AB SCIENCE

Corporate Presentation

May 2021

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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 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

- **Eight positive Phase 2B/3 read outs**, in amyotrophic lateral sclerosis (ALS), progressive forms of multiple sclerosis, Alzheimer's Disease, mastocytosis (ISM), in severe asthma (uncontrolled by oral corticosteroids and uncontrolled by inhaled corticosteroids), and in unresectable locally advanced pancreatic cancer and metastatic Castrate Resistant Prostate Cancer (mCRPC)

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 eight positive phase 2B/3 trials

Compound	Therapeutic area	Indication	Preclinical	Phase 1	Phase 2	Phase 2B/3	Confirmatory Phase 3
Masitinib	Neurology Diseases	1. Amyotrophic Lateral Sclerosis*					
		2. Progressive forms of Multiple Sclerosis*					
		3. Alzheimer's Disease*					
	Inflammatory Diseases	4. Indolent Systemic Mastocytosis*					
		5. Severe Asthma Uncontrolled with OCS*					
		6. Severe Asthma Uncontrolled with ICS*					
	Oncology	**7. Pancreatic Cancer***					
		8. Metastatic Prostate Cancer *					
	Viral Diseases	Moderate and severe COVID-19 *(anti-inflammatory)*					
		Mild and moderate COVID-19 *(anti-viral)*					
AB8939	Oncology	Acute Myeloid Leukemia					

**** Positive Phase 2B/3 Results Reported***

Masitinib Profile and Mechanism of Action

Orally-administered kinase inhibitor selectively targeting mast cells and macrophages

Masitinib targets mast cells

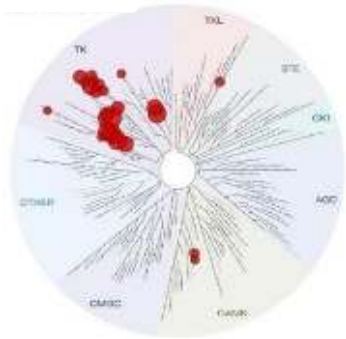
- Masitinib is a potent and selective inhibitor of c-Kit, Lyn, and Fyn kinases. These kinases play critical roles in the activation of mast cells
- Mast cells are a target in neurodegenerative diseases, inflammatory diseases and in oncology

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

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)
		Severe Asthma Uncontrolled with OCS	
		Severe Asthma Uncontrolled with ICS	
	Oncology	Pancreatic Cancer	▪ **Mast Cells** (c-Kit, Lyn, Fyn kinases) ▪ **Microglia** (MCSFR-1 kinase)
		Metastatic Prostate Cancer	
	Viral Diseases	Moderate and severe COVID-19 *(anti-inflammatory)*	▪ **Mast Cells** (c-Kit, Lyn, Fyn kinases) ▪ **Microglia** (MCSFR-1 kinase)
		Mild and moderate COVID-19 *(anti-viral)*	▪ (3CL protease)
AB8939	Oncology	Acute Myeloid Leukemia	▪ (microtubules)

Alzheimer's disease

A 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)

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

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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

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)

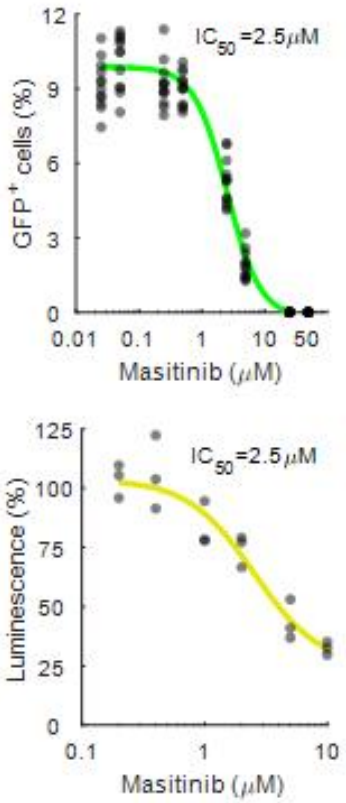
							p-value		Hazard	
Treatment group	Total	No. of Events	Percentage Events	No. Censored	Percentage censored	Median [95% CI]	KM p-Value	Log Rank	Ratio (95% CI)	p-Value
Masitinib 4.5 mg/kg/day	182	2	1.10	180	98.90	Not reached [;]	0.0446	0.0403	0.19 (0.0,0.8)	0.0276
Pooled Placebo	267	15	5.62	252	94.38	6.3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

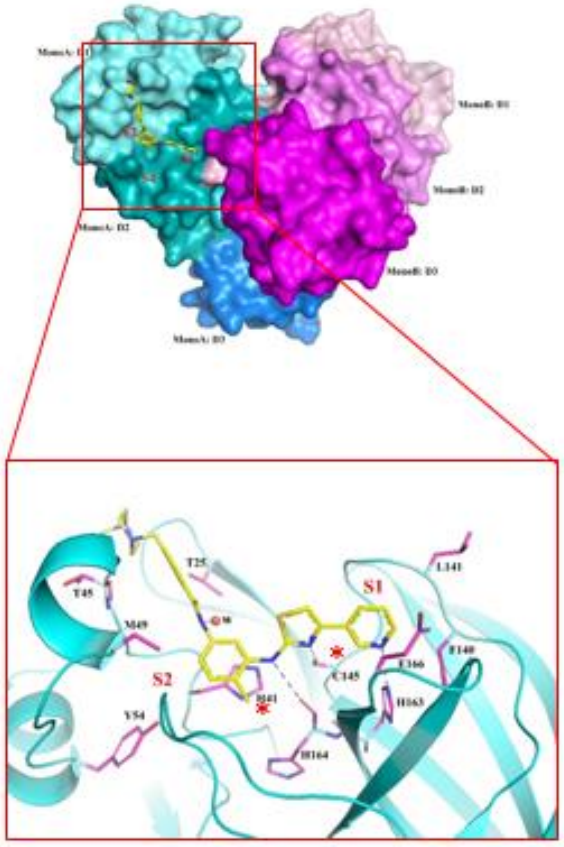
COVID-19

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

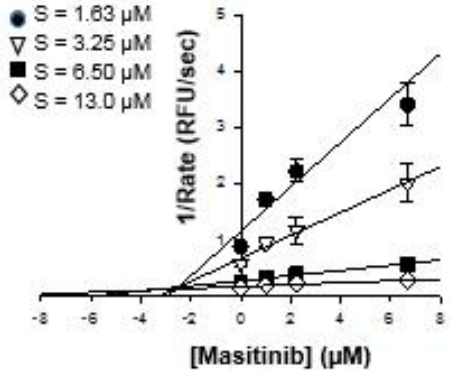
3CL inhibition in two cellular assays



Crystal structure of masitinib bound to 3CL active site



In vitro binding assay showing masitinib is a competitive Inhibitor of 3CL



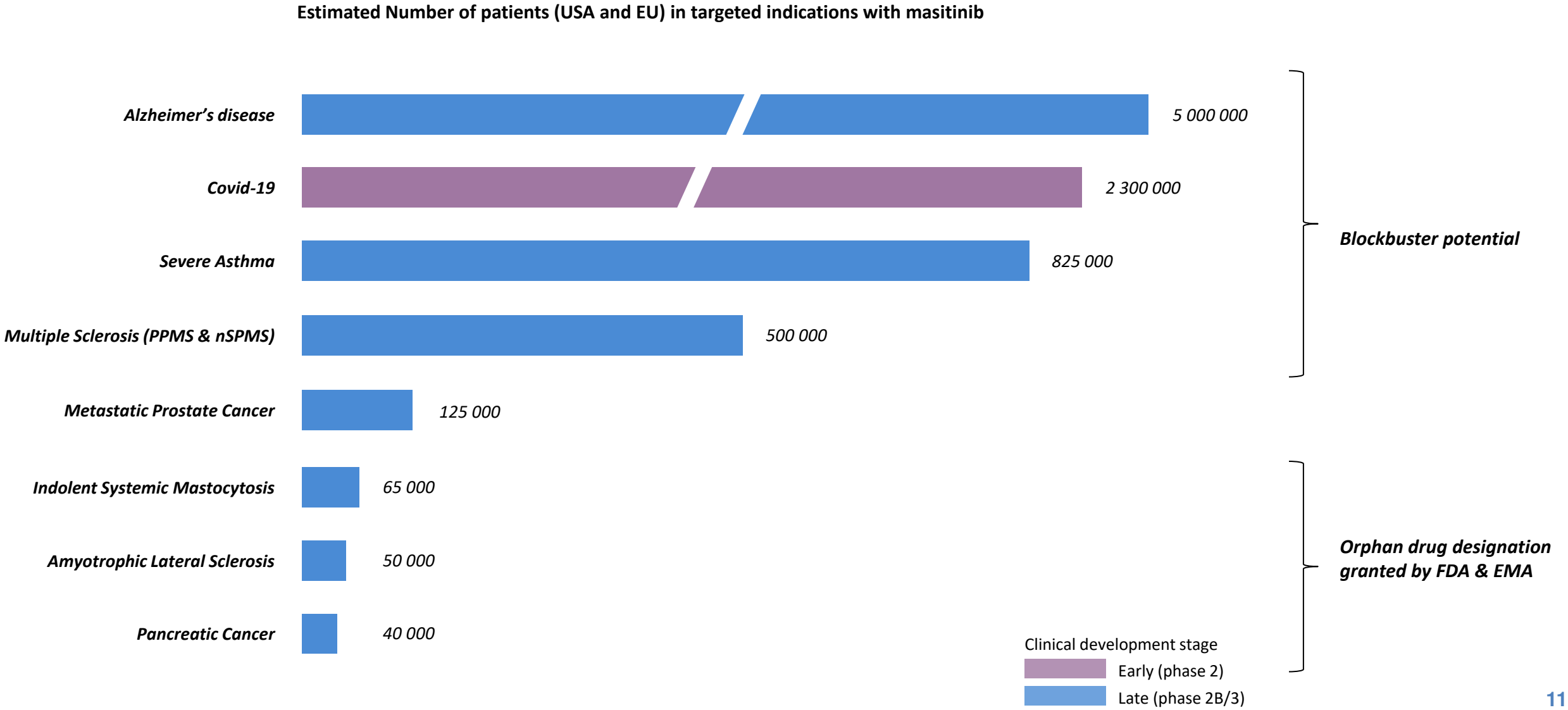
Competitive inhibition: K_i = 2.58 μM

- 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

Market Potential

Blockbuster potential but also addressing orphan diseases



Pathway to Registration

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

- Pancreatic Cancer – ***Decision 2021***
- Severe asthma – ***Decision 2021***
- Metastatic Prostate Cancer – **Decision 2021**

Confirmatory phase 3

- Amyotrophic Lateral Sclerosis – ***Initiated, expected completion early 2023***
- Indolent Systemic Mastocytosis – ***Initiated, expected completion early 2023***
- Progressive forms of Multiple Sclerosis – ***To be initiated in 2021***
- Alzheimer's disease - ***To be initiated in 2021***

Depending on study readout

- Covid-19 - **2021**

Financial Information

- **Euronext Paris:** AB.PA
- **Ordinary Shares Outstanding: 46.8M**
- **Cash position (€): 20.7M (as of Dec 31, 2020)**
- **Equity raise of 15M€ in Q4 2020**
- **State-guaranteed loan of 6M€ received in April 2021**
- **Equity Line in place (up to 4M shares)**

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

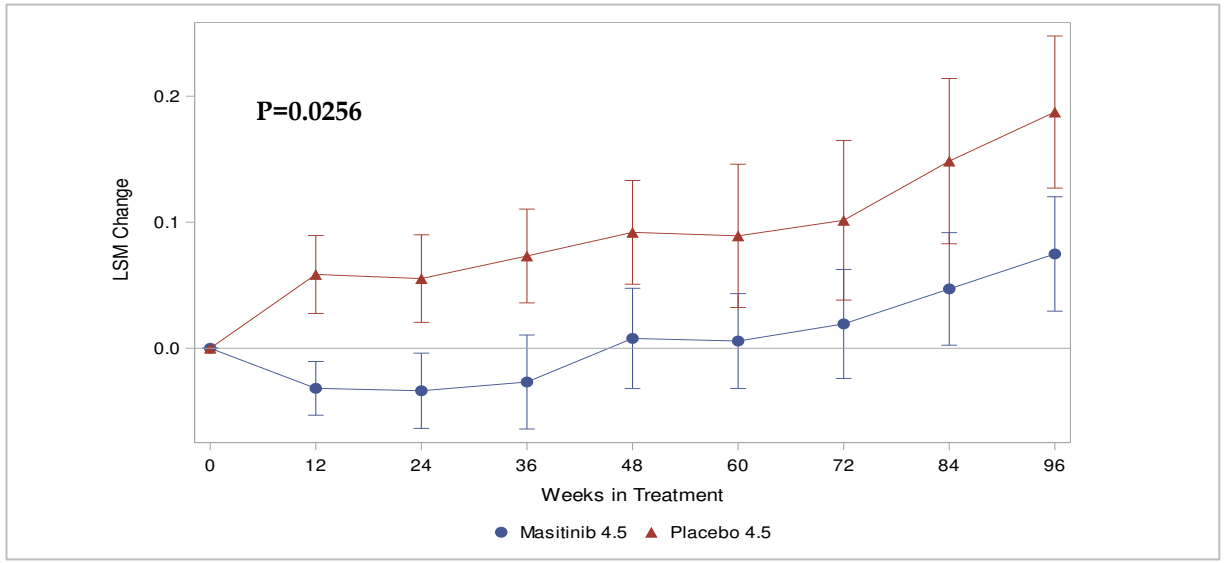
	Manufacturer	Masitinib Positioning		Label		First approved
		Primary Progressive MS	Non-active Secondary Progressive MS*	Active Secondary Progressive MS	Relapsing Remitting MS	
Distribution of patients *(Estimated Nbr of patients Europe + USA)*		**15%** *(~ 150 000)*	**35%** *(~ 350 000)*	**10%** *(~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

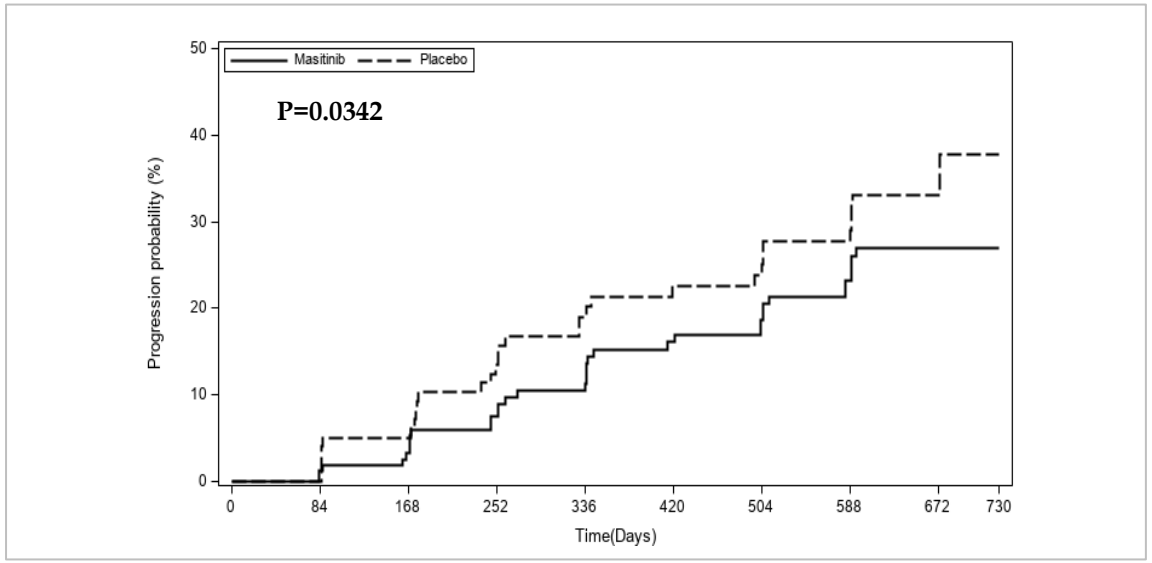
Multiple Sclerosis

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

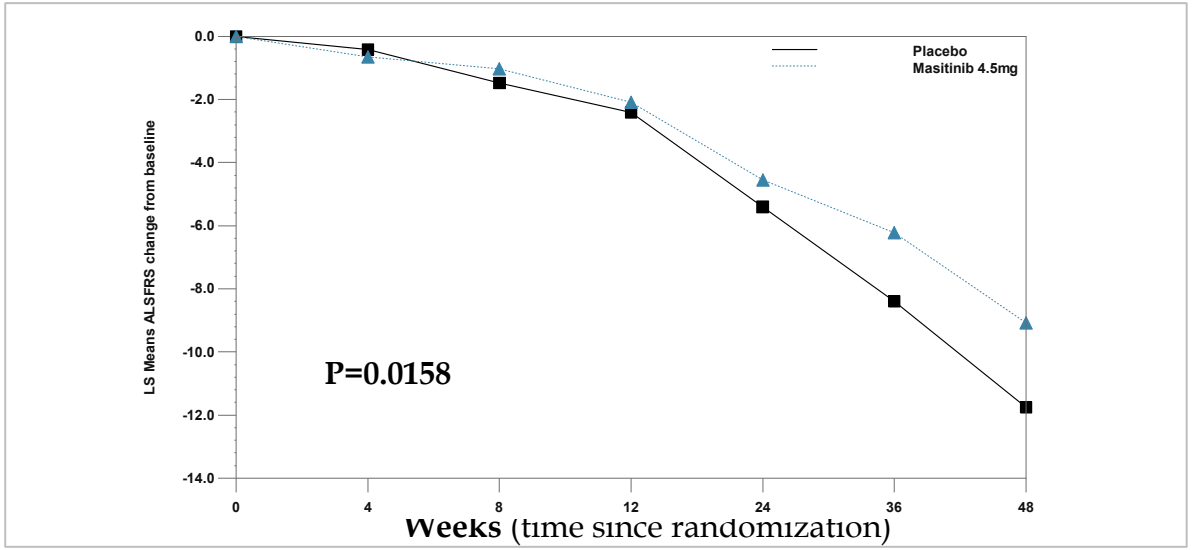
Presented at MSVirtual2020 joint ECTRIMS/ACTRIMS conference

ClinicalTrials.gov Identifier: NCT01433497

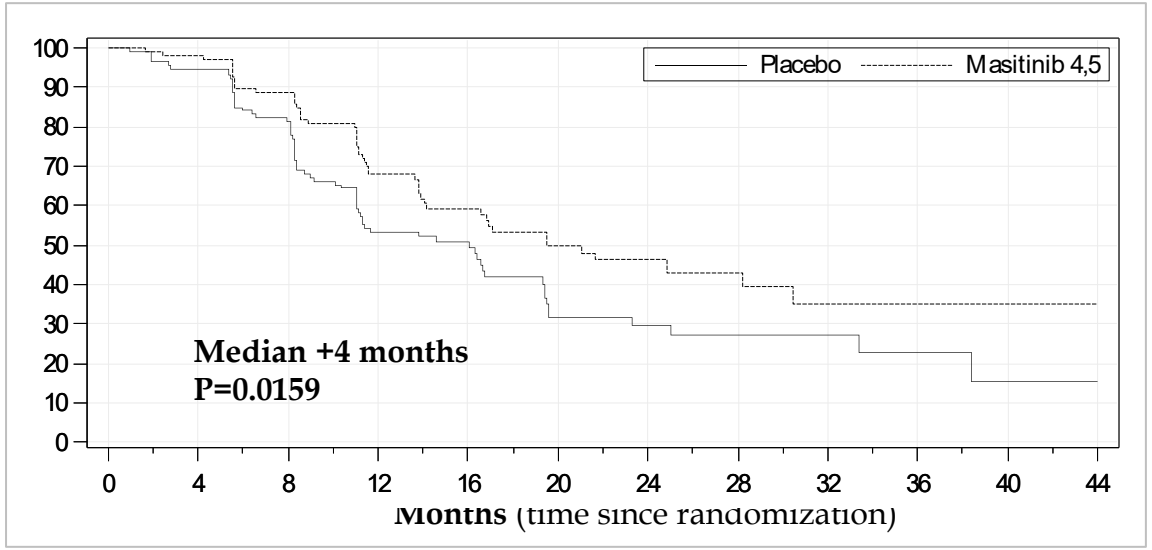
ALS

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

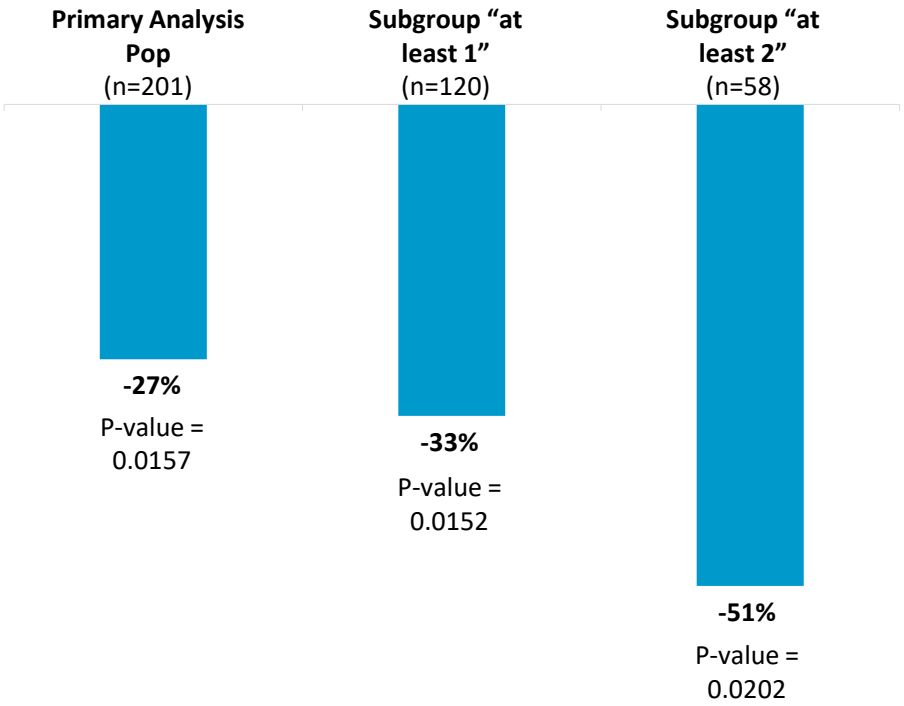
- Schwann Cells Orchestrate Peripheral Nerve Inflammation Through the Expression of CSF1, IL-34, and SCF in Amyotrophic Lateral Sclerosis. Glia 2020
- Mast cells and neutrophils mediate peripheral motor pathway degeneration in ALS. JCI Insight. 2018.
- Evidence for mast cells contributing to neuromuscular 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.

ALS

Clinical benefit further enhanced when treatment initiated early

51% slowing of functional deterioration (vs 27%)

% reduction in change in ALSFRS (primary endpoint)



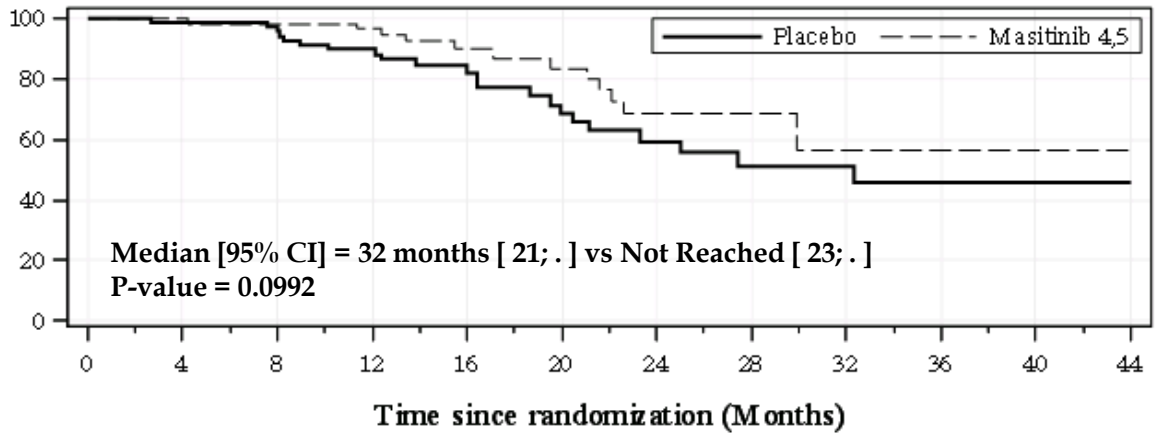
Primary Analysis : Normal = No fast progressors
At least 1 subgroup* : No 0, Diag 24, no slow no fast prog.
At least 2 subgroup*: No 0, No 1, Diag 24, no slow no fast prog.
** post-hoc analyses*
Diag 24' : Disease duration ≤24 months. 'No 0' : Exclude patients with a score of 0 on any of the 12 ALSFRS-R 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.

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

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)

Significant effect on cognitive function after 24 weeks of treatment

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

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Significant effect on daily activity after 24 weeks of treatment

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Dementia- M4.5 vs Placebo Pooled (FAS)

							p-value		Hazard	
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Baseline MMSE (FAS)	Masitinib + SoC (N = 182)	Pooled Placebo + SoC (N =267)
< 14	18 (9.9)	30 (11.2)
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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

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

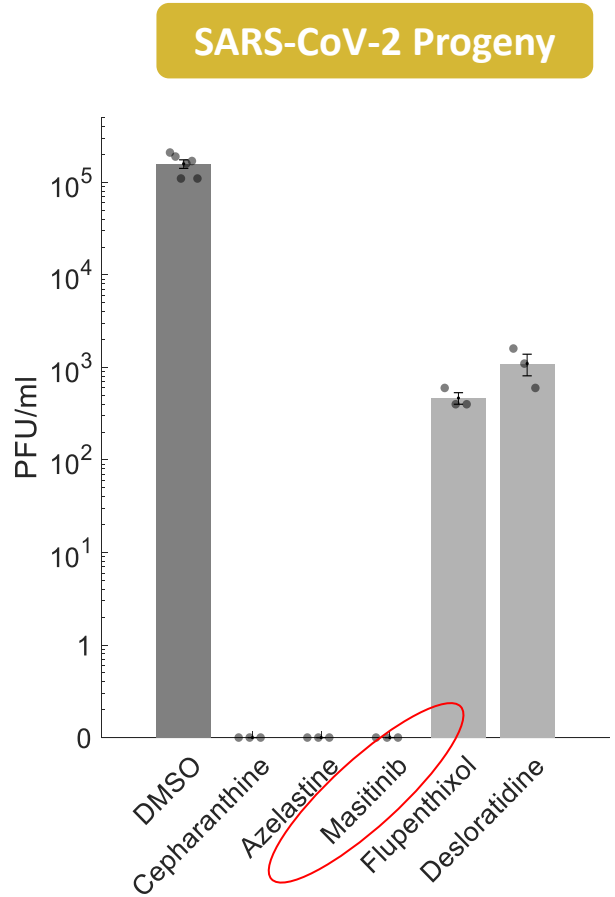
- Safety of masitinib and IsoQuercetin are well defined
- Targets the innate immune system cells upstream rather than the released interleukins downstream
- Can potentially prevent thrombosis (ICU and death)
- Can potentially treat the neurological symptoms
- Elderly people are the most exposed to death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

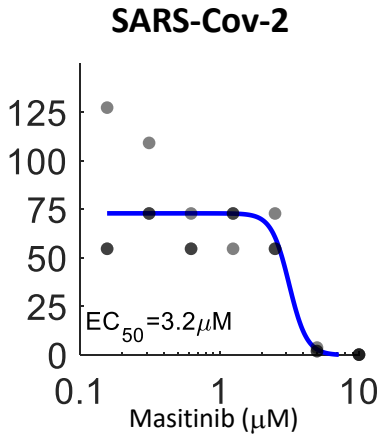
- Drug repurposing screen of **1,900 drugs** identified masitinib as the most potent anti-viral compound, since **masitinib totally abrogates SARS-CoV-2 progeny production** (Drayman et al. bioRxiv, 2020)



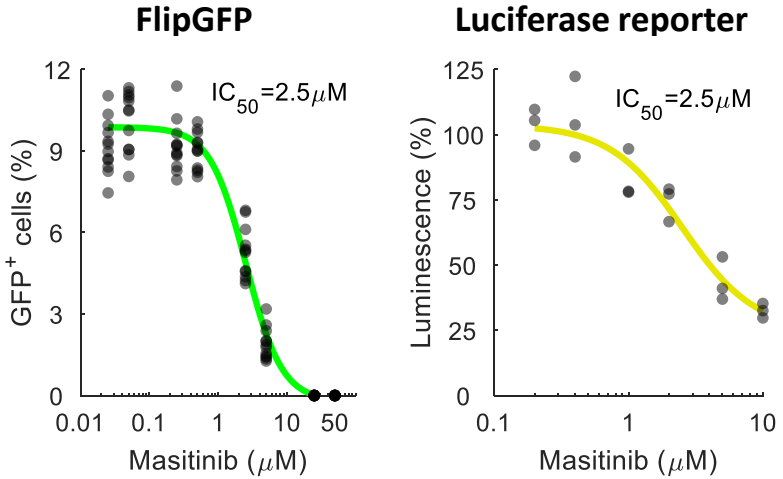
COVID-19

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



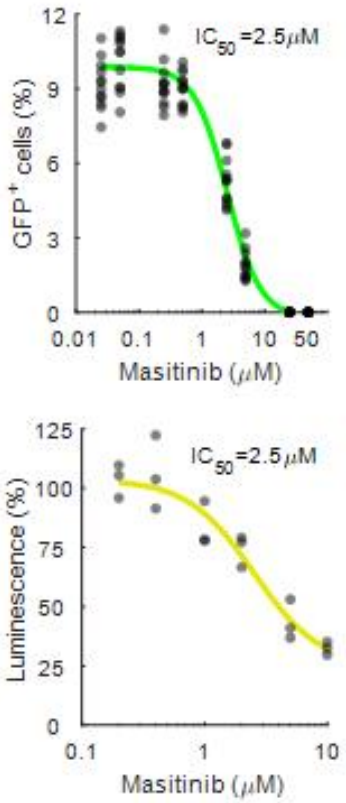
- The 3CL-protease is the main protease found in coronaviruses and is a key enzyme, as it cleaves several sites to produce non-structural proteins that are essential for genome replication and coronavirus virion production.
- Masitinib inhibits SARS-CoV-2 main 3CL-protease with an **IC_5=2.5 µM** in 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

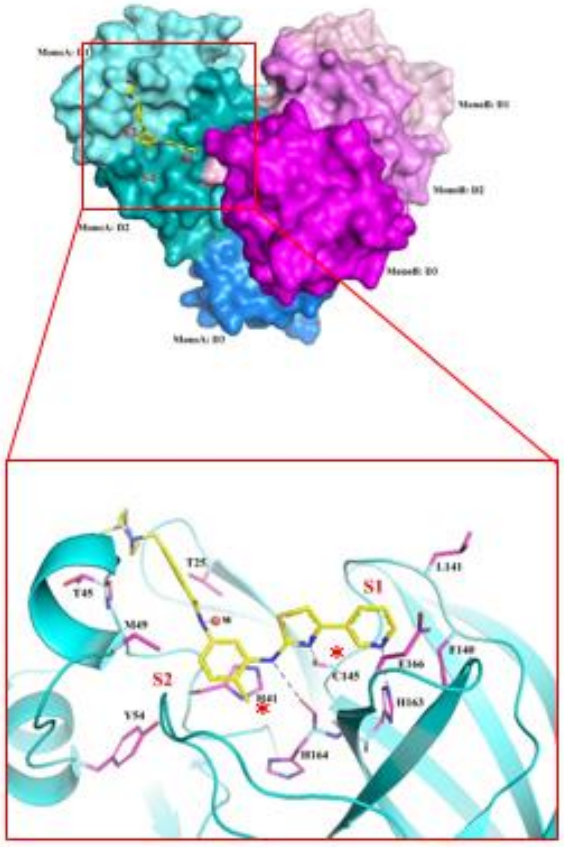
COVID-19

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

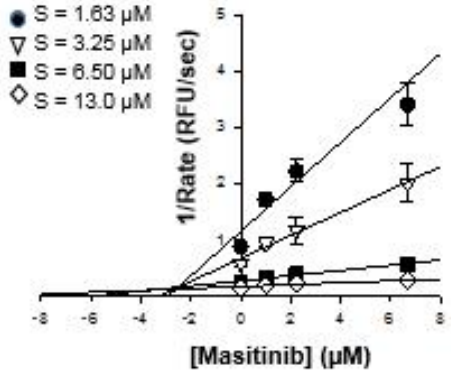
3CL inhibition in two cellular assays



Crystal structure of masitinib bound to 3CL active site



In vitro binding assay showing masitinib is a competitive Inhibitor of 3CL



Competitive inhibition: K_i = 2.58 μM

- 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)

Oncology

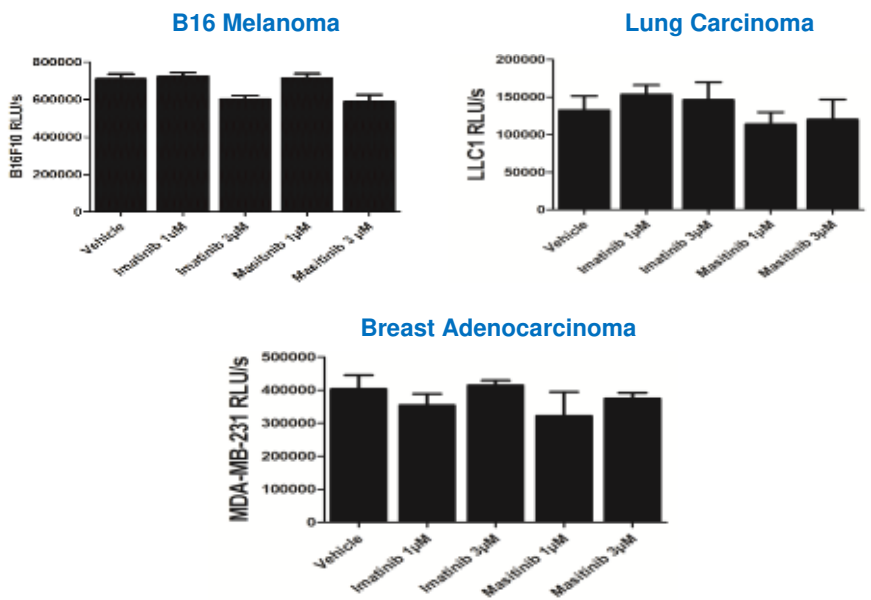
First Line Non Resectable Locally Advanced Pancreatic Cancer

First Line Metastatic Castrate Resistant Prostate Cancer (mCRPC)

Pharmacology Data - Masitinib targets tumor microenvronment

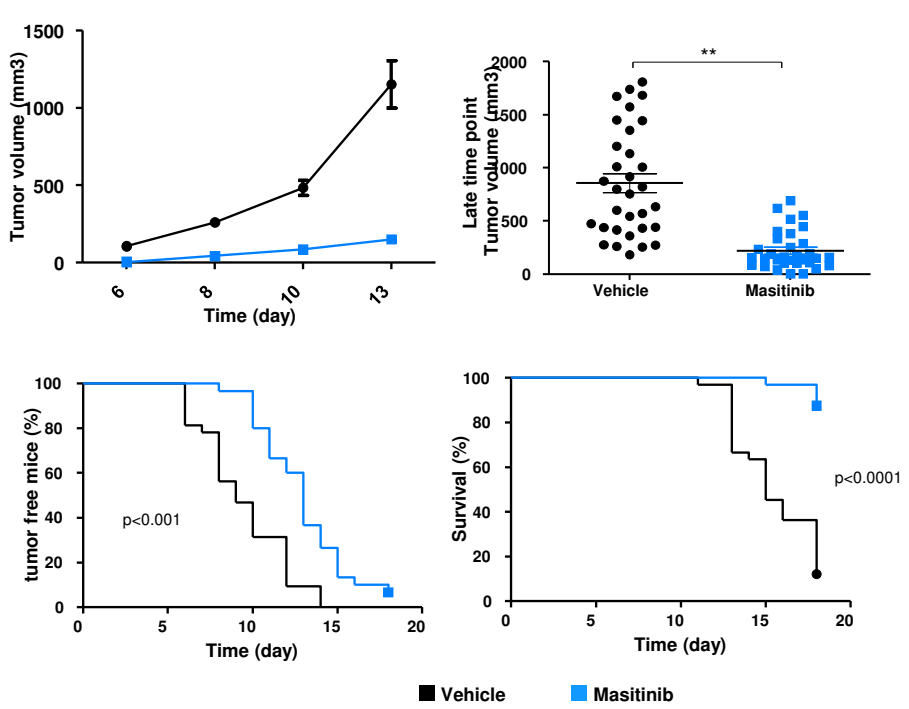
Masitinib has no direct “tumor killer” general activity but has shown efficacy on tumor proliferation in vivo, mediated through the tumor micro-environment

No direct effect on tumor cells *in vitro*…



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

…but decreases tumor volume growth *in vivo*



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

ClinicalTrials.gov Identifier: Pancreatic cancer NCT00789633 & NCT03766295

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.

Pancreatic cancer

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

Design

Design:

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

Randomisation: 2:1

Planned Enrolment : 377 patients

Primary endpoint: Overall Survival

Prespecified 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

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, as assessed by the patient is defined as Visual Analogue Scale > 20mm

OR

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

3) Chemotherapy naïve patient for the advanced/metastatic disease

Pancreatic cancer

Study AB12005 was positive and reached its primary objective to show statistically significant increase in survival

Primary Analysis

- 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 survival benefit detected in the overall population including both locally advanced and metastatic pancreatic cancer, suggesting that masitinib treatment should be initiated early in the course of the disease, prior to metastasis.

Secondary Endpoints

- PFS (+1.8 months, p=0.0391) was consistent with survival results,
- Masitinib reduced pain, supporting the rationale for targeting this population having pain at baseline

Safety

- Safety of masitinib 6.0 mg/kg/day in combination with gemcitabine compared favorably to that of gemcitabine as a single agent, with fewer adverse event and severe adverse events

	Masitinib (N = 246) - %	Placebo (N = 136) - %
At least one AE	96.3	99.3
Fatal AE	18.7	19.1
At least one serious AE (non-fatal)	19.1	21.3
At least one AE with Grade 3 or 4	74.8	83.1

ClinicalTrials.gov Identifier: NCT03766295

Prostate Cancer

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

Design

Design:

Double-blind, controlled study comparing masitinib + docetaxel to placebo + docetaxel in first-line metastatic Castrate Resistant Prostate Cancer (mCRPC)

Randomisation: 1:1

Planned Enrolment : 580 initially, resampled to 470 patients in subgroup after interim analysis

Primary endpoint: Progression Free Survival

Prespecified Statistical analysis: Alpha spending split between the overall population (2.5%) and pre-specified subgroup of patients that are identified by a biomarker (2.5%)

At interim analysis, the IDMCrecommended to continue the study in the pre-specified subgroup of patients

Main inclusion criteria

1) Histologically or cytologically confirmed mCRPC with one of the following criteria:

- Pre-treated with abiraterone with documented progressive disease, OR
- Indicated for initiating docetaxel treatment (e.g., widespread visceral disease or rapidly progressive disease).

2) Patient with evidence of progressive metastatic disease as assessed according to the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) recommendations

ClinicalTrials.gov Identifier: NCT03761225

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.

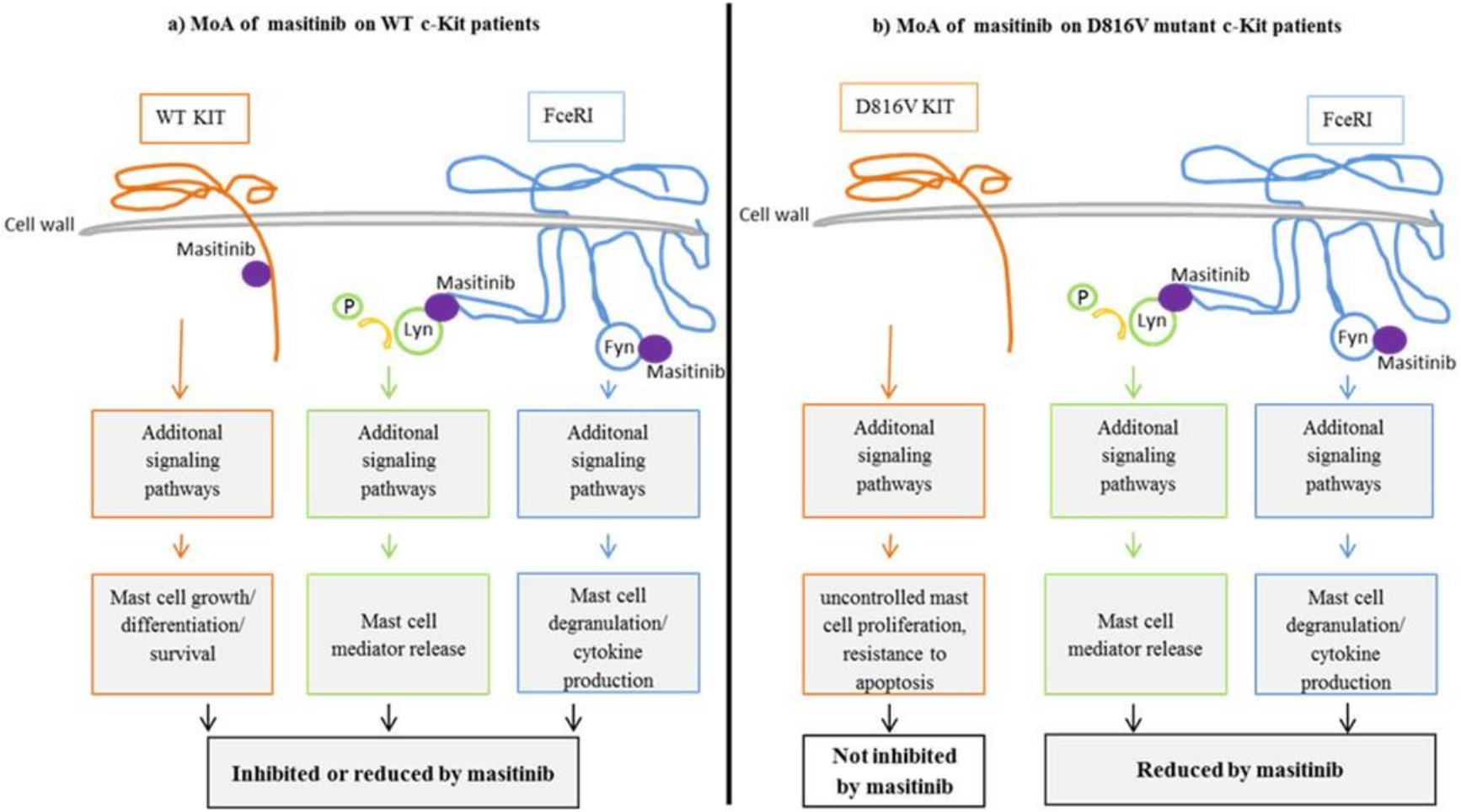
Inflammatory Diseases

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



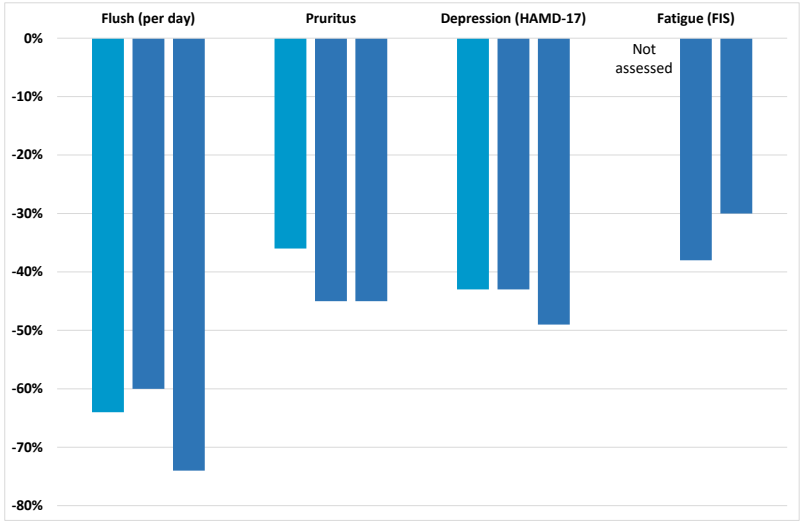
The c-Kit receptor is primarily responsible for mast cell growth, differentiation and survival with mast cell mediator release being initiated through the integration of downstream signaling pathways of c-Kit and FcεRI. D816V mutant c-Kit receptors result in uncontrolled mast cell proliferation and resistance 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

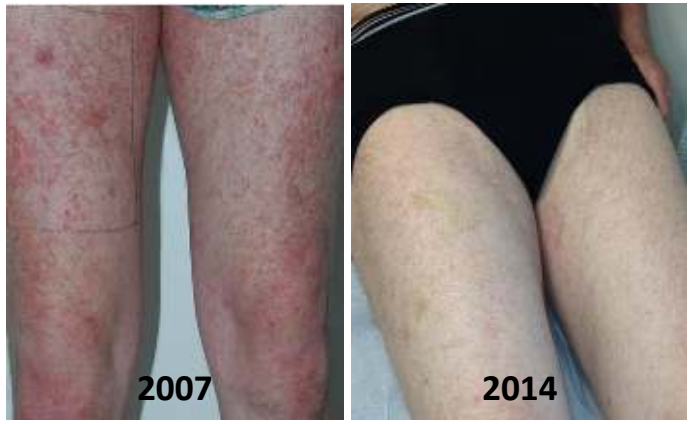
% Change from baseline at week 12



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

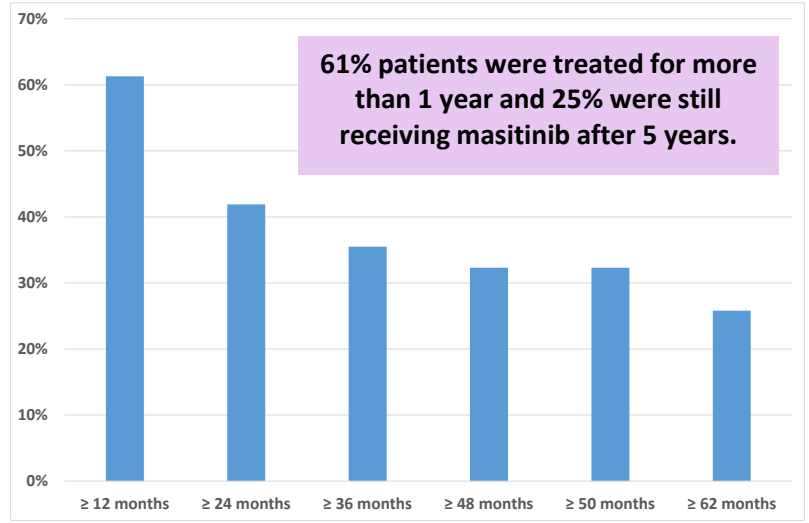
Phase 2 without c-Kit D816V (n=25,single arm)
(Middle columns represents patients with moderate baseline symptoms and right column represents patient with severe baseline symptoms)

Reduction in urticaria pigmentosa



Sustained efficacy

% of patients still under treatment



Pooled phase 2 (n=46,single arm)

ClinicalTrials.gov Identifier: NCT01266369 & NCT00831948

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: NCT00814736

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

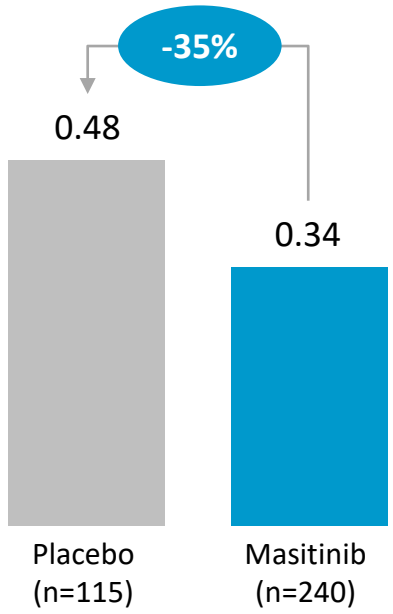
ClinicalTrials.gov Identifier: NCT04333108

Severe Asthma Uncontrolled with Oral Corticosteroids

Significant decreases in asthma exacerbations regardless of eosinophil level

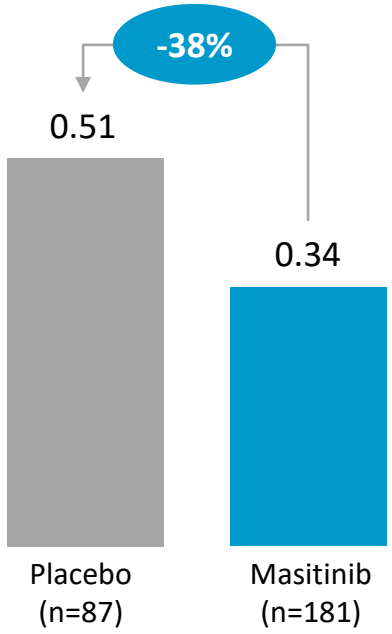
Annualized severe asthma exacerbation rate

Primary Analysis



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

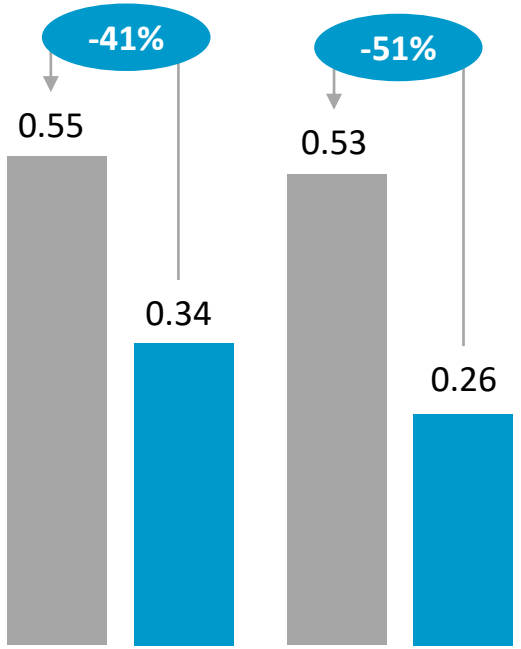
Sequential Analysis patients with EOS>150



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

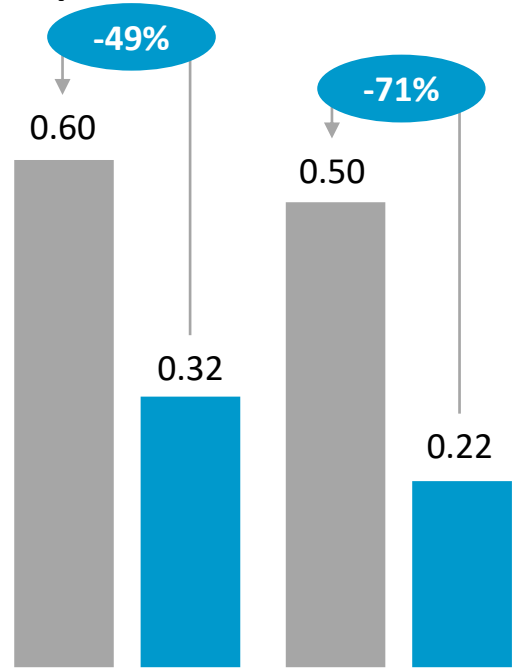
Greater benefit in patients with higher cumulative OCS

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

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

Positive results of study AB14001

- Significant 29% reduction in severe exacerbations relative to placebo (p=0.022)
  - Annualized 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)
- Significant 31% reduction in moderate and severe exacerbations relative to placebo (p=0.005)
- Significant improvement in quality of life (LS Mean change from baseline)
  - Δ ACQ = -0.2085 (p=0.039)
  - Δ AQLQ = 0.2741 (p=0.0177)

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

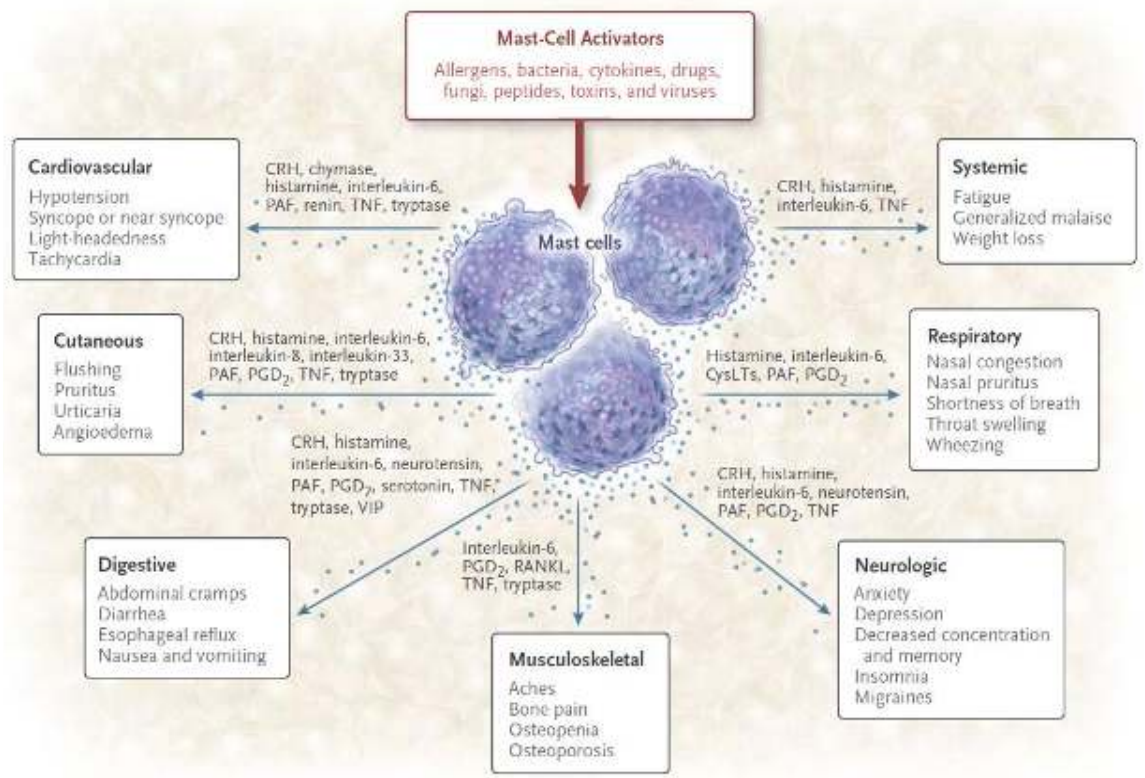
5 : Respir Med. 2006 Jul;100(7):1139-51. Epub 2006 May 18.
J Investig Allergol Clin Immunol 2012; Vol. 22(7): 460-475
Data from study AB07015 for the proportion of patients with oesinophil level between 150 and 300 and above 300

Back-up

Critical Role of Mast Cells & Macrophages / Microglia

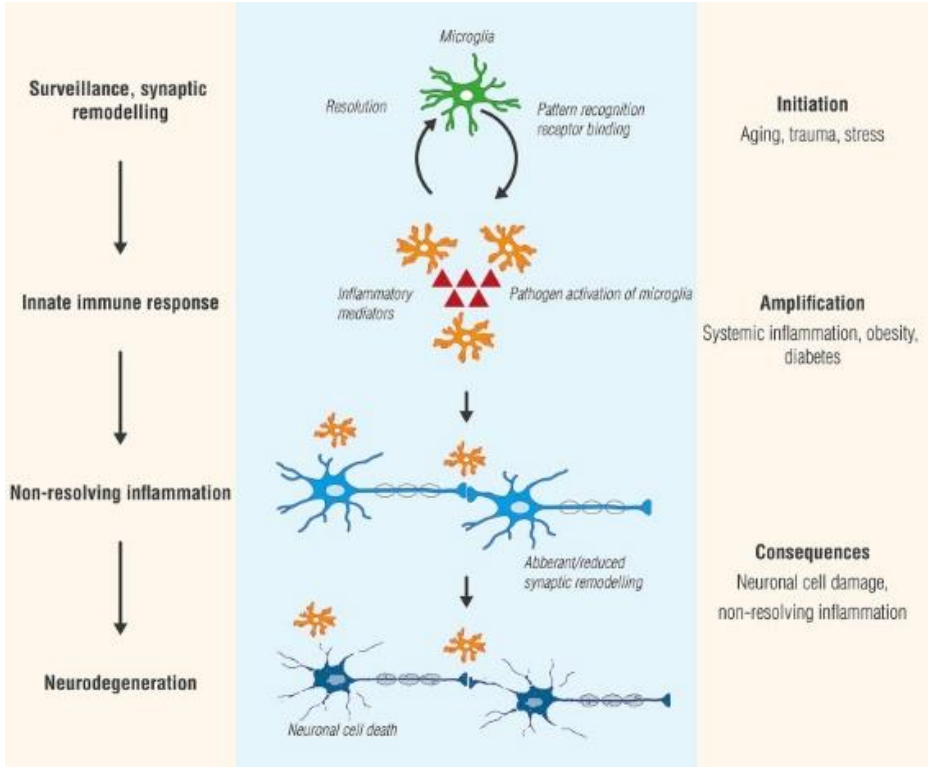
Mast cells and microglia contribute to neuro-inflammation, which is strongly influenced by their potential for mutual interaction and exacerbation of pathology

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 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

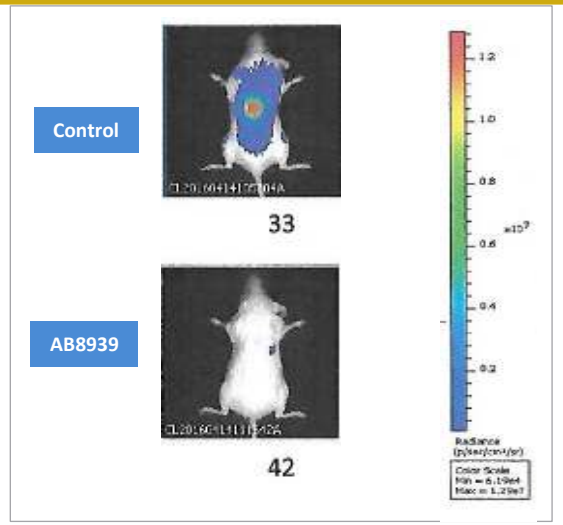
AB8939

Novel Microtubule-destabilizing Agent for Acute Myeloid Leukemia

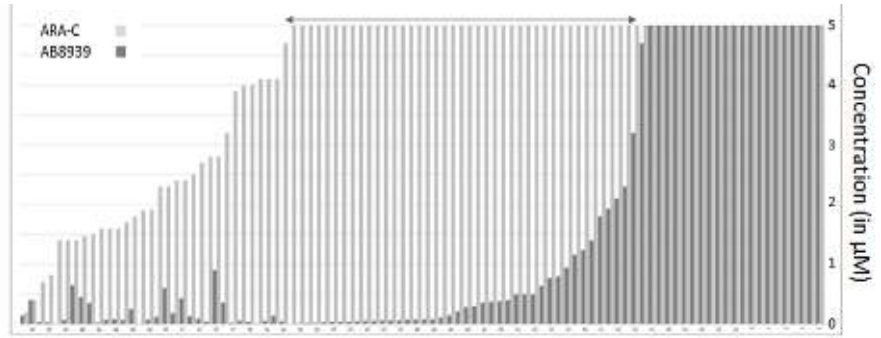
Key Differentiating factors

- 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

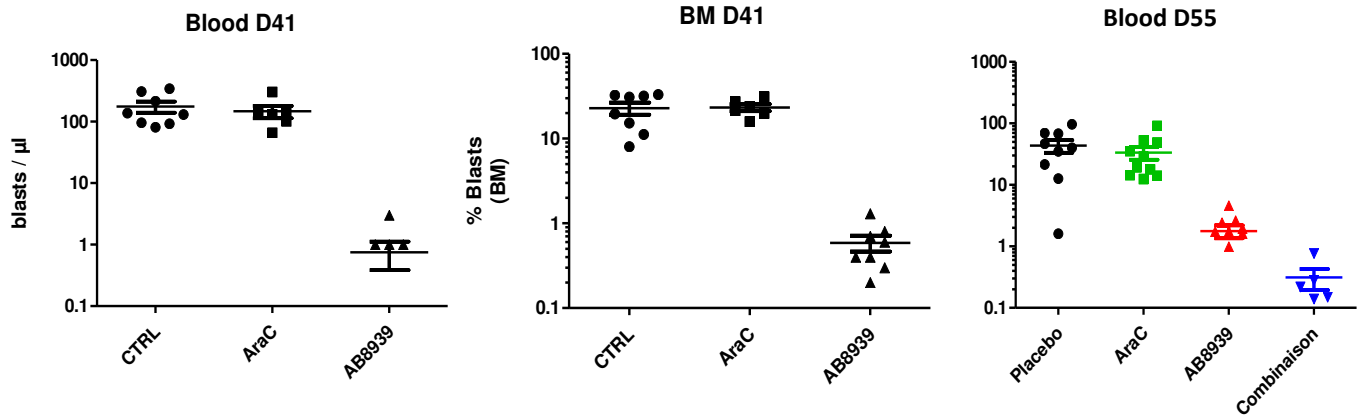


Activity of AB8939 in Ara-C resistant/refractory AML patent blasts



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

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
	Multiple sclerosis (MS)	Until 2031 *New patent filed in 2020*	Delivered *Pending*
	Alzheimer's disease	*New patent filed in 2020*	*Pending*
	Pancreatic cancer patients with pain	Until 2033	Delivered
	Metastatic castration resistance prostate cancer (mCRPC)	*New patent filed in 2021*	*Pending*
	Asthma (severe)	Until 2032 *New patent filed in 2019*	Delivered *Pending*
	Systemic mastocytosis (severe)	Until 2031 in the USA Until 2036 outside USA	Delivered Delivered / *Pending*
	Sickle cell disease	*New patent filed in 2019*	*Pending*
	COVID-19	*New patents filed in 2020*	*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