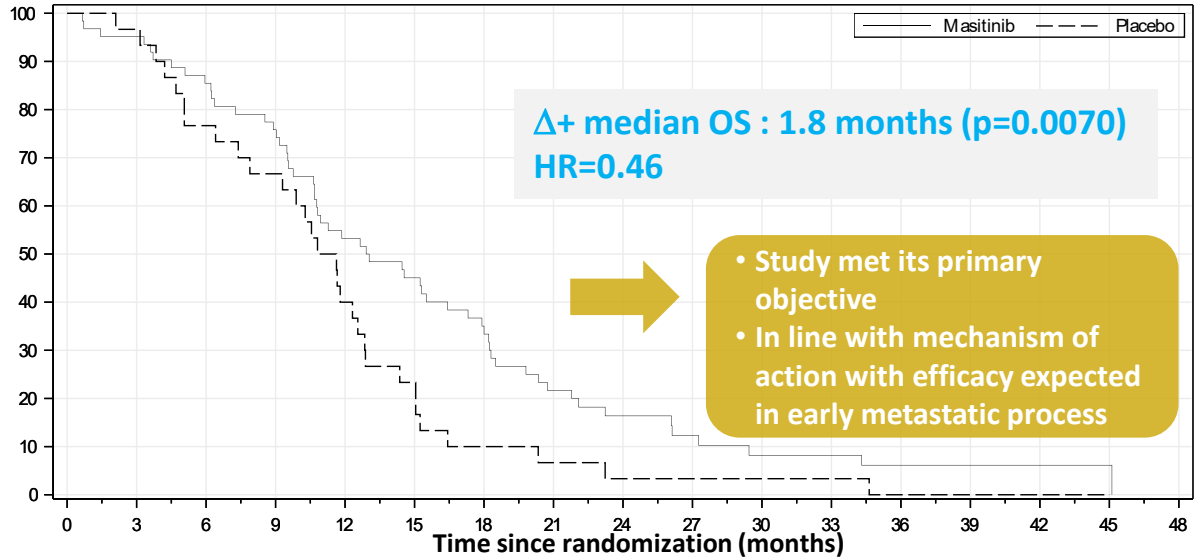
No benefit on survival in the Overall Population (metastatic + LAPC)

54% risk reduction of time to death in LAPC

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]			

3 patients without pain excluded from ITT population

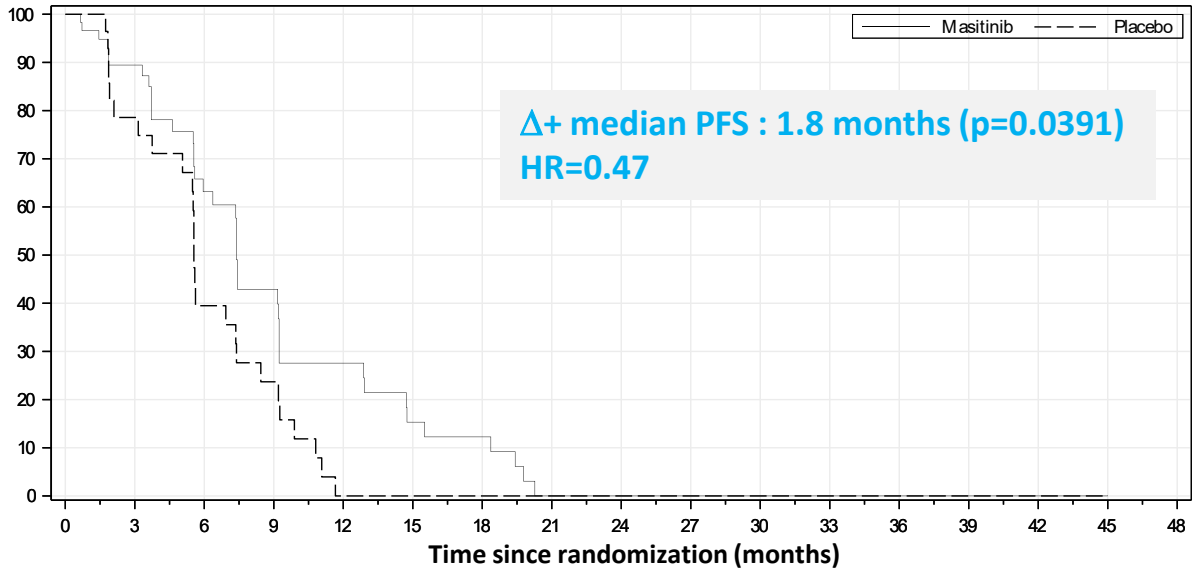
ClinicalTrials.gov Identifier: NCT03766295

Pancreatic cancer with pain

Progression free survival and response rate were in favor of masitinib and consistent with survival results

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]			

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%)

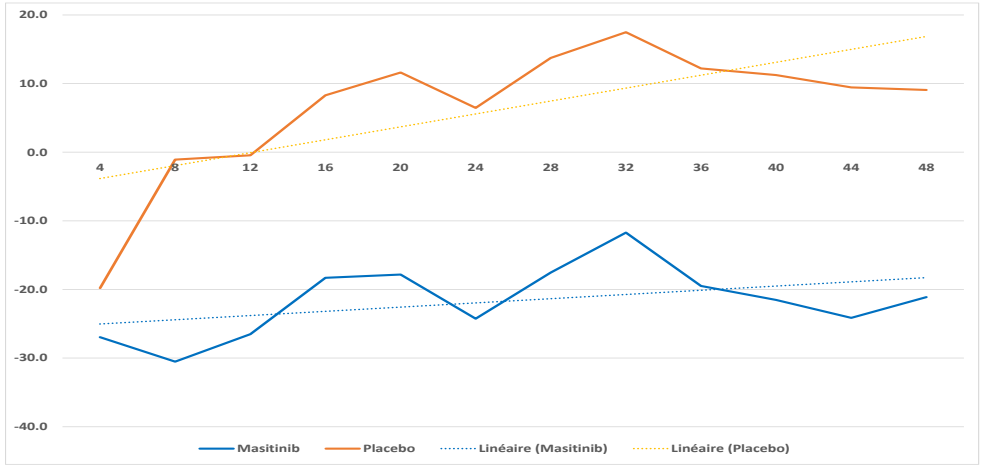
ORR : Objective Response rate = Complete response + Partial respon

Pancreatic cancer with pain

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

Significant improvement vs control in pain in locally advanced

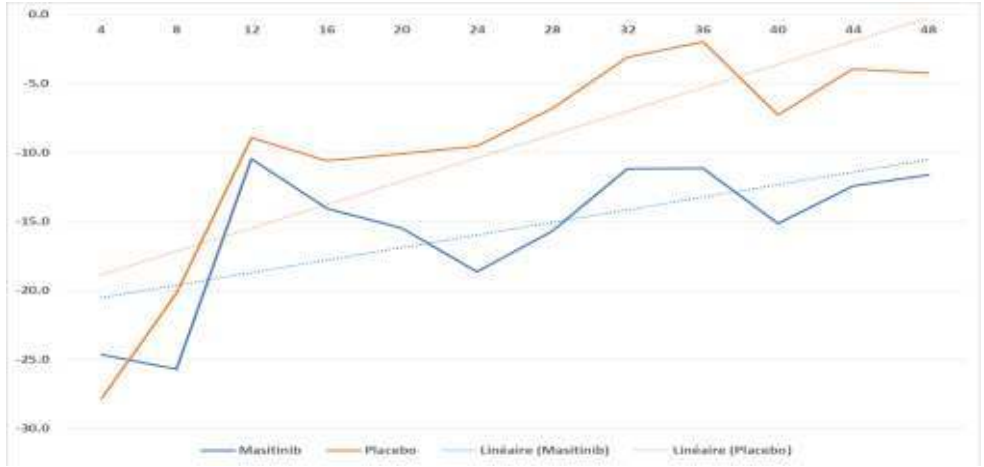
Locally advanced – Change from baseline in VAS (LS Mean)



Weeks

Numerical improvement vs control in pain in overall population

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



Weeks

ClinicalTrials.gov Identifier: NCT03766295

Metastatic Castrate Refractory Prostate Cancer (mCRPC)

Masitinib is positioned in combination with docetaxel as first-line treatment of mCRPC eligible to chemotherapy

Progression of the disease

	Stage of the desease	Registered Drug[1]
1	High-risk non Metastatic Castration Resistant Prostate Cancer (before chemotherapy)	Enzalutamide (Xtandi)
		Abiraterone (Zytiga)
		Apalutamide (Erleada)
2	Metastatic Castration Resistant Prostate Cancer early stage (before chemotherapy)	Sipuleucel T (Provenge)
		Abiraterone (Zytiga)
		Enzalutamide (Xtandi)
		Olaparib[2] (Lynparza)
		Rucaparib[2] (Rubraca)
3	**Metastatic Castration Resistant Prostate Cancer eligible to chemotherapy**	Docetaxel
4	Metastatic Castration Resistant Prostate Cancer after relapse from chemotherapy	Abiraterone (Zytiga)
		Enzalutamide (Xtandi)
		Cabazitaxel (Jevtana)

1: Not including treatment specific for bone metastases (Xofigo, Xgeva/Prolia,…). 2: PARP inhibitor

Metastatic Castrate Refractory Prostate Cancer (mCRPC)

Study AB12003 evaluated masitinib 6.0 mg/kg/day in combination with docetaxel versus docetaxel alone in first-line treatment of mCRPC

Design

Design

Prospective, multicenter, randomized, double blind, placebo-controlled, 2-parallel groups, phase 3 study

Groups

- Masitinib 6.0 mg/kg/day + Docetaxel at 75 mg/m² versus Placebo + Docetaxel at 75 mg/m²
- Randomisation: 1:1

Enrolment

- 451 patients in sub-group of early metastases (biomarker : ALP ≤ 250 IU/ml)
- 714 patients in the overall population

Primary endpoint: Progression Free Survival (PFS as per PCWG2)

Main inclusion criteria

1) Patient with histologically or cytologically confirmed metastatic Castrate Resistant Prostate Cancer (medical or surgical castration: androgens deprivation by GnHR agonist or antagonist or patient with surgical castration; hormonal castration confirmed biologically (testosterone < 0.5ng/ml) with one of the following criteria:
   - Pre-treated with abiraterone with progressed disease documented, OR
   - With indication for initiating docetaxel administration (e.g., widespread visceral disease or rapidly progressive disease).
2) Patient with evidence of progressive metastatic disease.
3) Patient with ECOG ≤ 1

Pre-specified Analysis Plan

The study tested the success of the primary endpoint in two populations

- Overall population
- Targeted subgroup of interest based on Alkaline Phosphatase (ALP) ≤ 250 IU/ml

Targeted subgroup of interest

- Patients most likely to respond to masitinib is predefined as patients with lower extent of metastases based on biologic biomarker (ALP ≤ 250 IU/ml)
- It was assumed that approximately that 67% of the overall population will constitute of the targeted subgroup

Control of Alpha Risk:

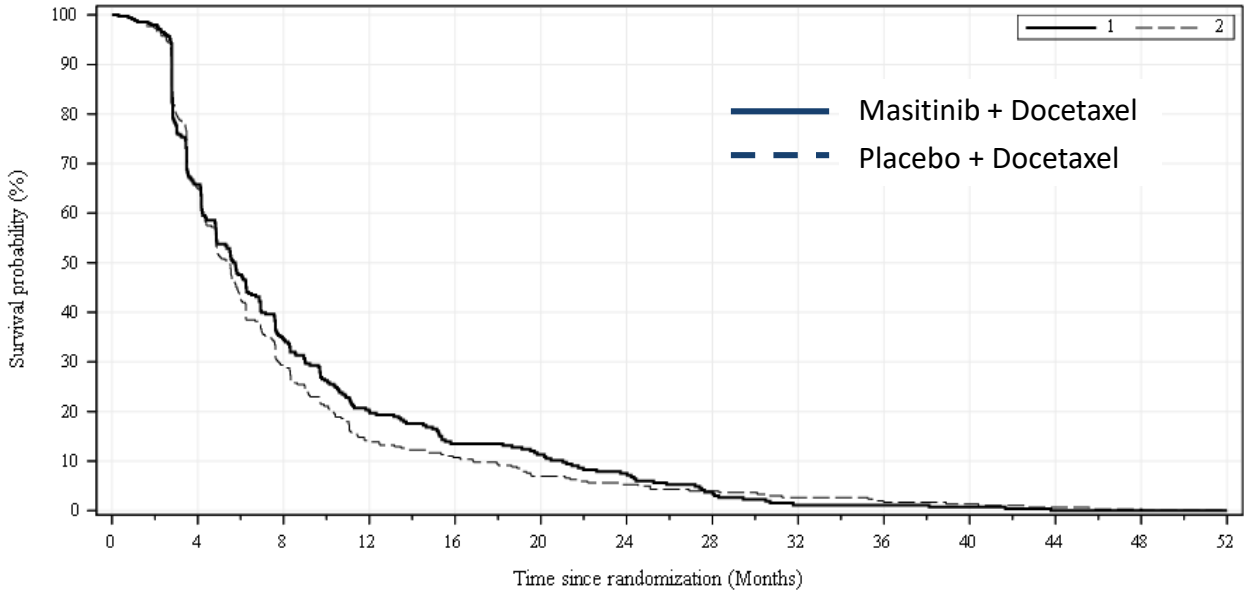
- Split with fallback procedure
- 4% in the targeted subgroup (ALP≤ 250 IU/ml). If positive then test at 5% on overall population

Metastatic Castrate Refractory Prostate Cancer (mCRPC)

There was no benefit in the overall population, yet the study met its primary analysis in the pre-specified targeted subgroup, demonstrating a statistically significant increase in PFS (p=0.0272)

No benefit on PFS in the Overall Population

Kaplan Meier Analysis of Overall PFS – Overall Population

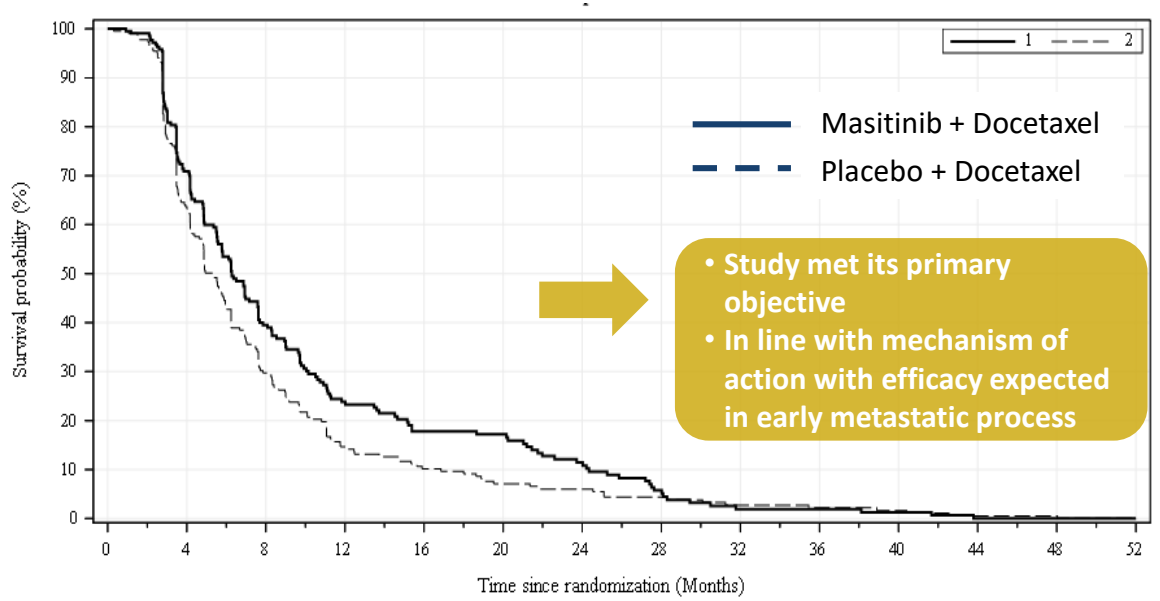


Treatment group	Total	No. of Events	% censored	Median [96.1% CI]	Log Rank p-value	Hazard Ratio (95% CI)
Masitinib	355	313	11.83	5.7 [4.9;6.3]	0.2977	0.94 (0.81,1.10)
Placebo	357	335	6.16	5.4 [4.9;5.9]		

2 patients without study drug administration excluded from ITT population

21% risk reduction of time to progression in patients with ALP ≤ 250 IU/ml

Kaplan Meier Analysis of Overall PFS – Targeted sub-population



Treatment group	Total	No. of Events	% censored	Median [96.1% CI]	Log Rank p-value	Hazard Ratio (96.1% CI)
Masitinib	225	191	15.11	6.3 [5.6;7.6]	0.0272	0.79 (0.64,0.97)
Placebo	225	209	7.11	5.4 [4.6;6.0]		

Oncology

Strong market potential across indications

Indication	Phase of Development	Annual cost of drugs registered in similar indication (USD)	No US Patients	No EU Patients	Penetration	Market Opportunity US (M€)	Market Opportunity EU (M€)
Prostate Cancer	Positive phase 2/3 interim analysis	• Xtandi (90,000) • Jevtana (48,000) • Zytiga (60,000) • Keytruda (145,000)	50,000[6]	75,000[6]	33%	1,000 *(based on a 60,000€ annual price)*	1,500 *(based on a 60,000€ annual price)*
Pancreatic Cancer	Positive phase 2/3 interim analysis	• Abraxane (240,000) • Tarceva (27,000) • Erlotinib (6,500)	[7,500 ; 15,000][7]	[12,500 ; 25,000][7]	25%	[125 ; 250] *(based on a 60,000€ annual price)*	[200 ; 375] *(based on a 60,000€ annual price)*

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

6 : National Cancer Institute, Prostate Cancer statistics
Scher 2015 – PLoSONE - Symptomatic mCRPC that has not been treated with or not progressed on chemotherapy

7 : National Cancer Institute, Pancreatic Cancer statistics, 2015
Data from study AB07012
Balaban EP, et al. Locally Advanced Unresectable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline Summary. J Oncol Pract. 2017 Apr;13(4):265-269. doi: 10.1200/JOP.2016.017376.

Masitinib in Viral Diseases

COVID-19

COVID-19

Cytokine storm syndrome and lung injury may be avoided by inhibiting mast cell and macrophage activity

Innate immune Cells	Implication in cytokine storm	Evidence of masitinib activity
Mast Cells	▪ Mast cells contribute to inflammation by activating inflammatory compounds (IL-6, IL-1, TNFα) (Kritas 2020) ▪ Mast cell degranulation promotes lung lesions (Hu Y, 2012) ▪ Altered mast cell activity contribute to pulmonary disorders (Jin, 2018)	▪ Inhibition of mast cells activity through c-Kit, LYN, and FYN. ▪ Efficacy in patients with mastocytosis in a phase 3 (Lortholary Lancet 2017) ▪ Prevention against acute chest syndrome in an animal model of sickle cell disease (SCD). ▪ Efficacy in pneumology in severe persistent asthma.
Macrophages	▪ Macrophage Activation Syndrome in COVID-19 (McGonagle D, 2020) ▪ Macrophages could contribute to viral spread, excessive inflammation and activation-induced lymphocytic cell death during COVID-19 infection (Park MD, 2020)	▪ Masitinib inhibits macrophage colony-stimulating factor 1 receptor MCSF1R with an IC50=90nM. ▪ MCSF1 receptor is crucial for the differentiation and survival of the macrophages (Stanley ER, 2014) ▪ In asthma mouse model of airway inflammation, Masitinib inhibited of 40% the infiltration of macrophages

COVID-19

First Phase 2 evaluating masitinib anti-inflammatory activity in adult hospitalized patients with moderate and severe COVID-19 without limitation of age (i.e. patients above 80 enrolled)

Phase 2 design

Design: Double blind, placebo controlled, randomized 1:1, comparing masitinib titration up to 6.0 mg/kg/day in combination with IsoQuercetin + Best supportive care with placebo + Best supportive care

Main inclusion criteria: Adult ≥ 18 years of age at time of enrolment (no limitation of age) with moderate and severe COVID-19 (classification 3 to 5 on WHO 7-point ordinal scale)

Enrolment: 200 patients

Duration: 30 days

Primary endpoint: Clinical status of patients at day 15 using the 7-point ordinal scale.

Key differentiating factors

The combination masitinib + IsoQuercetin differentiates from other strategies on key points

- Safety of masitinib and IsoQuercetin are well defined
- Targets the innate immune system cells upstream rather than the released interleukins downstream
- Can potentially prevent thrombosis (ICU and death)
- Can potentially treat the neurological symptoms
- Elderly people are the most exposed to death and masitinib and Isoquercetin combination is highly suited to treat aged people because of synergistic effect on senescent cells (enrolment of patients above 80 years old)

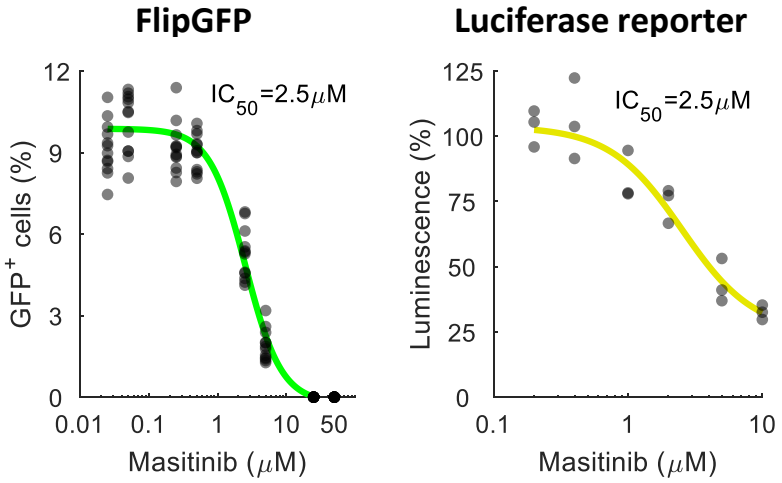
Status
Actively recruiting patients

ClinicalTrials.gov Identifier: NCT04622865

COVID-19

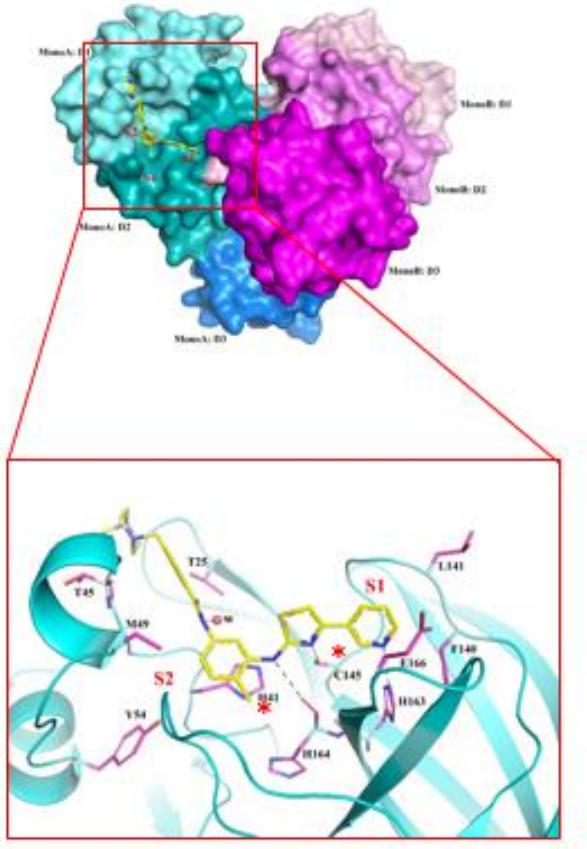
Publication in *Science* shows that masitinib completely inhibited in multiple assays 3CLpro activity, the SARS-CoV-2 main protease necessary for its viral replication cycle

Masitinib inhibits SARS-CoV-2 main 3CL-protease



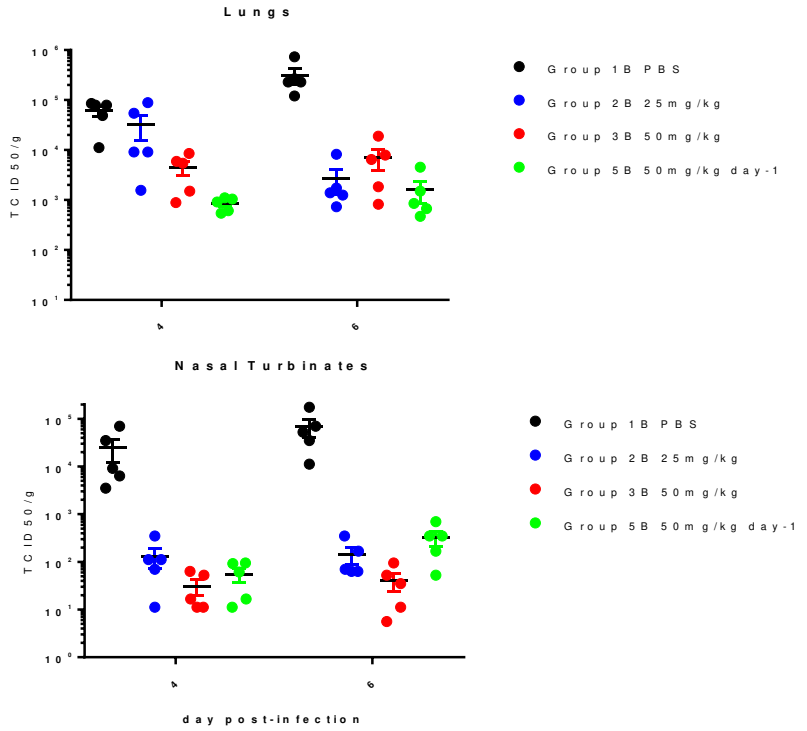
IC_5=2.5 µM in FlipGFP and luciferase reporter assays

Masitinib directly binds to the active site of 3CLpro, thereby having a direct antiviral activity by blocking its enzymatic activity



Masitinib inhibits efficiently the replication of SARS-CoV-2 *in vivo,* decreasing by ~2-3 Logs the viral load

Viral titers in Lung and nasal turbinates in masitinib-treated Tg-K18-hACE2 mice compared to placebo at 4dpi and 6 dpi.



COVID-19

Second Phase 2 evaluating masitinib anti-viral activity in ambulatory or hospitalized patients with symptomatic mild and moderate COVID-19

Phase 2 design

Design: Double-Blind, Placebo-Controlled, Multiple Doses, Comparative study

Main inclusion criteria:

- Symptomatic ambulatory adult with score 2 or 3 of the 10-score WHO scale OR Hospitalized adult with score 4 or 5 of the 10-score WHO scale.
- Symptoms with onset ≤5 days
- Positive test for COVID-19 ≤72 hours prior to randomization

Enrolment: 78 patients

Duration: 10 days

Primary endpoint: Time-weighted average change from baseline in viral shedding

Key differentiating factors

- Well established pharmacokinetic profile is at multiple doses, and is favourable for COVID-19 treatment, unlike peptidomimetic drugs targeting 3CL-protease, which are likely to be associated with bioavailability concerns.
- Synergistic effect between masitinib and Merck's Molnupiravir evidenced *in vitro*.
- Remains effective against all variant of concerns tested, including variant Delta.
- Well-established safety profile

Status

Authorized ; Patients recruitment to be initiated

ClinicalTrials.gov Identifier: NCT05047783

COVID-19

Blockbuster Opportunity

Indication	Phase of Development	Treatment cost of authorized drugs (USD)	No US Patients	No EU Patients	Penetration	Market Opportunity US (M€)	Market Opportunity EU (M€)
Hospitalized Patients with Moderate to Severe COVID-19	Phase 2 study to evaluate efficacy of masitinib combined with Isoquercetin in the moderate and severe forms COVID-19	• Eli Lilly monoclonal antibody cocktail (~5,000) • Regeneron antibody cocktail (~2,500)	600,000[1]	900,000[1]	25%	[375 - 750] *(based on treatment price between 2,500 and 5,000€)*	[550 – 1,100] *(based on treatment price between 2,500 and 5,000€)*
Non-hospitalized and hospitalized patients with symptomatic Mild to Moderate COVID-19	Phase 2 study to evaluate the anti-viral efficacy of masitinib in the symptomatic mild to moderate forms of COVID-19	Molnupiravir (~710 per treatment course)	1,100,000[2]	1,650,000[2]	25%	200 *(based on treatment price of 700€)*	300 *(based on treatment price of 700€)*

Source :

1 :

- As of September 15, 2021, the number of current active cases in Europe and in the US amounts to approxiamtely 13,500,000 (source: Worldometer COVID-19 Data)
- Regarding the expected trend of Covid-19 active cases in the next 12 months in Europe and in the US, AB Science made the following assumptions:
  - Between September 2021 and September 2022, decrease of the number of active cases in Europe and in the US, due to the massive vaccination campaign, to reach 5,000,000 by September 2022
  - September 2022 and beyond: steady number of active cases in Europe and US, amounting to 5 million approximately
- In this indication, since masitinib targets moderate and severe forms of Covid-19, the number of eligible patients amounts to approximately 30% of all Covid-19 patients (source : COVID-19: Clinical features, Kenneth McIntosh, September 2021)

2 :

- Same assumptions have been considered for the expected number of active cases in Europe and in the US
- In this indication, since masitinib targets mild and moderate forms of Covid-19, the number of eligible patients amounts to approximately 55% of all Covid-19 patients (source : COVID-19: Clinical features, Kenneth McIntosh, September 2021)

Masitinib – Main Publications

Neurology

Program	Data	Publications
ALS	Preclinical	• Trias et al, 2020 : Schwann Cells Orchestrate Peripheral Nerve Inflammation Through the Expression of CSF1, IL-34, and SCF in Amyotrophic Lateral Sclerosis • Trias et al, 2018 : Mast cells and neutrophils mediate peripheral motor pathway degeneration in ALS • Trias et al, 2017 : Evidence for mast cells contributing to neuromuscular pathology in an inherited model of ALS • Trias et al, 2016 : Post-paralysis tyrosine kinase inhibition with masitinib abrogates neuroinflammation and slows disease progression in inherited amyotrophic lateral sclerosis
	Phase 3	• Mora et al, 2021 : Long-term survival analysis of masitinib in amyotrophic lateral sclerosis • Mora et al, 2019 : Masitinib as an add-on therapy to riluzole in patients with amyotrophic lateral sclerosis: a randomized clinical trial
Alzheimer's Disease	Phase 2	• Piette et al, 2011 : Masitinib as an adjunct therapy for mild-to-moderate Alzheimer's disease: a randomised, placebo-controlled phase 2 trial
	Phase 2B/3	• 2021 Alzheimer's Association International Conference (AAIC)
MS progressive	Phase 2	• Vermersch et al, 2012 : Masitinib treatment in patients with progressive multiple sclerosis: a randomized pilot study
	Phase 2B/3	• MSVirtual2020 joint ECTRIMS/ACTRIMS conference

Masitinib – Main Publications

Immunology, oncology and viral diseases

Program	Data	Publications
Mastocytosis	Phase 2	• Paul et al, 2010 : Masitinib for the treatment of systemic and cutaneous mastocytosis with handicap: a phase 2a study
	Phase 3	• Lortholary et al, 2017 (Lancet) : Masitinib for treatment of severely symptomatic indolent systemic mastocytosis: a randomised, placebo-controlled, phase 3 study
Severe Asthma	Preclinical	• Lee-fowler et al, 2012 : The tyrosine kinase inhibitor masitinib blunts airway inflammation and improves associated lung mechanics in a feline model of chronic allergic asthma
	Phase 2	• Humbert et al, 2009 : Masitinib, a c-kit/PDGF receptor tyrosine kinase inhibitor, improves disease control in severe corticosteroid-dependent asthmatics
	Phase 3	• EAACI Virtual 2020 Congress / ERS 2020 Congress
Pancreatic Cancer	Preclinical	• Humber et al, 2010 : Masitinib combined with standard gemcitabine chemotherapy: in vitro and in vivo studies in human pancreatic tumour cell lines and ectopic mouse model
	Phase 2	• Mitry et al, 2010 : Safety and activity of masitinib in combination with gemcitabine in patients with advanced pancreatic cancer
	Phase 3	• Delplanque et al, 2015 : A randomized, placebo-controlled phase III trial of masitinib plus gemcitabine in the treatment of advanced pancreatic cancer
Metastatic Prostate Cancer	Phase 3	• American Urological Association (AUA) 2021 Annual Meeting
Covid-19	Preclinical	• Drayman et al, 2021 : Masitinib is a broad coronavirus 3CL inhibitor that blocks replication of SARS-CoV-2

AB8939

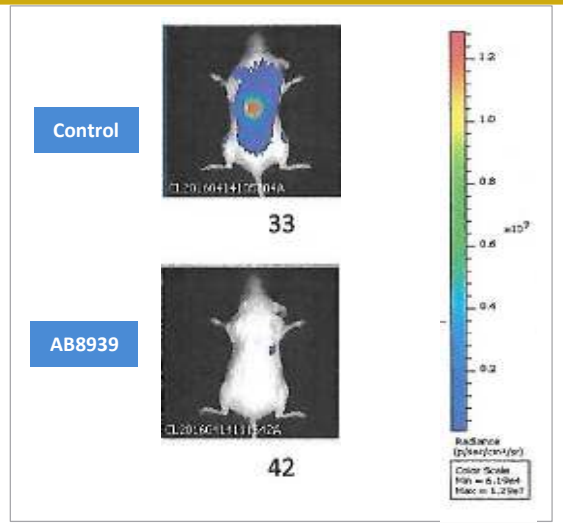
AB8939

Novel Microtubule-destabilizing Agent for Acute Myeloid Leukemia

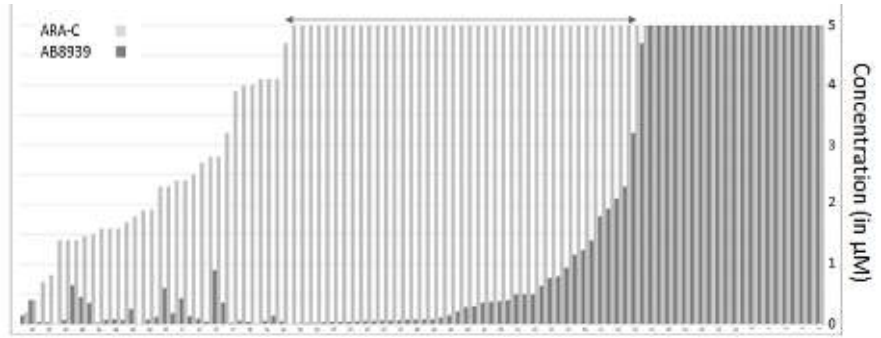
Key Differentiating factors

- Overcomes P-glycoprotein (Pgp) and myeloperoxidase (MPO) mediated resistance
- Active in Ara-C resistant/refractory AML
- Activity seen across all AML subtypes
- Alone or combined with Ara-C, improved survival and reduced disease burden relative to Ara-C
- Active in azacitidine resistant AML, with greatly reduced hematotoxicity
- Drug profile support development of AB8939 as a treatment of relapsed/refractory AML patients unable to receive intensive chemotherapy

Detection of AMKL26 PDX blasts in mice following single agent AB8939 treatment



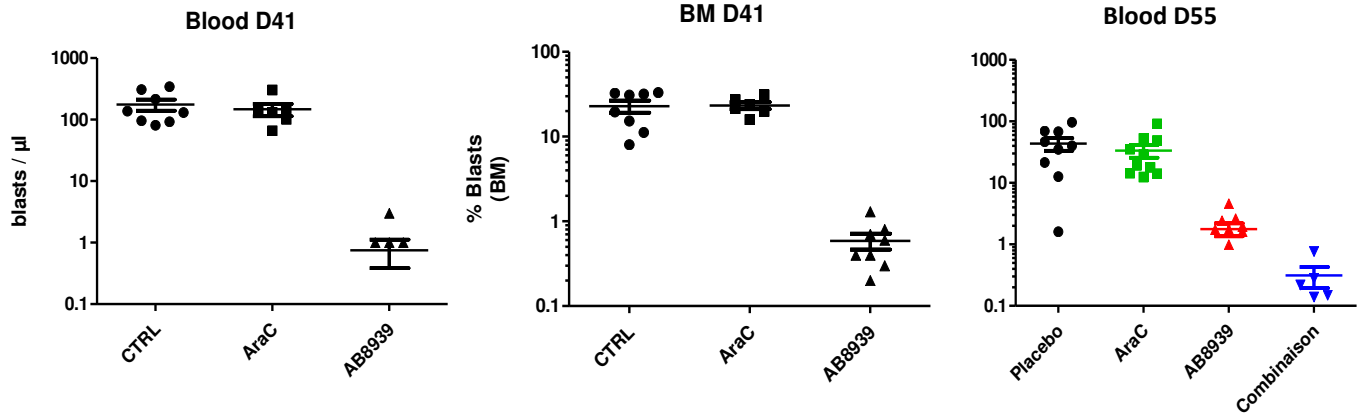
Activity of AB8939 in Ara-C resistant/refractory AML patent blasts



Sample cells from AML patients

In proliferation assays, 66% of Ara-C-resistant blasts were sensitive to AB8939 and overall 69% of blasts had nanomolar sensitivity ($IC_{50} \leq 500$ nM)

Activity in Ara-C resistant PDX model



Blasts detection in blood and bone marrow (BM) of the PDX#5 mouse model at D41 post graft and at D55 post graft

Relapsed/ Refractory Acute Myeloid Leukemia (AML)

Phase 1/2 to assess the safety, pharmacokinetics, and efficacy of AB8939 in patients with Relapsed/ Refractory AML

Phase 1/2 design

Design: Open-label, Uncontrolled, Multiple Doses, phase 1 study

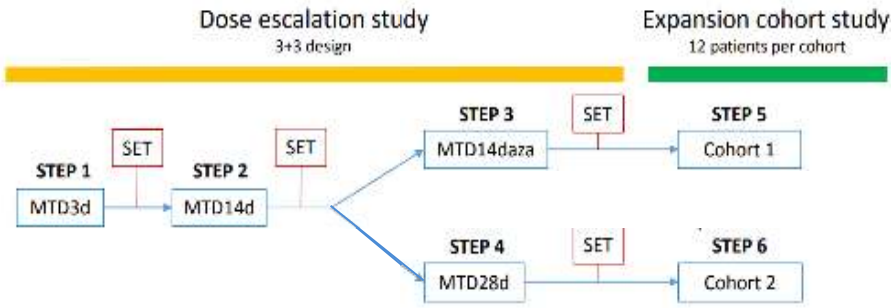
Main inclusion criteria:

- Patients with documented diagnosis of AML
- Patients in 2nd or 3rd line of treatment (if eligible in 1st line to high dose chemotherapy) OR in 2nd line of treatment (if not not eligible to high dose chemotherapy)
- Patients with refractory melyodisplastic syndrome in 2nd or 3rd line of treatment , and with high risk at prognostic based on the IPSS-R scoring system.
- Patients not eligible to hematopoietic stem cell transplantation (HSCT) at the time of inclusion

Enrolment: 72 patients expected

Duration: up to 28 days

Phase 1/2 Objectives



Phase 1 : Dose escalation

- Identify Maximum Tolerated Dose (MTD)
- Determine the pharmacokinetics profile
- Recommend dose of expansion cohort

Phase 2 : Expansion cohort

- Identify MTD of AB8939 + azacitidine at 14 days and AB8939 alone at 28 days
- Determine early efficacy

Status

Authorized ; Patients recruitment to be initiated