AB SCIENCE

Corporate Presentation

November 2020

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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 potential opportunity in viral diseases as masitinib has been shown *in vitro* to block 3CL protease activity**
- New compound: AB8939, next generation, synthetic microtubule destabilizer not binding to PgP

Late stage pipeline

- **Five positive Phase 2B/3 read outs**, in amyotrophic lateral sclerosis (ALS), progressive forms of multiple sclerosis, mastocytosis (ISM), and in severe asthma (uncontrolled by oral corticosteroids and uncontrolled by inhaled corticosteroids)

Strong IP position

- **IP 100% owned** by AB Science and unpartnered
- Patent protection until 2037 in ALS and up to 2036 in other indications

Pipeline

Diversified portfolio with five positive phase 2B/3 trials

Compound	Therapeutic area	Indication	Preclinical	Phase 1/2	Phase 2B/3	Confirmatory Phase 3
Masitinib	Neurology Diseases	Amyotrophic Lateral Sclerosis*				
		Progressive forms of Multiple Sclerosis*				
		Alzheimer's Disease				
	Inflammatory Diseases	Indolent Systemic Mastocytosis*				
		Severe Asthma Uncontrolled with OCS*				
		Severe Asthma Uncontrolled with ICS*				
	Oncology	Metastatic Prostate Cancer				
		Pancreatic Cancer				
	Viral Diseases	Moderate and severe COVID-19				
AB8939	Oncology	Acute Myeloid Leukemia				

** Positive Phase 2B/3 Results Reported*

Pathway to Registration

Regulatory pathway to NDA validated for three indications

Confirmatory phase 3

- Amyotrophic Lateral Sclerosis - ***Inititated***
- Indolent Systemic Mastocytosis - ***Inititated***
- Progressive forms of Multiple Sclerosis – ***To be Inititated in 2021***

Interaction with health authorities for NDA filing or confirmatory phase 3 study

- Severe asthma – ***Decision 2021***

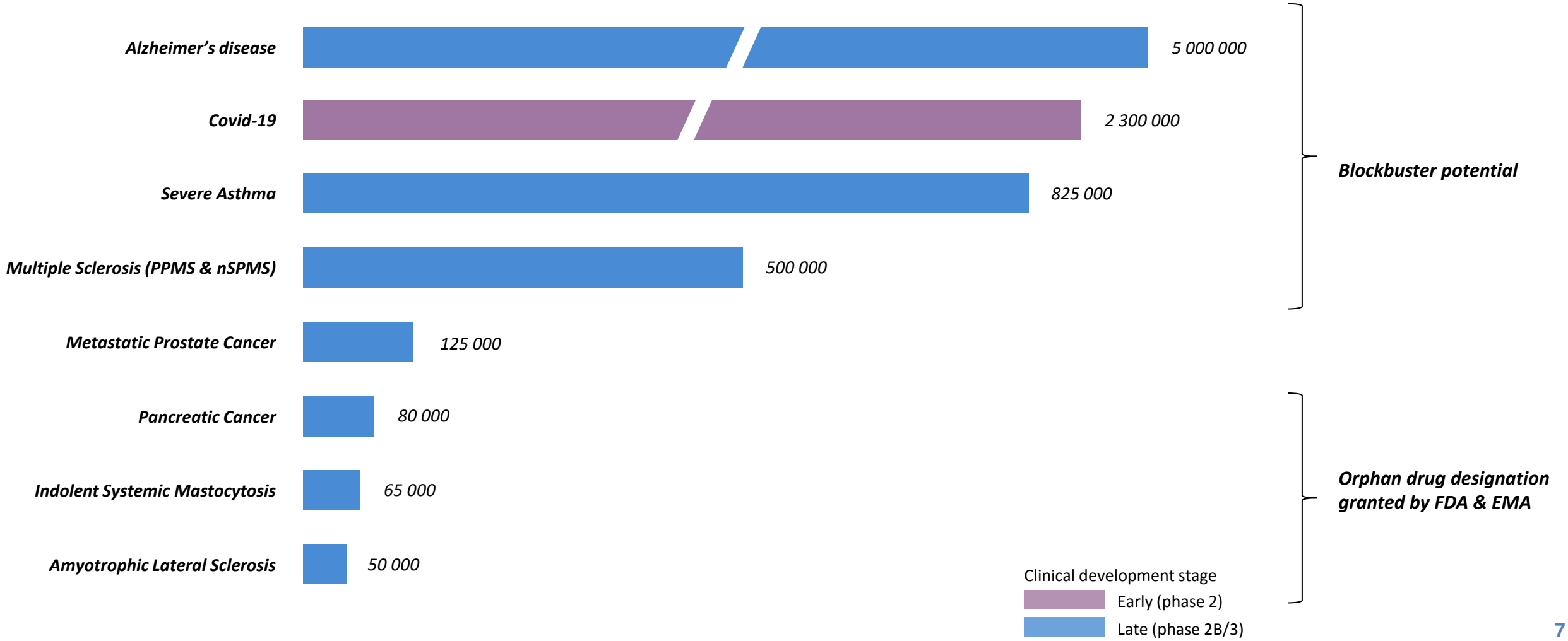
Depending on study readout

- Alzheimer's Disease – ***Q4 2020***
- Pancreatic Cancer – ***Q4 2020***
- Metastatic Prostate Cancer – **2021**
- Covid-19 - **2021**

Market Potential

Blockbuster potential but also addressing orphan diseases

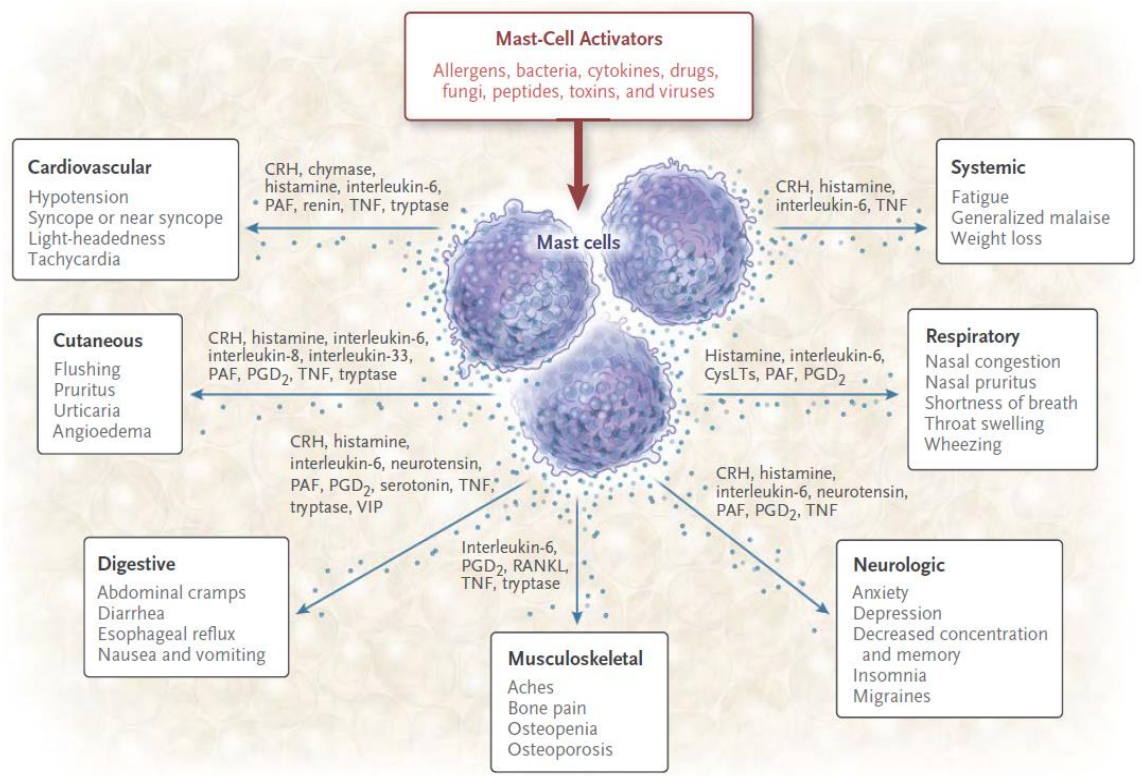
Estimated Number of patients (USA and EU) in targeted indications with masitinib



Critical Role of Mast Cells & Macrophages/Microglia

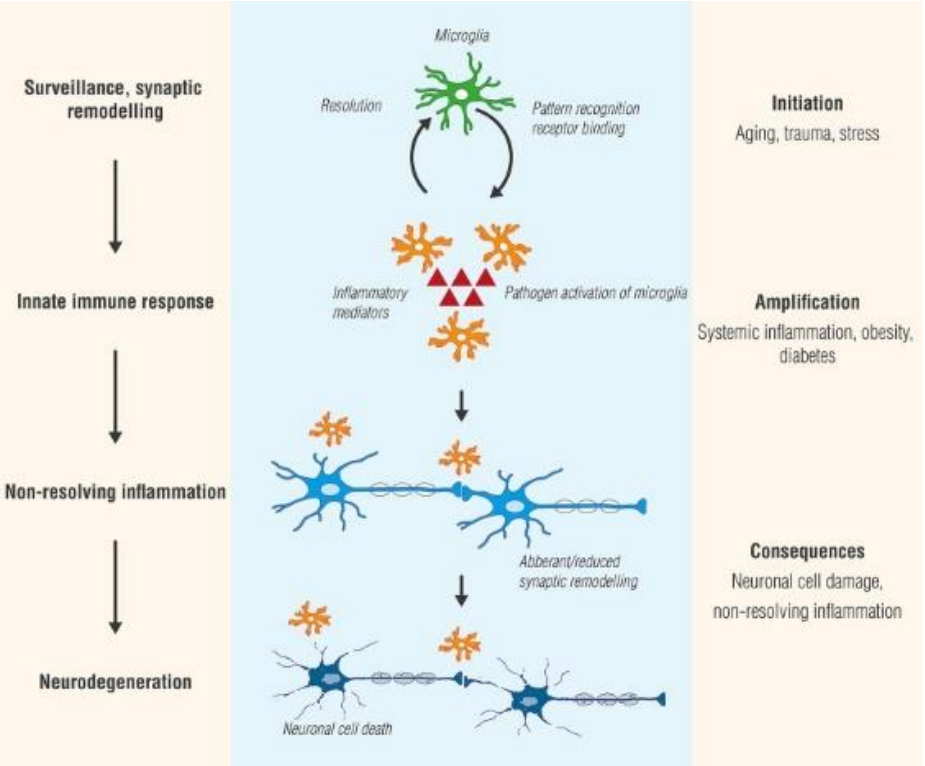
Mast cells and microglia contribute to neuro-inflammation, which is strongly influenced by their potential for mutual interaction and exacerbation of pathology

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

Masitinib Profile and Mechanism of Action

Orally-administered kinase inhibitor selectively targeting mast cells and macrophages

Masitinib targets mast cells

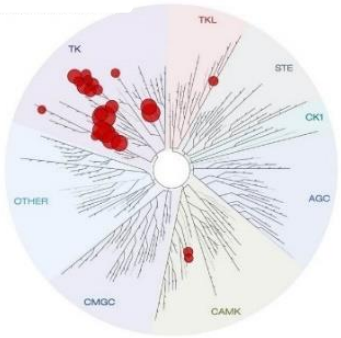
- Masitinib is a potent and selective inhibitor of c-Kit, Lyn, and Fyn kinases. These kinases play critical roles in the activation of mast cells
- Mast cells are a target in neurodegenerative diseases, inflammatory diseases and in oncology

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

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	3,317	2,120	1,515	662	50
Oncology subjects	3,321	1,114	513	196	45
Total	**6,752**	**3,234**	**2,028**	**858**	**95**

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

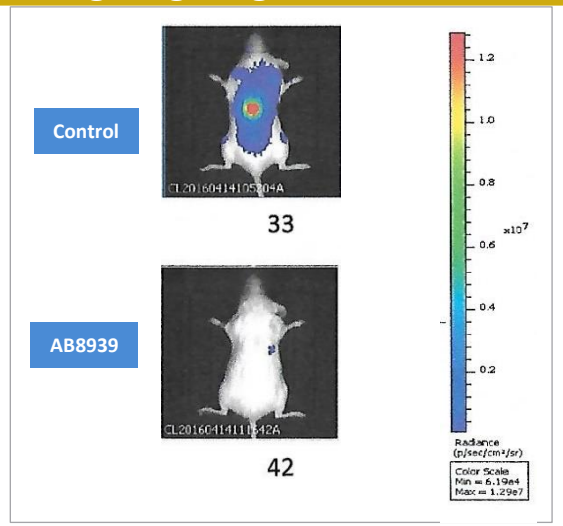
AB8939

Novel Microtubule-destabilizing Agent for Acute Myeloid Leukemia

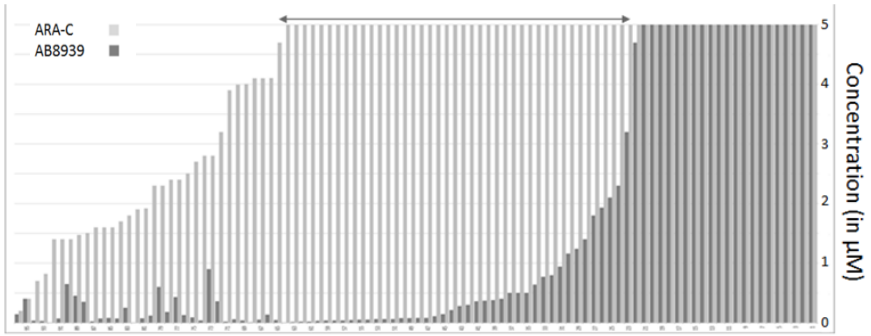
Key Differentiating factors

- 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



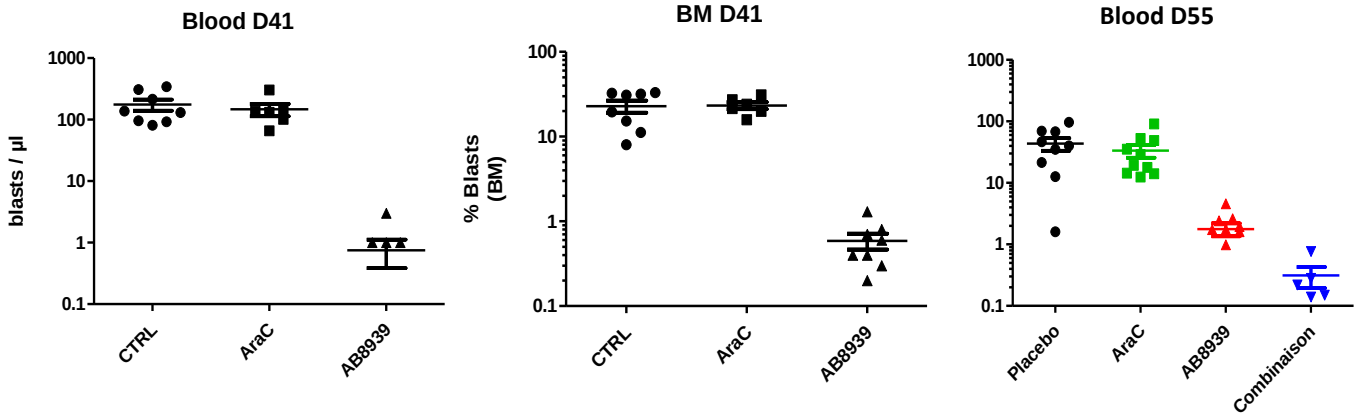
Activity of AB8939 in Ara-C resistant/refractory AML patent blasts



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

Upcoming newsflow

Important catalysts are expected through Q4 2020 and 2021

Q4 2020

- Report top-line results from phase 2B/3 with masitinib in Alzheimer Disease (n=720)
- Report top-line results from phase 3 with masitinib + gemcitabine in pancreatic cancer (n=380)

2021

- Report top-line results from phase 3 with masitinib + docetaxel in metastatic prostate cancer (n=470)
- Report top-line results from phase 2 with masitinib + Isoquercetin in COVID-19 patients (n=200)

Neurology Diseases

Multiple Sclerosis (PPMS and nSPMS)

Amyotrophic Lateral Sclerosis (ALS)

Alzheimer's Disease (AD)

Multiple Sclerosis

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

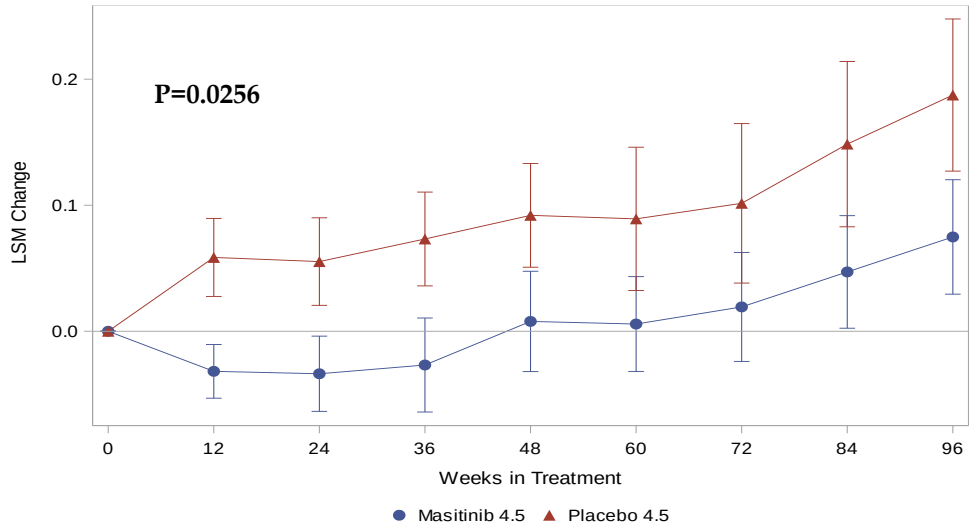
	Manufacturer	Masitinib Positioning		Label		First approved
		Primary Progressive MS	Non-active Secondary Progressive MS*	Active Secondary Progressive MS	Relapsing Remitting MS	
Distribution of patients *(Estimated Nbr of patients Europe + USA)*		**15%** *(~ 150 000)*	**35%** *(~ 350 000)*	**10%** *(~ 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.*

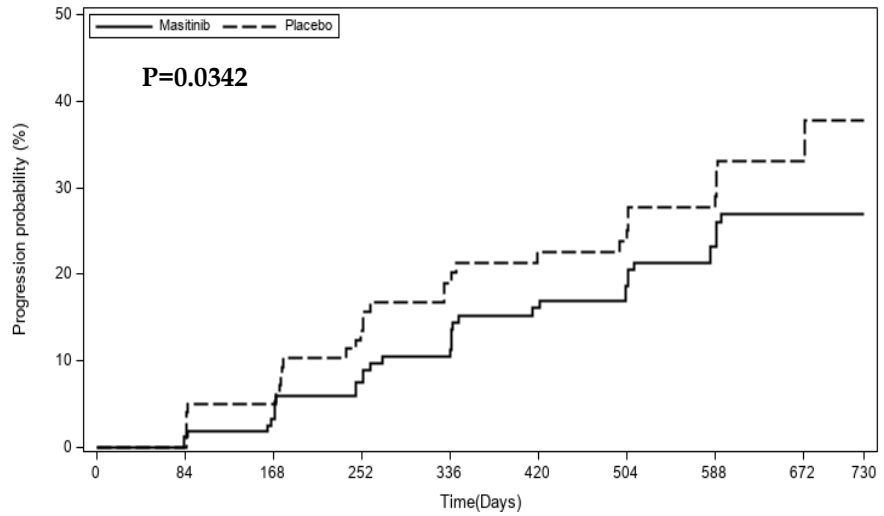
Multiple Sclerosis

Phase 2B/3 demonstrated significant benefit on disability progression

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

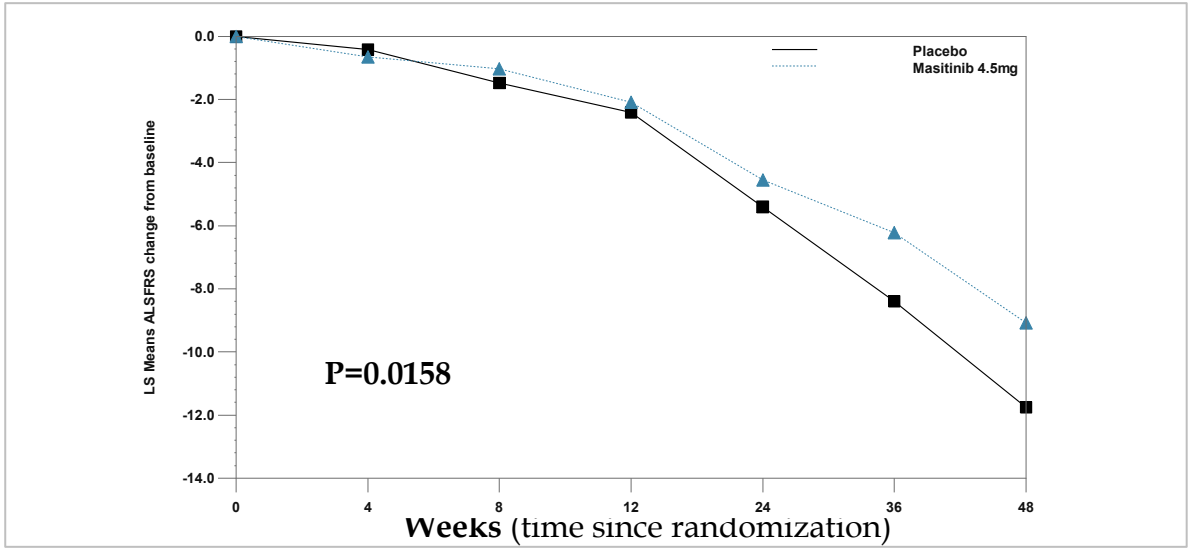
Presented at MSVirtual2020 joint ECTRIMS/ACTRIMS conference

ClinicalTrials.gov Identifier: NCT01433491

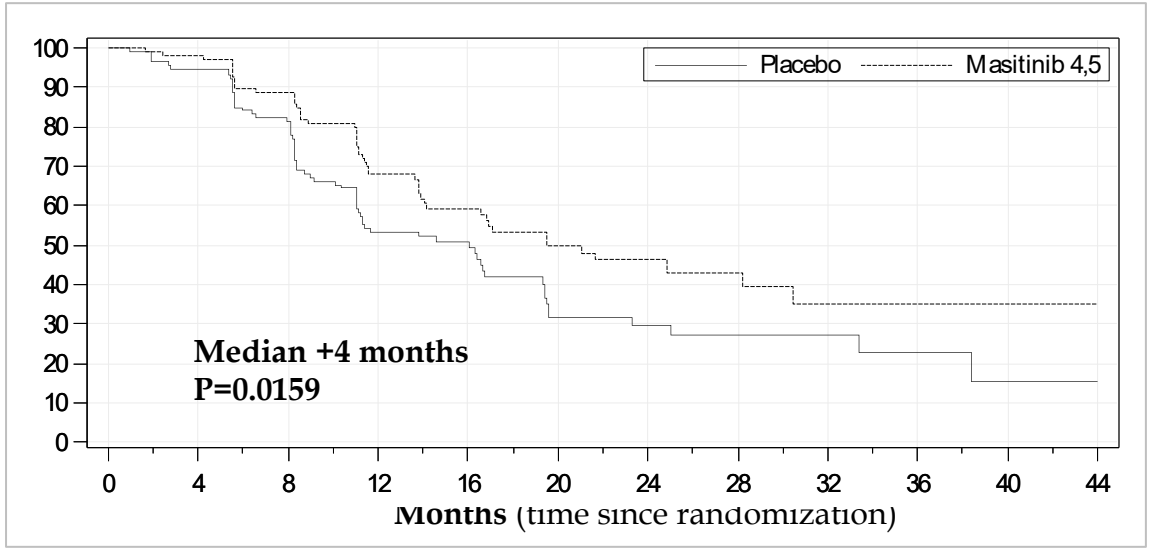
ALS

Phase 2B/3 demonstrated significant delay in disease progression

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.

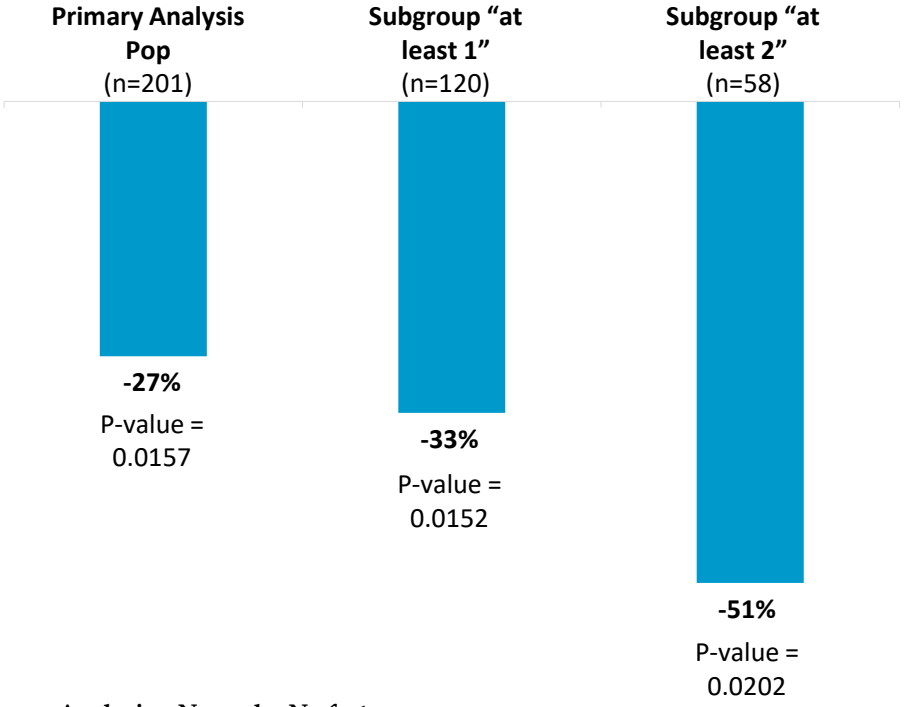
Amyotroph Lateral Scler Frontotemporal Degener. 2020 Feb;21(1-2):5-14. doi: 10.1080/21678421.2019.1632346. ClinicalTrials.gov Identifier: NCT02588671

ALS

Clinical benefit further enhanced when treatment initiated early

51% slowing of functional deterioration (vs 27%)

% reduction in change in ALSFRS (primary endpoint)



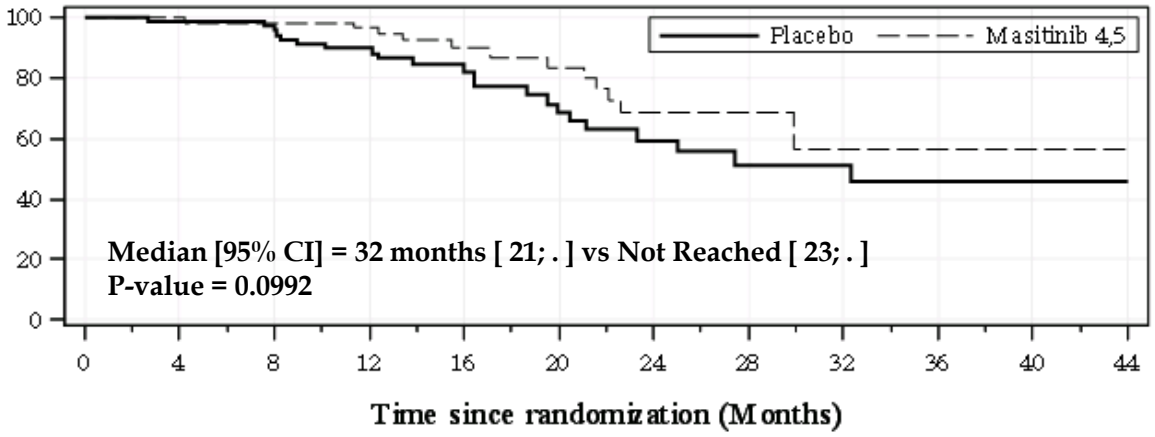
Primary Analysis : Normal = No fast progressors
At least 1 subgroup* : No 0, Diag 24, no slow no fast prog.
At least 2 subgroup*: No 0, No 1, Diag 24, no slow no fast prog.
** post-hoc analyses*
Diag 24' : Disease duration ≤24 months. 'No 0' : Exclude patients with a score of 0 on any of the 12 ALSFRS-R individual component items. 'No 1' : Exclude patients with a score of 1 on any of the 12 ALSFRS-R individual component items. 'slow' : <1-point decline over 3 months prior to randomization. 'Fast' : >4-point decline over 3 months prior to randomization

Significant improvement on Combined Assessment of Function & Survival

At least 1 subgroup	Diff. of means	p-value
Control	15.79	0.0159
Masitinib 4.5		

Trend of improvement on Overall Survival

Subgroup "at least 1"



Similar analysis was performed in the At least 2 subgroup (At least 2 on each item, Diag 24, no slow no fast). Similar trend was observed but not significant due to the size of the subgroup.

ClinicalTrials.gov Identifier: NCT02588671

ALS

Next Step — Confirmatory phase 3 study, with design optimized based on first phase 3 study

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, 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), Exclusion of fast progressors (more than a 4-point decline over 3 months prior to randomization). 50 fast progressors included for exploratory analysis, FVC ≥ 60%

Enrolment: 500 patients

Primary endpoint: Change in the ALSFRS-R score at 48 weeks.

Duration: 48 weeks

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

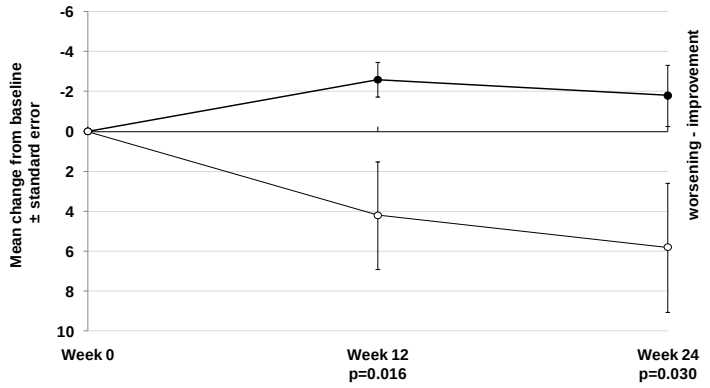
ClinicalTrials.gov Identifier: NCT04333108

Alzheimer’s disease

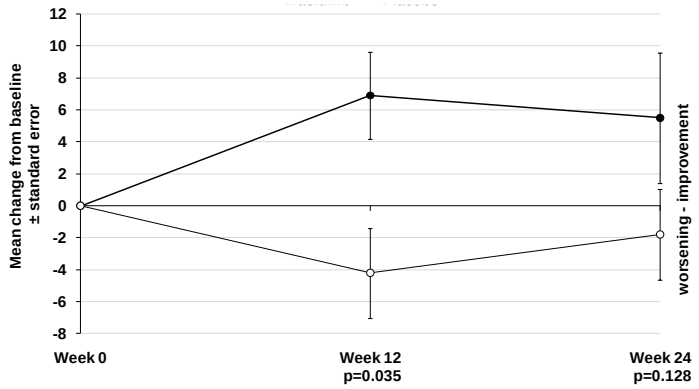
Phase 2B/3 has been completed

Activity on cognition established in proof of concept study

Change in ADAS-Cog



Change in ADCS-ADL



Phase 2a (n=34)

- ● Masitinib
- ○ Placebo

3(2):16. doi:

10.1186/alzrt75.

On-going phase 2B/3 design

Design: Double blind, placebo controlled, comparing masitinib 4.5 mg/kg/day vs. placebo (randomization 1:1) and masitinib titration up to 6.0 mg/kg/day vs. placebo (randomization 2:1)

Main Inclusion Criteria: Dementia of Alzheimer's type, according to DSM-IV criteria, Probable Alzheimer' disease according to NINCDS-ADRDA criteria, and MMSE ≥ 12 and ≤ 25

Enrolment: 720 patients

Primary endpoint: Change on ADAS-Cog at 24 weeks (effect on cognition and memory), or Change on ADCS-ADL at 24 weeks (effect on self-care and activities of daily living)

Duration: 24 weeks

ClinicalTrials.gov Identifier: NCT01872598

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
(3) Ragonese P *et al*. Incidence of amyotrophic lateral sclerosis in Sicily: A population based study. *Amyotroph Lateral Scler*. 2012; 13(3):284-7
(4) Abhinav K *et al*. Amyotrophic lateral sclerosis in South-East England: a population-based study. The South-East England register for amyotrophic lateral sclerosis (SEALS Registry). *Neuroepidemiology*. 2007;29:44-8
(5) Imam I *et al*. The epidemiology of motor neurone disease in two counties in the southwest of England. *J Neurol*. 2010; 257:977-81
(6) Hoppitt T *et al*. A systematic review of the incidence and prevalence of long-term neurological conditions in the UK. *Neuroepidemiology*. 2011; 36:19-28
(7) Gundersen MD *et al*. Incidence and Clinical Features of Amyotrophic Lateral Sclerosis in Møre and Romsdal County, Norway. *Neuroepidemiology.* 2011;37:58–63

3 : Weili Xu et al. Epidemiology of Alzheimer's Disease. 2013.doi: 10.5772/54398 and https://www.j-alz.com/editors-blog/posts/when-do-we-diagnose-severe-alzheimers-disease

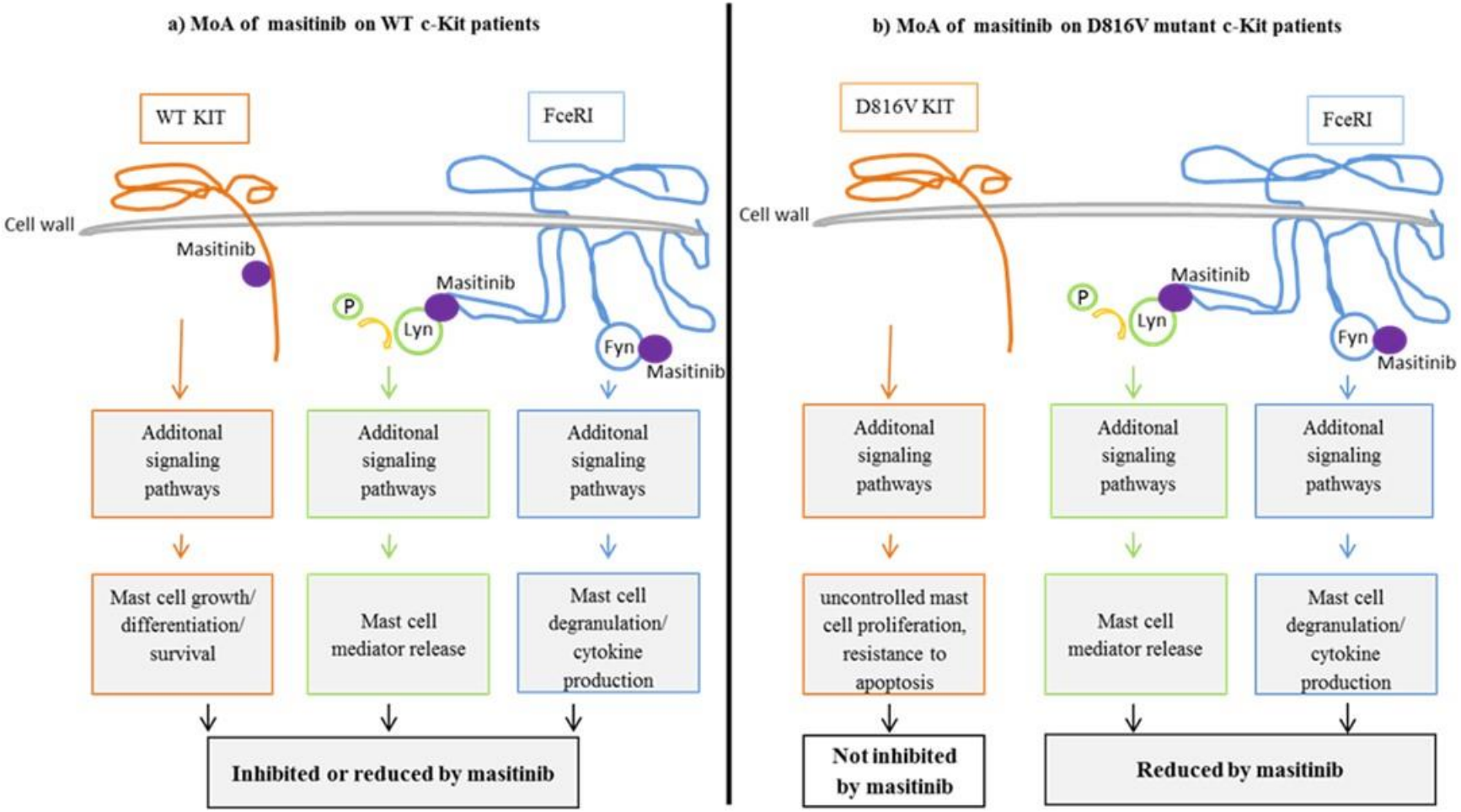
Inflammatory Diseases

Indolent Systemic Mastocytosis (ISM)

Severe Asthma

Indolent Systemic Mastocytosis

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



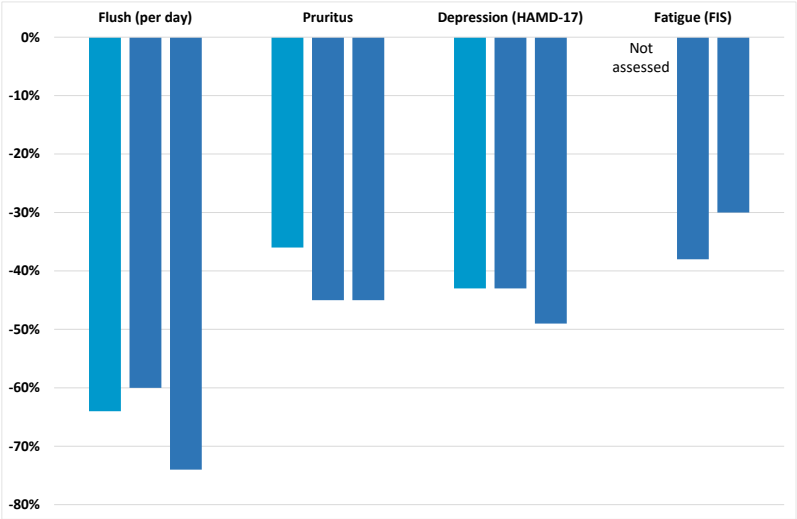
The c-Kit receptor is primarily responsible for mast cell growth, differentiation and survival with mast cell mediator release being initiated through the integration of downstream signaling pathways of c-Kit and FcεRI. D816V mutant c-Kit receptors result in uncontrolled mast cell proliferation and resistance to apoptosis. Masitinib inhibits WT c-Kit, Lyn and Fyn. In WT c-Kit mast cells (panel a) masitinib directly inhibits mast cell activation via inhibition of WT c-Kit, while mast cell mediator release and cytokine production are inhibited through targeting of Lyn and Fyn. In D816V mutant c-Kit mast cells (panel b) masitinib inhibits mast cell degranulation and cytokine production via Lyn and Fyn inhibition.

Indolent Systemic Mastocytosis

Effectiveness regardless of c-Kit mutation status confirmed in phase 2 and sustainable

Improvement in disease symptoms

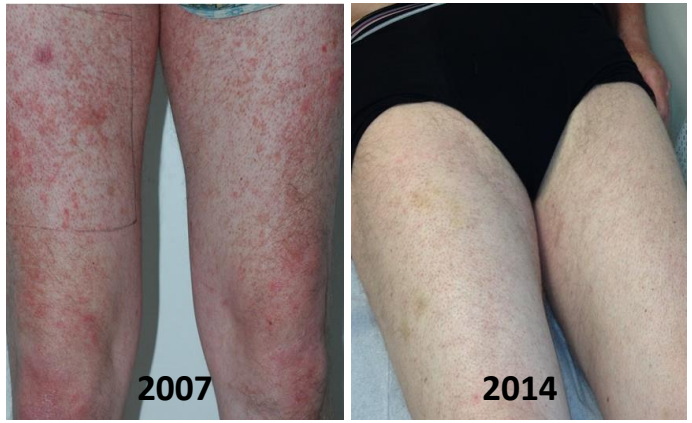
% Change from baseline at week 12



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

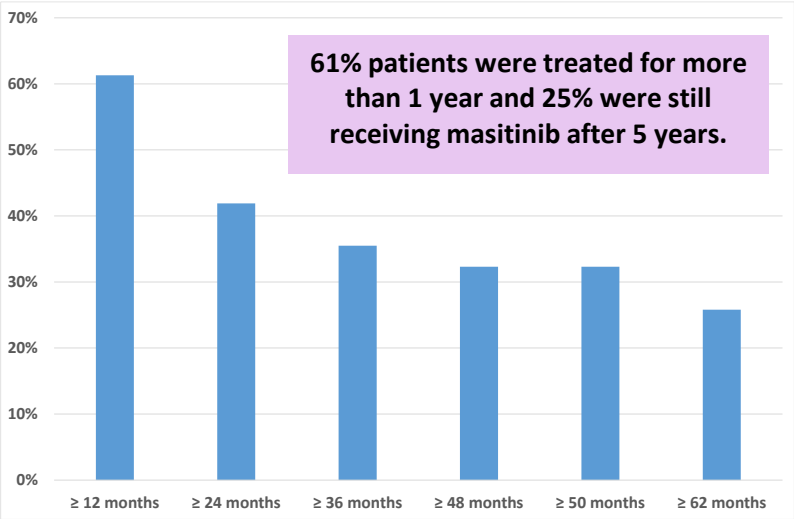
Phase 2 without c-Kit D816V (n=25,single arm)
(Middle columns represents patients with moderate baseline symptoms and right column represents patient with severe baseline symptoms)

Reduction in urticaria pigmentosa



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)

ClinicalTrials.gov Identifier: NCT01266369 & NCT00831974

Indolent Systemic Mastocytosis

Phase 3 demonstrates significant reduction in symptoms

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

Next Step Confirmatory phase 3 study, with design optimized based on first phase 3 study

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

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.

Duration: 24 weeks

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

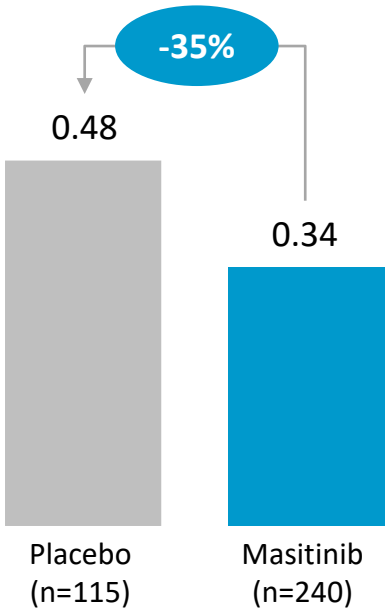
ClinicalTrials.gov Identifier: NCT04333108

Severe Asthma Uncontrolled with Oral Corticosteroids

Significant decreases in asthma exacerbations regardless of eosinophil level

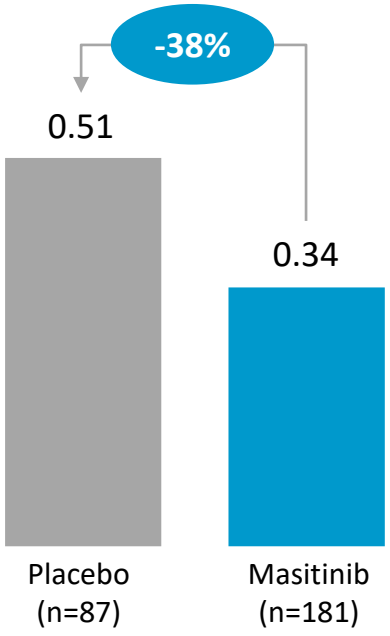
Annualized severe asthma exacerbation rate

Primary Analysis



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

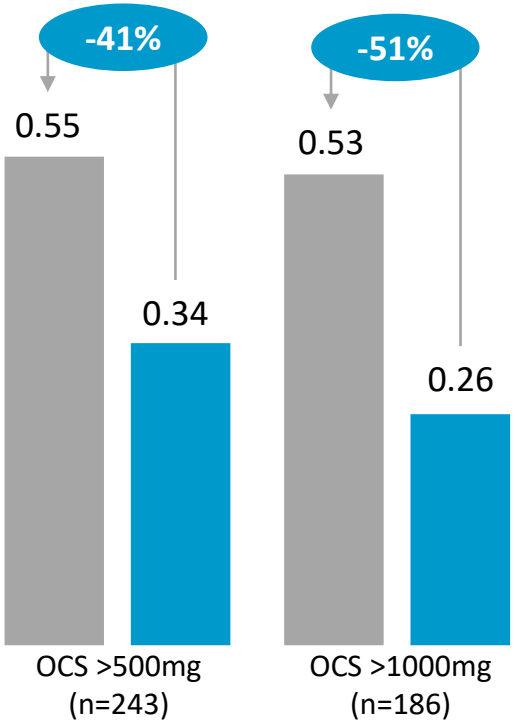
Sequential Analysis patients with EOS>150



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

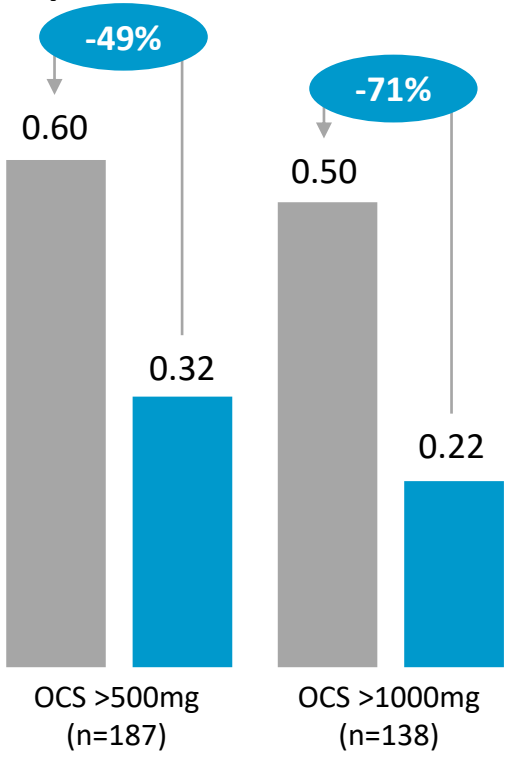
Greater benefit in patients with higher cumulative OCS

Sensitivity Analysis



P-value = 0.0092 P-value = 0.0060

Sensitivity Analysis patients with EOS>150



P-value = 0.0049 P-value = 0.0003

Higher cumulative OCS is indicative of more severe asthma

Presented at EAACI Virtual 2020 Congress / European Respiratory Society (ERS) 2020 Congress

ClinicalTrials.gov Identifier: NCT01449162

Severe Asthma Uncontrolled with Inhaled Corticosteroïds

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

Design of study AB14001

- Prospective, multicenter, randomized, double-blind, placebo-controlled, 2-parallel groups, phase 3 study
- Enrollment of patients with blood eosinophil level >150 cells/µL, which differs from the population usually addressed by biological treatments, targeting patients with high eosinophils (>300 cells/µL or above) defined as Th2-high eosinophilic asthma
- Participants received masitinib (3.0 mg/kg/day), given orally twice daily, with a dose escalation to 4.5 mg/kg/day after 4 weeks of treatment, followed by dose escalation to 6.0 mg/kg/day after 4 weeks of treatment
- The primary endpoint was the annualized severe asthma exacerbation rate for the overall time on treatment, as for study AB07015 in severe asthma uncontrolled with OCS

Top-line results of study AB14001

- Statistically significant 29% reduction in severe exacerbations relative to placebo (p=0.022)
- Frequency of severe asthma exacerbations was 0.43 in the masitinib arm, versus 0.62 in the placebo arm
- Duration of exposure was well-balanced between the treatment-arms (16 months in the masitinib arm and 17 months in the placebo arm)
- Sensitivity analysis based on the rate of moderate and severe asthma exacerbations was consistent with the primary analysis and detected a statistically significant 31% reduction in exacerbations (p=0.005) between masitinib and placebo. The frequency of moderate and severe asthma exacerbations was 0.55 in the masitinib arm, versus 0.80 in the placebo arm
- Detailed results will be presented at an upcoming medical meeting

Inflammatory Diseases

Strong market potential across two 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[4]	40,000[4]	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[5]	550,000[5]	33%	3,000 *(based on a 30,000€ annual price)*	5,500 *(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

4 : 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

5 : 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

Oncology

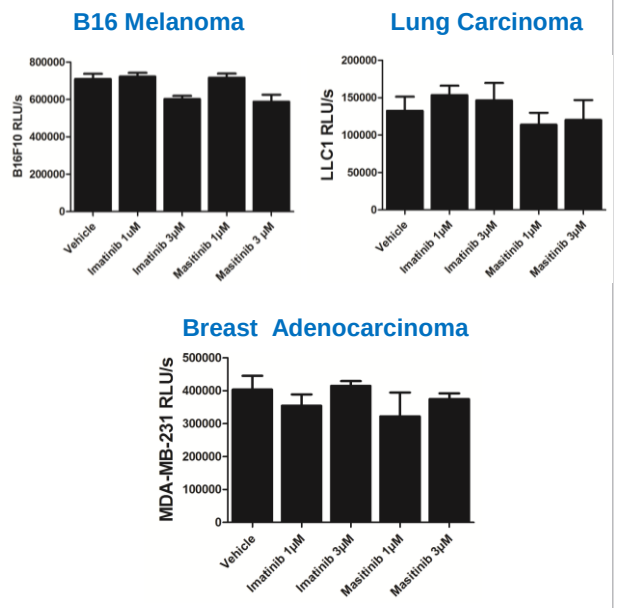
First Line Metastatic Castrate Resistant Prostate Cancer (mCRPC)

First Line Non Resectable Locally Advanced or Metastatic Pancreatic Cancer

Pancreatic cancer and Prostate Cancer

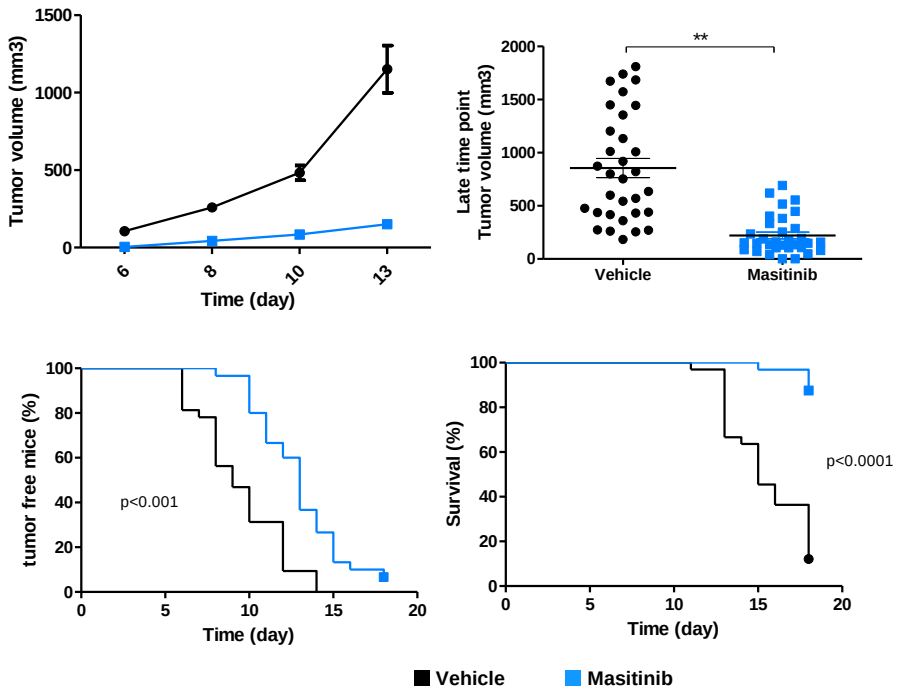
Masitinib has no direct "tumor killer" general activity but has shown efficacy on tumor proliferation in vivo, mediated through the tumor micro-environment

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.

Two on-going phase 3 combining masitinib with chemotherapy

Pancreatic cancer

- Double-blind, controlled study comparing masitinib + gemcitabine to placebo + gemcitabine in first-line non resectable locally advanced or metastatic pancreatic cancer
- **Primary endpoint:** Overall Survival
- **Enrolment:** 380 patients

Prostate cancer

- Double-blind, controlled study comparing masitinib + docetaxel to placebo + docetaxel in first-line metastatic Castrate Resistant Prostate Cancer
- **Primary endpoint:** PFS
- **Enrolment:** 470 patients

ClinicalTrials.gov Identifier: Pancreatic cancer NCT00789633 & NCT03766295. Prostate Cancer NCT03761225

Oncology

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€)
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)	30,000[7]	50,000[7]	25%	500 *(based on a 60,000€ annual price)*	750 *(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

8 : National Cancer Institute (https://seer.cancer.gov/statfacts/html/amyl.html)

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 COVID-19-induced inflammation by activating the early release of inflammatory compounds (IL-6, IL-1, TNFα) (Kritas 2020) ▪ Mast cell degranulation, promote lung lesions during viral infection (Hu Y, 2012) ▪ Altered mast cell activity, in response to respiratory viruses, contribute to pulmonary disorders such as allergic asthma exacerbations or pulmonary edema (Jin, 2018)	▪ Masitinib inhibits mast cells activity through c-Kit, LYN, and FYN. ▪ Masitinib showed efficacy in patients with severe mastocytosis in a phase 3 (Lortholary Lancet 2017) ▪ Masitinib showed prevention against acute chest syndrome in an animal model of sickle cell disease (SCD). ▪ Masitinib has showed efficacy in pneumology in severe persistent asthma.
Macrophages	▪ There is evidence for Macrophage Activation Syndrome emerging in the COVID-19 setting that is supported by the abnormal laboratory parameters (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 a asthma mouse model of airway inflammation, Masitinib inhibited of 40% the infiltration of macrophages

COVID-19

Phase 2 initiated in moderate and severe forms of the COVID-19 without limitation of age (i.e. patients above 80 will be 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

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

Duration: 30 days

Key differentiating factors

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

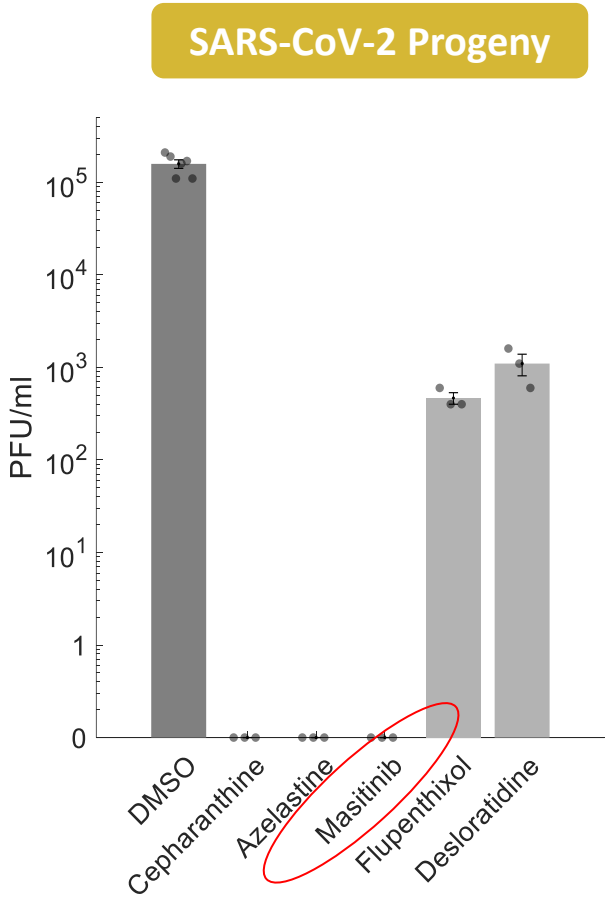
- Safety of masitinib and IsoQuercetin are well defined
- Targets the innate immune system cells upstream rather than the released interleukins downstream
- Can potentially prevent thrombosis (ICU and death)
- Can potentially treat the neurological symptoms
- Elderly people are the most exposed to death 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)

COVID-19

In addition, an independent drug repurposing screen identified masitinib as the most potent drug blocking replication of SARS-CoV-2 *in vitro*

- Drug reprofiling screening of around **12,000 drugs**, using SARS-CoV-2 infected VERO6 cells-based assay, identified **masitinib among the top 50** most active compounds (Riva et al, 2020, Nature)

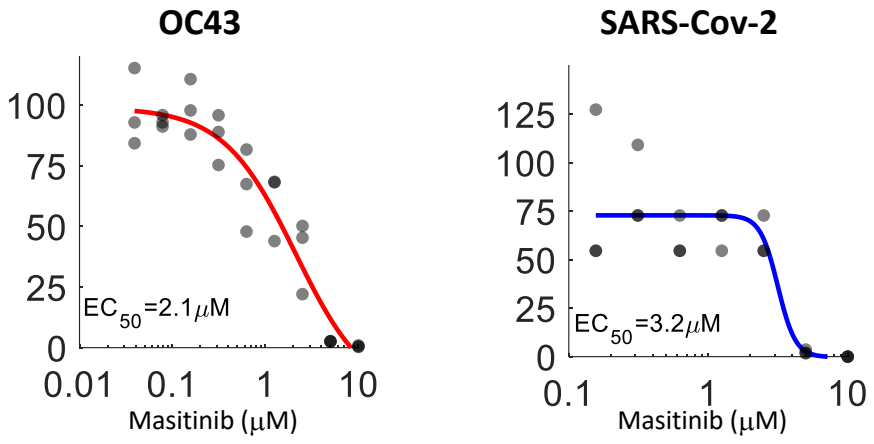
- Drug repurposing screen of **1,900 drugs** identified masitinib as the most potent anti-viral compound, since **masitinib totally abrogates SARS-CoV-2 progeny production** (Drayman et al. bioRxiv, 2020)



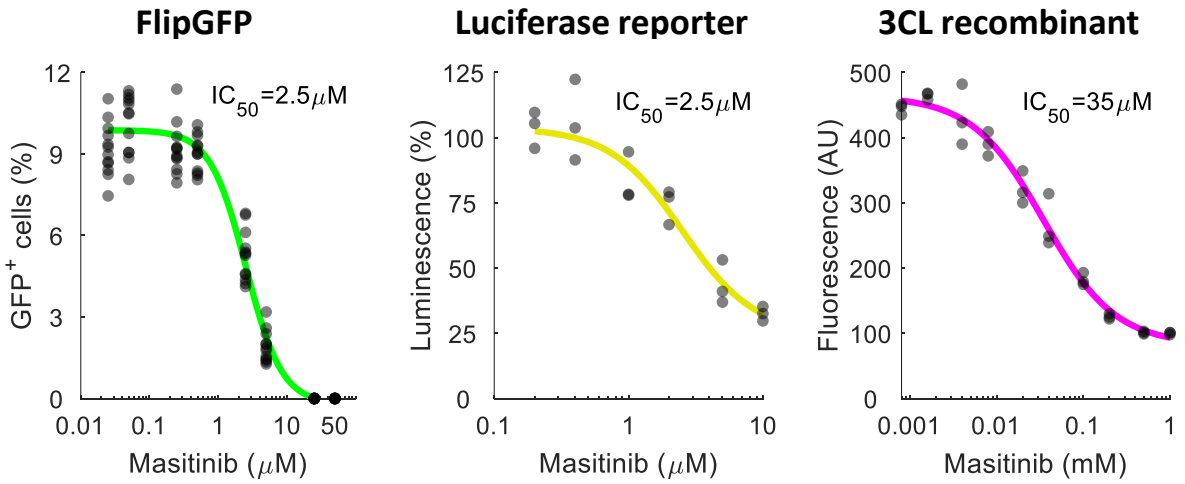
COVID-19

Masitinib completely inhibited in multiple assays 3CLpro activity, the SARS-CoV-2 main protease necessary for its viral replication cycle

Virus Replication



3CL Protease Assay

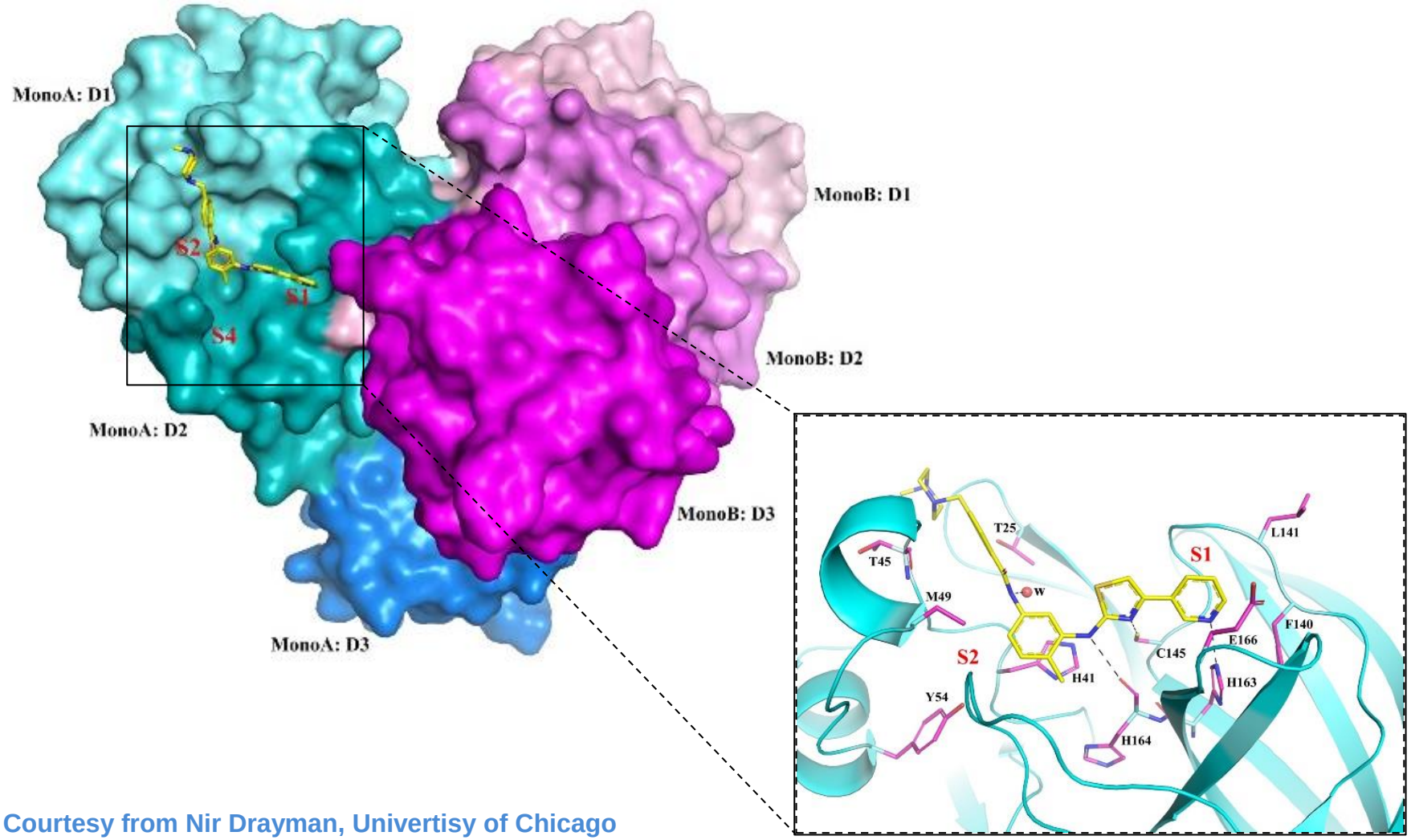


- The 3CL-protease is the main protease found in coronaviruses and is a key enzyme, as it cleaves several sites to produce non-structural proteins that are essential for genome replication and coronavirus virion production.
- Masitinib inhibits SARS-CoV-2 main 3CL-protease with an **IC_5=2.5 µM** in FlipGFP and luciferase reporter assays, similar to the EC_{50} value determined against SARS-CoV-2 in cells-based assays.
- These results were confirmed *in vitro*, using purified recombinant 3CL-protease and a methyl-amino coumarin (AMC)-tagged peptide. They strongly suggest that direct interaction of masitinib with the viral 3CL-protease is responsible for its effects on SARS-CoV-2 replication.

Courtesy from Nir Drayman, Univertisy of Chicago

COVID-19

X-ray crystallography revealed that masitinib directly binds to the active site of 3CLpro, thereby having a direct antiviral activity by blocking its enzymatic activity



- Masitinib's three active groups (pyridine, aminothiazole and toluene rings) contribute to the majority of interactions between masitinib and 3CL-protease.
- They bind the key active site residues and effectively block the peptide substrate access to the protease catalytic dyad, thus preventing polyprotein cleavage

Courtesy from Nir Drayman, Univertisy of Chicago

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€)
Patients infected by Covid-19, not hospitalized or hospitalized (but not requiring ICU)	• Phase 2 study in the moderate and severe forms of Covid-19 with oral masitinib in combination with Iso-Q • Planned clinical development for masitinib as anti-viral treatment for Covid-19	• Eli Lilly monoclonal antibody cocktail (~5,000) • Regeneron antibody cocktail (~2,500)	800,000[1]	1,500,000[1]	25%	[500 – 1,000] *(based on treatment price between 2,500 and 5,000€)*	[1,000 – 2000] *(based on treatment price between 2,500 and 5,000€)*

Source :

1 :

- As of October 30, 2020, the number of current active cases in Europe and in the US amounts to approxiamtely 9,000,000 (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:
  - By the end of 2020: monthly increase by 20% of the number of current actives cases in EUR and in the US, due to the resurgence of the virus in many countries
  - Between January 2021 and June 2021: monthly decrease by 5% of the current active cases in EUR and US, due to restrictive measures implemented by national governments
  - Availability of a vaccine in July 2021, which will decrease the number of active cases by 75% in a 6 months period, ie by the end of 2021
  - January 2022 and beyond: Steady number of active cases in Europe and US

- Since masitinib will targets mild/asymptomatic infections and moderate/severe (without ICU) infections, the proportion of Covid-19 patients eligible to masitinib therapy amounts to 95% (Source: World Health Organization Covid-19 Report, March 2020)

Back-up

Financial Information

- **Euronext Paris:** AB.PA
- **Ordinary Shares Outstanding: 44.8M**
- **Cash position (€): 10.6M (as of June 30, 2020)**
- **Convertible Bond (€): 4.5 M issued on October 2020**

Masitinib - Intellectual Property

Masitinib IP rights are secured until 2037 in ALS and between 2031 and 2036 in other indications

Protection	Item	Duration of protection	Status
Patent on composition of matter and PTE	• Patent on composition of matter has been filed and delivered. It will be further extended until 2028 through patent term extension (PTE)	Until 2028	Delivered
Synthesis process patent	• A further protection until 2028 has been achieved through synthesis 'process' patent	Until 2028	Delivered
Orphan drug status	• Masitinib has been granted orphan drug designation by both EMA and FDA for ALS, Severe Systemic Mastocytosis, and pancreatic cancer	Exclusivity of 7 years for FDA and 10 years for EMA	Delivered
Phase 3 'Method of use' patents	• Amyotrophic lateral sclerosis (ALS)	Until 2037	Delivered
	• Pancreatic cancer patients with pain	Until 2033	Delivered
	• Asthma (severe)	Until 2032	Delivered
	• Systemic mastocytosis (severe)	Until 2031 in the USA Until 2036 outside USA	Delivered Pending
	• Multiple sclerosis (MS)	Until 2031 New patent Filed in 2020	Delivered Pending

Masitinib - 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 • Petrov et al, 2017 : ALS Clinical Trials Review: 20 Years of Failure. Are We Any Closer to Registering a New Treatment ?
	Phase 3	• Mora et al, 2019 : Masitinib as an add-on therapy to riluzole in patients with amyotrophic lateral sclerosis: a randomized clinical trial
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
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

Masitinib - Publications

Immunology & Oncology

Program	Data	Publications
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
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
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