PART 1

NICE National Institute for Health and Care Excellence

Midostaurin for treating advanced systemic mastocytosis [ID1573]

Lead team presentation

Chair: Stephen O'Brien

Lead Team: Mudasar Mushtaq, Ugochinyere Nwulu, Andrea Manca

ERG: Liverpool Reviews and Implementation Group (LRiG)

Technical team: Zain Hussain, Jamie Elvidge, Linda Landells

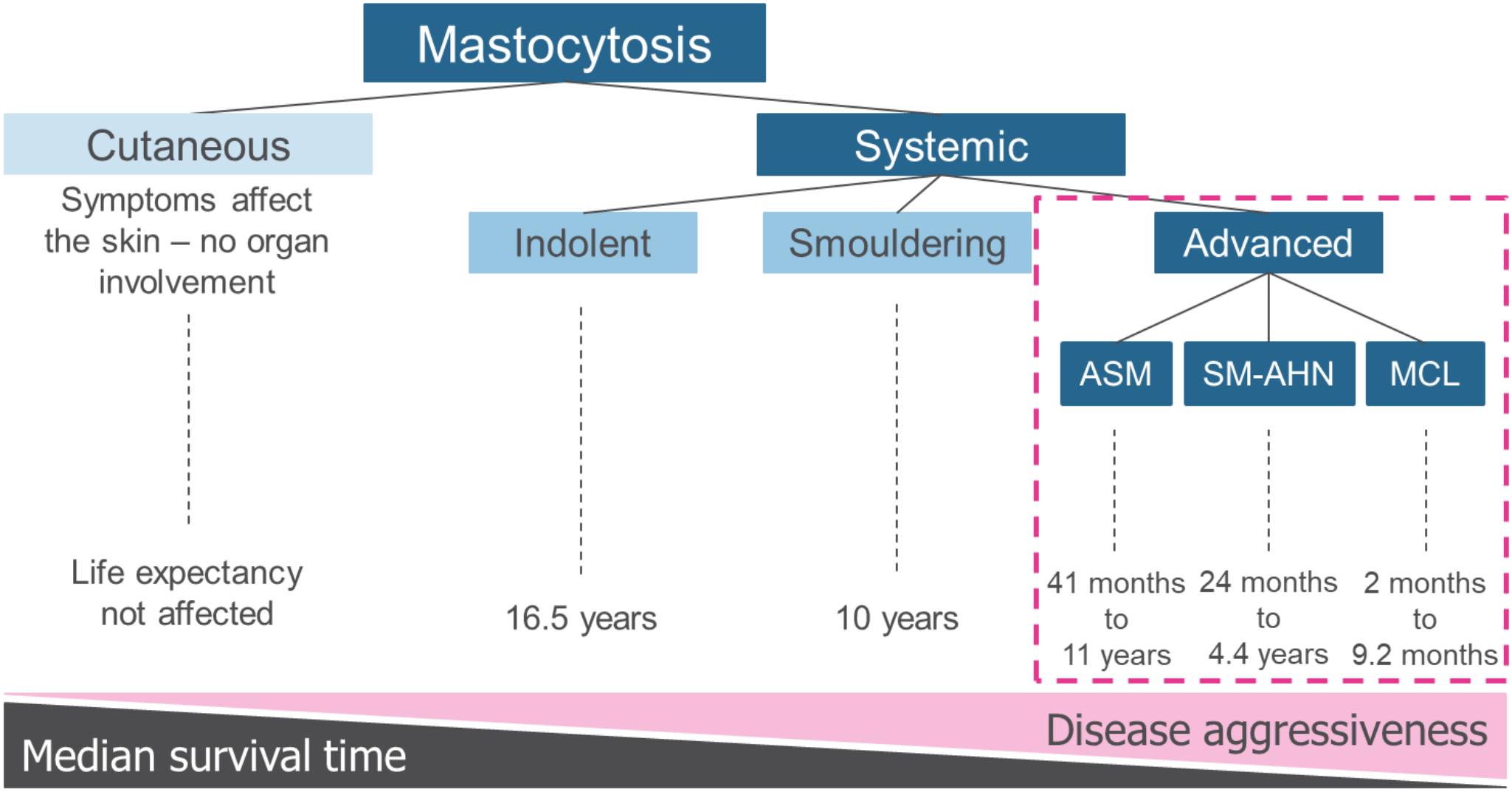
Company: Novartis

ACM1: 1st September 2020

Disease background – Mastocytosis

- A heterogenous group of rare diseases characterised by excessive mast cells, a type of white blood cell that plays a key role in inflammatory immune response.
- An estimated 1 in 10,000 people have systemic mastocytosis (SM), mostly adults
- **Advanced** SM is a severe form of mastocytosis (<10% of SM)
  - An estimated 173 people eligible for treatment in England (based on Danish data and clinical expert opinion)
- 3 advanced SM subtypes:
  - aggressive SM (**ASM**)
  - SM with an associated haematological neoplasm (**SM-AHN**)
  - mast-cell leukaemia (**MCL**)
- Can cause damage to internal organs (spleen, liver, lymph nodes, GI tract).
- Other symptoms include fractures, anaemia, rashes, itching, hot flushes, vomiting, diarrhoea and anaphylaxis.

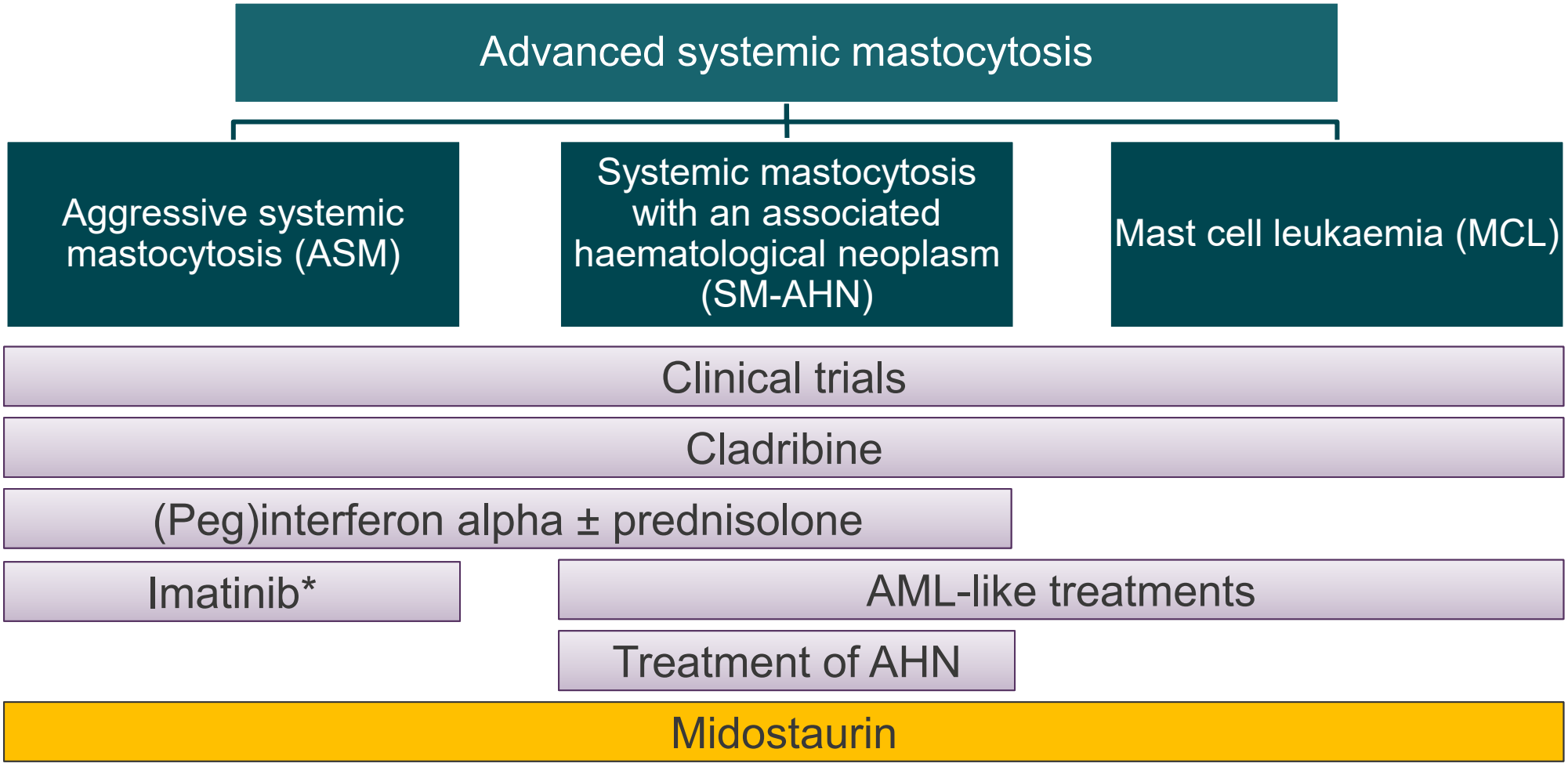
Subtypes of advanced SM



Source: Company submission

Treatment pathway is complex, not well defined

- Midostaurin is the only licenced treatment for advanced SM in the UK
- Current treatment is highly individualised.



*restricted to people who do not have the KIT mutation

Midostaurin (Rydapt, Novartis)

Marketing authorisation	Treatment of adults with ASM, SM-AHN and MCL
Mechanism of action	Kinase inhibitor, that blocks different receptor tyrosine kinases including FLT3 and KIT
Administration	Oral
List price	£22,439.76 per 28-day cycle (£5,609.94 per pack 56 capsules of 25 mg) • Lifetime mean: XXXXXX per patient (company's base-case model)
Commercial arrangement	Simple discount scheme in place (AML) • Lifetime mean: XXXXXX per patient (company's base-case model) Indication-specific arrangement proposed for SM • Lifetime mean: XXXXXX per patient (company's base-case model)

Patient and carer perspectives

- Symptoms of mastocytosis are challenging for patients and carers and affect all aspects of life; physically, socially, emotionally and psychologically.

> "I have had to close down my business and take early medical retirement, due to inability to concentrate and a memory which is similar to early Alzheimer patients."

> "Being covered all over my face, neck, torso and limbs in rashes is horrendous for my self-esteem. I avoid looking in mirrors and going out places."

- Mastocytosis is a rare disease, where clinicians lack knowledge and experimental choice of treatment could pose risks due to being ineffective and potential side-effects.
- Midostaurin is the only licensed treatment that addresses underlying cause of mastocytosis. It is well tolerated and improves quality of life.

> "The treatment has improved their daily life. My family member now has around 8 hours a day of reasonably normal life, we are able to go on holiday and out to events which we would not have been able to do otherwise."

Company's submission (summary)

Comparators	Current clinical management (CCM) • a mix of therapies form a composite comparator
Subgroups	Advanced SM, SM-AHN + MCL
Clinical trial	2 single arm, non-randomised, open label, phase 2 trials • D2201: International, N=116 (3 UK centres, N=4) • A2213: N=26 (US centres only)
Key results	D2201 (data cut-off 24th August 2017): • [redacted] A2213 (data cut-off 1st March 2017): • Median OS (months): 40.0 (95% CI, 27.3 to 52.7)
Comparison with comparators	All trials are single arm Comparison with historical data (Germany, France).
Key result	Reiter et al. (German registry; multivariable analysis): HR (95% CI): 0.52 (0.32 to 0.84)
Model	Partitioned survival model. Four health states: progression-free (sustained response), progression-free (lack or loss of response), progressed and death

*** for primary efficacy population**
CI: Confidence interval; HR: Hazard ratio; OS: Overall survival

Clinical effectiveness – Midostaurin

Trial	Design	Number of participants			
		All	ASM	SM-AHN	MCL
D2201	Open-label, single-arm, international	116	22	73	21
A2213	Open-label, single-arm, US	26	3	7	16

Study & data cut	Median follow up (range)	Analysis group	No. of patients alive	Median OS (95% CI): months	Survival rate: (95% CI)	
					3 years	5 years
D2201 Dec 2014	43 months (29 to 70)	PEP* (n=89)	35 (39%)	26.8 (17.6 to 34.7)	38.2% (27.5 to 48.8%)	Not reported
		FAS (n=116)	35 (30%)	29.9 (20.3 to 42.0)	42.4% (32.6 to 51.8%)	Not reported
D2201 Aug 2017	[redacted]	PEP* (n=89)	[redacted]	[redacted]	[redacted]	[redacted]
		FAS (n=116)	[redacted]	[redacted]	[redacted]	[redacted]
A2213 Mar 2017	124 months (82 to 140)	PEP[a] (n=26)	4 (15%)	40.0 (27.3 to 52.7)	Not reported	Not reported

* Patients who had measurable C-findings considered related to SM.

[a] PEP is same as FAS.

FAS: Full analysis set; PEP; Primary efficacy population

Clinical effectiveness – Midostaurin

D2201 Kaplan-Meier curves for midostaurin OS*, PFS† and DoR† (with parametric fit) for **overall advanced SM population**.

Source: Company submission (appendices)

Time (years)	0	1	2	3	4	5	6	7	8
At risk - OS	89	58	41	31	23	20	9	4	2

*24th August 2017 data cut, primary efficacy population.
†1st December 2014 data cut, primary efficacy population.

Clinical effectiveness – Midostaurin

D2201 Kaplan-Meier curves for midostaurin OS **by subgroup**.

24th August 2017 data cut, primary efficacy population.

Source: Company submission

Comparative effectiveness versus CCM

- 2 comparative studies using historic controls.

Treatment arm	Number of patients (n)						Median duration of follow-up
	ASM	SM-AHN	MCL	MCS	Progressive SSM	Advanced SM	
Reiter et al.							
Midostaurin (pooled D2201 and A2213)	16	59	14	-	-	**89**	79.5 months (range 51.4 to 234 months)*
CCM (German registry)	9	28	5	-	-	**42**	84.2 months (range 22.3 to 176.3 months)
Chandesris et al.							
Midostaurin (French compassionate use programme)	4	18	3	1	2	**28**	18.5 months (range 3 to 36 months)
CCM (French registry)	5	33	2	2	2	**44**	NR

*1st July 2016 data cut (updated using 24th August 2017 data cut in response to technical engagement)
MCS: Mast cell sarcoma; SSM; smouldering systemic mastocytosis.

Comparative effectiveness versus CCM

Analysis method	Midostaurin		Registry control		HR (95% CI)†
	N	Median OS (95% CI), months	N	Median OS (95% CI), months	
Reiter et al.					
Primary (from diagnosis, unadjusted)	89	41.4 (31.0 to 49.1)	42	19.5 (13.0 to 35.3)	0.50 (0.33 to 0.76)
Multivariable*	**89**	**-**	**42**	**-**	**0.52 (0.32 to 0.84)**
Propensity score matched	42	27.8 (19.3 to 44.6)	42	19.5 (13.0 to 35.3)	0.64 (0.33 to 1.24)
Sensitivity analysis (from start of last treatment, unadj)	115	28.7 (19.2 to 34.7)	39	5.7 (2.2 to 11.7)	0.44 (0.29 to 0.67)
Chandesris et al.					
Univariable (matched)	28	NR	44	NR	0.447 (NR)
Multivariable (matched)	28	NR	44	NR	0.333 (NR)

*Company's preferred analysis for OS HR estimate.
†1st July 2016 data cut (analyses was updated using 24th August 2017 data cut to estimate OS HR for D2201 alone and pooled D2201+A2213 in response to technical engagement)
NR: Not reported

Comparative effectiveness versus CCM

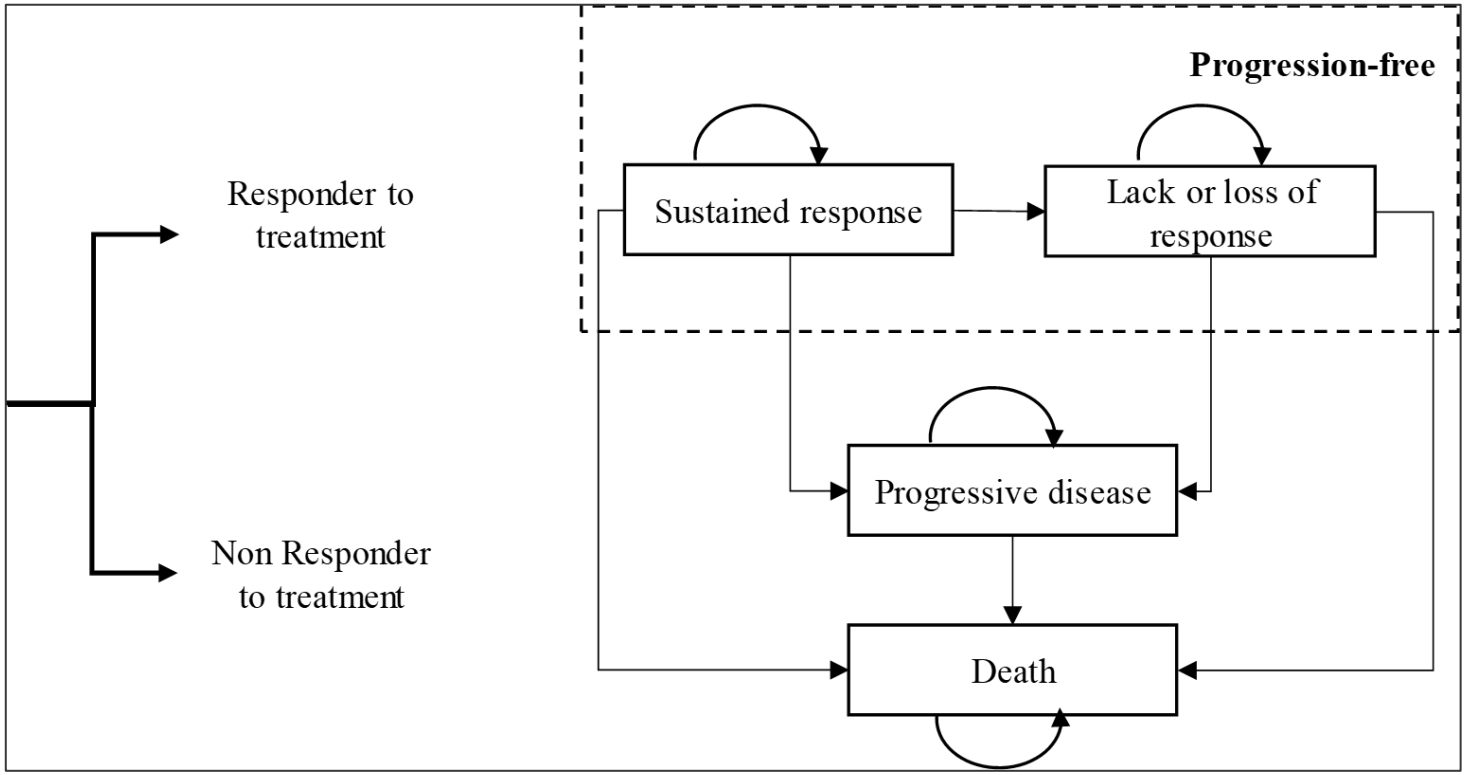
Predicted OS, PFS and DoR estimates for CCM

- OS and PFS: Reiter OS HR applied to midostaurin curves
- DoR: Reiter DoR HR applied to midostaurin PFS curve.

Source: Company submission (appendices)

Company's model structure

- 4 health states: progression-free (with sustained response), progression-free (with lack or loss of response), progressed and death.
- Lifetime time horizon (38 years)
- Patients enter the model in either of 2 progression-free health states.



Source: Company submission

Key issues resolved post technical engagement	Status
Issue 1: Generalisability of clinical practice in D2201 and A2213 to UK NHS practice	Resolved
Issue 3a: Are ASM, SM-AHN and MCL distinguishable in clinical practice?	Resolved
Issue 4b: Pooling of D2201 and A2213 data for comparative effectiveness with German registry.	Resolved
Issue 8b: Appropriateness of manually restricting utility values	Resolved
Issue 11: Would additional data collection through the Cancers Drugs Fund reduce the uncertainty?	Resolved

Key issues unresolved post technical engagement	Status	Impact	Slide
Issue 2: Appropriateness of comparator treatment(s) used in UK clinical practice	For discussion		19-20
Issue 3b: Treatments for subgroups offered in NHS England **Issue 3c:** Pooling SM-AHN and MCL subgroups	For discussion		22
Issue 4a: Comparability of studies using historic controls to clinical practice in England	For discussion		21
Issue 5: Reliability and appropriateness of OS HR to predict OS for CCM	For discussion		23-24
Issue 6: Use of OS HR to estimate PFS for comparator	For discussion		25
Issue 7: Appropriateness of partitioning health sates based on response status	For discussion		26-27
Issue 8a: Impact of using alternative mapping approaches	For discussion		28
Issue 9: Duration of midostaurin treatment benefit	For discussion		29-30
Issue 10: End of life criteria	For discussion		31-33

 **Model driver**

 **Unknown impact**

 **Small/Moderate impact**

Issue 2: Comparator treatments

Background
- No licensed treatment other than midostaurin.
- Company's model includes CCM, a composite comparator of most commonly used treatments, including AML-like treatments
- Proportion of treatments is informed by clinical expert opinion.

Technical team comments
- The extent to which different treatments are used in clinical practice is uncertain.
- Unclear whether AML-like treatments are appropriate comparators.

Stakeholder comments
- Difficult to estimate a percentage of treatments used (heterogeneity & small numbers).
- Management is usually tailored by subgroup, severity and patient characteristics.
- AML-like treatments are used sporadically, primarily for SM-AHN subgroup.

Company comments
- Comparators were determined based on feedback from 5 UK clinical experts.
- 4 experts indicated AML-like treatments formed part of advanced SM management.
- Provided scenario cost-effectiveness analysis vs. individual treatments (changed cost only).

Issue 2: Comparator treatments

Comparator	Company Advanced SM	Company SM-AHN + MCL	German registry	French registry
Cladribine	53.7%	51.1%	Reiter et al. Does not include any data on treatment received.	Chandesris et al. Patients had previously received: • Cladribine 49% • Steroids 41% • Thalidomide 18% • TKI other than midostaurin 13% • Interferon 8% • mTOR inhibitor 5% • Other 5%
Interferon alpha	2.1%	1.5%		
Peg-interferon alpha	24.2%	23.7%		
Imatinib	4.5%	3.6%		
Dasatinib	-	-		
Nilotinib	-	-		
AML-like treatment (azacitidine)	7.5%	9.2%		
AML-like treatment (other)	8.0%	9.8%		
Thalidomide				

Is a composite comparator including AML-like treatments appropriate and reflective of NHS clinical practice?

Issue 4a: Generalisability of registry data to NHS

Background
- Registry data from Germany (base case) and France used as sources of comparative effectiveness evidence.

ERG comments
- Reiter et al. is the best available source of indirect comparative evidence.

Technical team comments
- Non-RCTs are associated with a higher risk of bias, may introduce uncertainty.

Stakeholder comments
- Expects some variations in SM management between France and UK.
- Patients with different SM subgroups from German and French registry control group are similar to those expected in NHS.

Company comments
- D2201 included treatment centres from Germany and France.
  - considered reflective of UK NHS clinical practice by clinical experts.

Are clinical practice and outcomes from Germany and France generalisable to England?

Issue 3b/3c: Subgroups

Background
- Company presented 1 subgroup analysis: pooled SM-AHN + MCL subgroups
- Assume a common composite comparator (see slide 18).

Technical team consideration
- Subgroups are clinically distinct with varying symptoms, life expectancies and treatments.
- Unclear whether SM-AHN and MCL subgroups should be pooled.

Stakeholder comments
- Treatment of SM-AHN and MCL subgroups is different.
- Treatment should either be combined in one composite comparator for all advanced SM or separated for the 3 individual subgroups.

Company comments
- Treatment options are broadly similar for subgroups.
- SM-AHN and MCL have lower life expectancy and greater unmet need than ASM.
- With low prevalence of MCL, not possible to conduct separate analysis.

Is the subgroup analysis for pooled SM-AHN + MCL population appropriate?

Which treatments are offered for each subgroup in NHS England?

Issue 5: Hazard ratio to predict CCM survival

Background

- Company applied multivariable OS HR (0.52) from Reiter et al. to midostaurin OS curve to:
  - estimate OS for CCM (for overall population (advanced SM) & SM-AHN+MCL subgroup).
  - estimate OS for using individual comparators in scenario analysis.

ERG comments

- Company's clinical experts suggested a very wide range of plausible HRs: 0.33 to 0.64.
- Reliability of results from Reiter et al. is questionable.
  - Small number of patients
  - Different protocols for D2201 and A2213 trials
  - Treatments received by German registry control not known
  - Insufficient information about recruitment methods
  - Results in abstract inconsistent with results presented elsewhere.
- OS HR is a key driver of cost-effectiveness results.
- Base-case midostaurin curve (spline hazard 1-knot) selected appropriately.

Technical team comments

- OS survival curve for midostaurin appears to be reasonable.
- OS estimates for comparators (via the HR) may be uncertain.
  - Limitations of using non-RCT Reiter study
  - Several HRs provided by the company

Issue 5: Hazard ratio to predict CCM survival

Stakeholder comments

- OS should be adjusted for age and disease subgroup.
- HR should be interpreted with caution as median age differs between pooled midostaurin and registry control group.

Company comments

- D2201 is the largest and most robust source of evidence in advanced SM.
- Clinical experts judged appropriate to assume similar effectiveness of each comparator and for the SM-AHN+MCL subgroup.
  - Due to lack of evidence and small subgroup sample sizes.
- Provided updated Reiter analyses using August 2017 data cut, including using D2201 only.

	D2201 July 2016	D2201 August 2017	
	D2201 & A2213	D2201 & A2213	D2201 only
From diagnosis (unadj)	0.50 (0.33 to 0.76)	XXXXX	XXXXX
Multivariable (base case)	**0.52 (0.32 to 0.84)**	XXXXX	XXXXX
Propensity score matched	0.64 (0.33 to 1.24)	XXXXX	XXXXX
From start of last tmt (unadj)	0.44 (0.29 to 0.67)	XXXXX	XXXXX
From start of last tmt (multiv)	NR	XXXXX	XXXXX

Is the Reiter study a reliable source for the HR? Which HR should be used? Is it appropriate to apply it to individual treatments and subgroups?

Issue 6: Hazard ratio to predict CCM PFS

Background
- Company used OS HR to estimate PFS for CCM

ERG comments
- Could not identify clinical evidence either in support of or against the company's approach.
- The company's PFS curve fit for midostaurin appears to be reasonable.
- PFS HR is not a key driver of cost effectiveness.

Technical team comments
- Appropriateness of using OS HR for PFS is uncertain.

Company comments
- Clinical experts agreed this to be appropriate in presence of data limitations.
- A 5x higher PFS HR increased base-case ICER by 3.6%.
  - highlights little impact of PFS HR on cost-effectiveness results.

What is the most appropriate HR to estimate PFS of comparator(s)?

Is it reasonable to use the HR for OS, in the absence of alternative data?

Issue 7: Partitioning PFS by response status

Background
- Company's model included 2 PFS health states based on treatment response
- **Sustained response** and **lack/loss of response** → assigned different utility values
- Based on clinical expert advice that quality of life differs by treatment response.

ERG comments
- Inconsistent to partition PFS but not OS, given both outcomes differ by response status.
- Concerns over reliability of response rates and duration data used to partition PFS.
- Exploratory analysis using average PFS utility for both PFS states.

Technical team comments
- Inconsistent to stratify PFS and not OS
- Should consider analyses with 1 PFS state and with both PFS and OS stratified by response status.

Stakeholder comments
- D2201 results by response status suggest it may be helpful to stratify both PFS and OS according to treatment response.

Issue 7: Partitioning PFS by response status

Company comments

- Recognise uncertainties in response data due to paucity of data.
- Using the same utility value for all patients in the PFS health state is conservative.
- Partitioning OS by response would further rely on:
  - uncertain response rates
  - strong assumption that response rates may be used as surrogate for OS.
- Re-ran utility regression model on D2201 individual patient data with 1 PFS state.

ERG critique

- The ERG's exploratory analysis used an average utility value because the individual patient data were not available to re-run the company's regression.

Utility values using regression based on partitioned PFS and non-partitioned PFS state:

	Original regression (partitioned PFS)	New regression (1-PFS state)
PFS: response	XXXXX	XXXXX
PFS: no response	XXXXX	
Post progression	XXXXX	XXXXX

Should the utility value in the PFS state depend on response status (2 states), or not (1 state)? Should OS have been partitioned by response status?

Issue 8a: Alternative utility mapping approaches

Background

- Company model used Gray et al. mapping algorithm to estimate EQ-5D utility values from SF-12 data collected in D2201.

Technical team comments

- There may be better approaches than using Gray et al. (2006) to estimate EQ-5D utility values, such as Conigliani et al. (2015).

Company comments

- Company conducted scenario analysis using alternative linear model mapping algorithms
  - minimal effect on cost-effectiveness results.
- Mapping algorithms explored include:
  - Gray et al. (2006) – used in base-case analysis
  - Franks et al. (2003)
  - Franks et al. (2004)
  - Lawrence et al. (2004)

Has the company appropriately considered range of mapping algorithms to derive utility values to inform economic model?

Issue 9: Duration of midostaurin treatment effect

Background
- Base-case model assumes HR (treatment benefit) lasts for the person's lifetime.

ERG comments
- Likely that PFS and OS rates for midostaurin and CCM would become equal at some point.
- Exploratory analysis illustrating the effect of this at 3 years.

Technical team comments
- Response to treatment may be durable over time, but benefit unlikely to last for 38 years.

Stakeholder comments
- Experience with 1 patient who has been on midostaurin for >10 years without progression
- Reasonable to assume patients with response to midostaurin maintain benefits relative to current treatments.
- Would not expect a sustained response following midostaurin withdrawal. Noted that in D2201, minority of patients on treatment at 1 year, and 19% at 3 years.

Company comments
- Midostaurin is disease modifying → plausible the effect would continue after stopping.
- Acknowledge uncertainty in long-term HR → provided scenarios equalising at 3, 5, 10 yrs.
- D2201 and A2213 suggest long survival for midostaurin patients → progression and mortality should not be equalised before 10 years.

What is the most plausible duration of sustained treatment effect for midostaurin?

Issue 10: End of life criteria

Background
- Company provided analysis for all advanced SM and SM-AHN + MCL subgroup.

ERG comments
- Only **MCL** subgroup clearly meets short life expectancy criterion (based on median OS)
- Life extension criterion is dependent on validity of Reiter et al. OS HR.

Technical team comments
- End of life criteria should be assessed independently for subgroups.

Stakeholder comments
- Considerable variability in survival estimates. Conventional estimates of median survival with current treatment are: ASM 3.5 years, SM-AHN 2 years, MCL 6 months.
- Midostaurin certainly extends survival by at least 3 months.

Company comments
- Reiter et al: median OS is 19.5 months (95% CI: 13.0 to 35.3).
- Base-case model: mean OS is 1.90 years (advanced SM) and 1.46 years (subgroup).
- Some studies e.g. Lim et al. include indolent disease, which has much longer survival.
- Reiter et al. data indicates life extension criterion is met.

Are the end of life criteria met?

Issue 10: End of life criteria

Criterion	Subgroup	Data source	OS with CCM
			Median
Short life expectancy: normally < 24 months	Advanced SM	Reiter et al.	19.5 months
	ASM	Lim et al.	41 months
		Jawhar et al	132 months
	SM-AHN	Lim et al.	24 months
		Cohen et al.	52.8 months
	MCL	Lim et al.	2 months
		Budnik et al.	9.2 months
Extension to life: normally ≥ 3 months	**Subgroup**	**Data source**	**OS increase with midostaurin**
			Median
	Advanced SM	Company's base case	XXXXX months
		Reiter et al.	21.9 months
	SM-AHN+MCL	Company's base case	XXXXX months

Issue 10: End of life criteria

Scenario	Mean CCM life expectancy (months)	
	Advanced SM	AH-AHN + MCL
HR: Multivariable, 2016 data, pooled trials		
Lifetime midostaurin benefit	22.8	17.5
10-year midostaurin benefit	23.6	17.8
5-year midostaurin benefit	26.2	18.9
3-year midostaurin benefit	29.6	20.9
HR: PS matched, 2016 data, pooled trials		
Lifetime midostaurin benefit	29.7	22.4
10-year midostaurin benefit	31.0	22.8
5-year midostaurin benefit	33.9	24.3
3-year midostaurin benefit	37.0	26.3
HR: multivariable, 2017 data, pooled trials		
Lifetime midostaurin benefit	23.6	18.1
10-year midostaurin benefit	24.5	18.4
5-year midostaurin benefit	27.2	19.6
3-year midostaurin benefit	30.6	21.6
HR: multivariable, 2017 data, D2201 only		
Lifetime midostaurin benefit	25.1	19.1
10-year midostaurin benefit	26.1	19.5
5-year midostaurin benefit	28.8	20.8
3-year midostaurin benefit	32.3	22.8

Cost-effectiveness results

- All ICERs using midostaurin's existing PAS are >£100K.
- Company has proposed a confidential commercial arrangement to NHS England.

- **All ICERs will be presented in part 2 (including comparator PAS).**