Slides for PUBLIC – no ACIC information

NICE National Institute for Health and Care Excellence

Chlormethine gel for treating mycosis fungoides-type cutaneous T-cell lymphoma

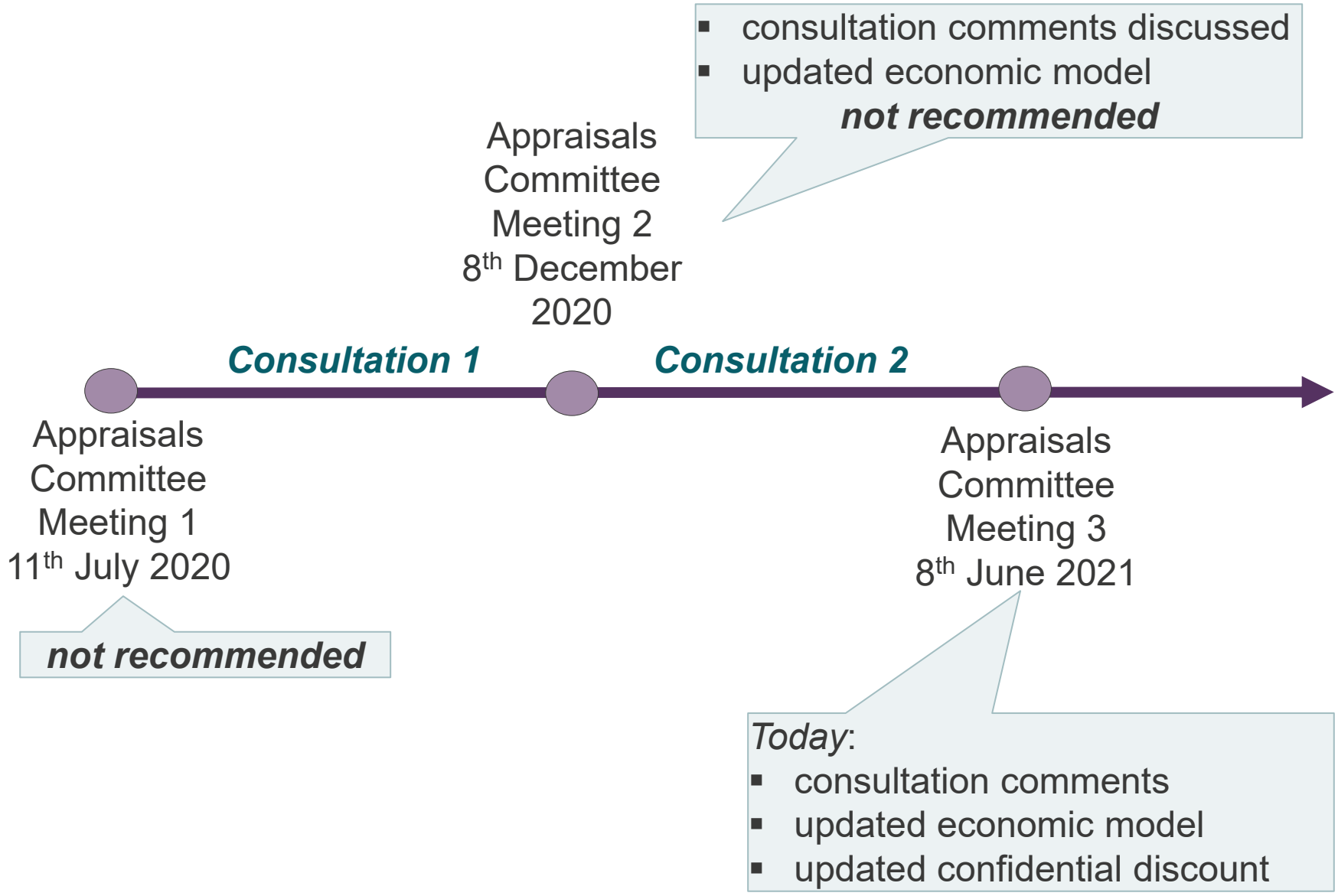
3rd Appraisal Committee meeting

Chair presentation

Lead team: Mark Upton, G.J. Melendez-Torres, Pamela Rees
ERG: Aberdeen Health Technology Assessment Group
Chair: Jane Adam
Technical team: Heather Stegenga, Joanna Richardson, Janet Robertson
Company: Recordati Rare Diseases/ Helsinn Healthcare SA

8th June 2021

Topic history



Key issues

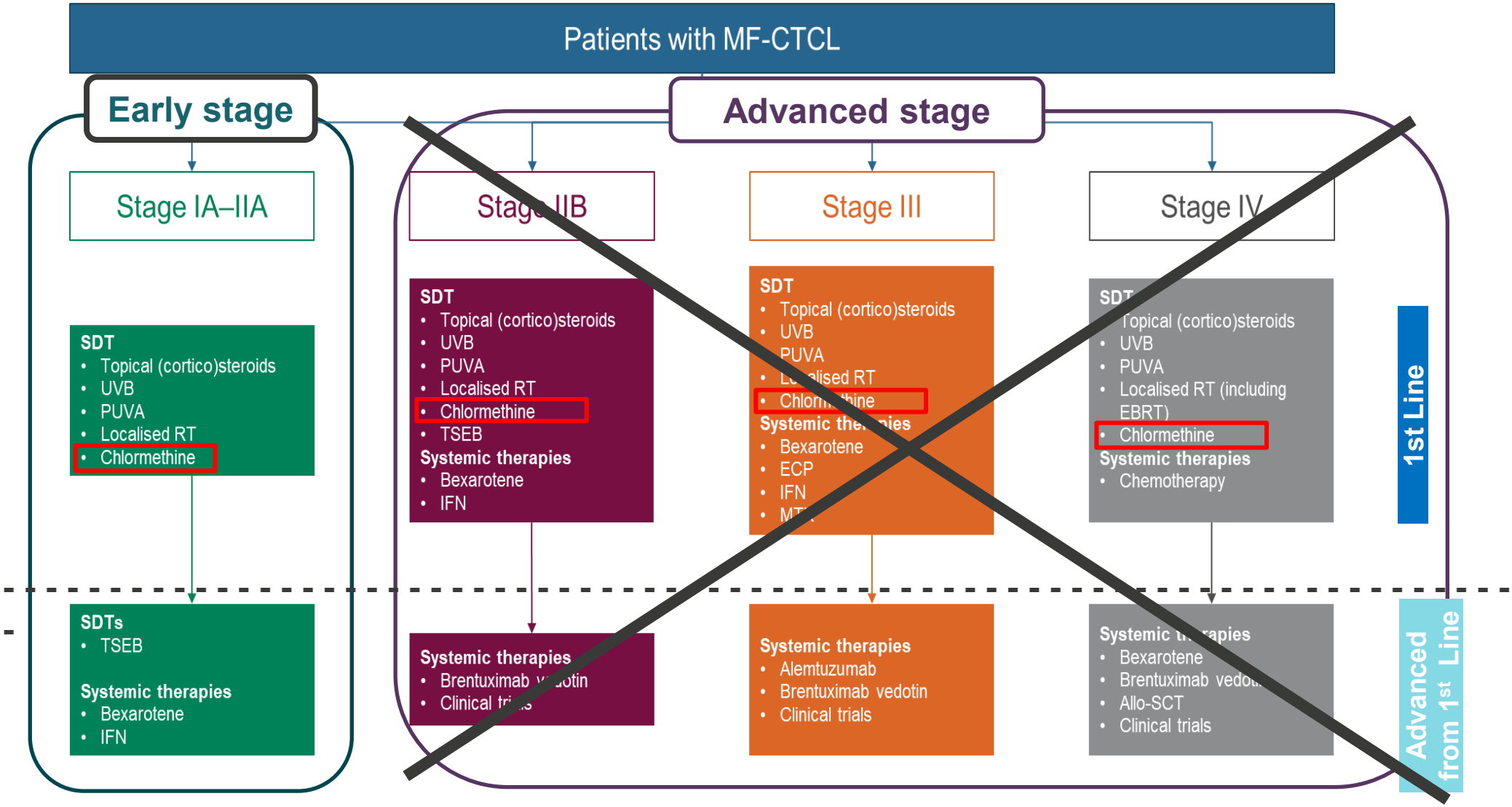
- Are the two updated models, based on specific populations, appropriate for decision making?
  - Stage IA only – low skin burden
  - Early disease (stages IA, IB, IIA) – mixed low and high skin burden

- Is the treatment considered clinically and cost effective for either of these groups, taking into account new confidential pricing?

Chlormethine gel (Ledaga, Recordati Rare Diseases/ Helsinn Healthcare SA)

Mechanism	• DNA alkylating agent which disrupts DNA replication in rapidly proliferating cells. • Previously available as ointment (withdrawn)
Marketing authorisation received 3rd March 2017	• For the topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma in adult patients.
Administration and dose	• Topical therapy applied to affected areas of skin once daily • Chlormethine gel contains chlormethine equivalent to 0.02% (w/w) chlormethine hydrochloride
Indicative list price	• £1,000 per 60g tube (excluding VAT) • **Updated patient access scheme (PAS) agreed: simple discount.**

Treatment pathway



Chlormethine gel is being proposed as first-line option in **early stage disease** among other options which patient cycle through until symptoms no longer respond.

Skin directed therapies not expected to affect underlying disease progression or mortality, but may delay use of systemic therapies (which may be used, even if disease has not spread).

Early stage cutaneous T-cell lymphoma

Stage IA
- < 10% of skin covered in red patches or plaques
- No blood or lymph node, or internal organ involvement

Low skin burden

Stage IB
- 10% or more of skin covered in patches or plaques
- No blood or lymph node, or internal organ involvement

High skin burden

Stage IIA
- Any amount of skin surface covered with patches or plaques
- Lymph nodes: enlarged and inflamed but are not cancerous

Mixture of low and high skin burden

PROCLIPI registry data suggests that [redacted]* of people with stage IIA have low skin burden.

The company note that [redacted] of people with stage IIB+ (advanced disease) also have low skin burden; however, in response to ACD2 the company is no longer asking the committee to consider advanced stage disease.

NICE

** Corrected by company during committee meeting as an error in company consultation response.*

Key trial: Study 201 – early stage disease

Trial design	A multi-centre, randomised **non-inferiority** study (1:1, observer-blinded phase II study (n=260))
Intervention	Chlormethine gel (n=130)
Comparator	Chlormethine ointment (n=130)
Population	Stage IA, IB or IIA MF-CTCL previously treated with at least one skin-directed therapy for MF-CTCL. [39% with phototherapy, 86% topical corticosteroids] Mean % body surface area affected [redacted] and [redacted] for low and high skin burden respectively*
Outcomes	• **Primary**: CAILS response rate (skin response 50% or more) • **Secondary**: mSWAT response rate (used in the model),
Follow up	• 12 months to assess the development of secondary non-melanoma skin cancers

Abbreviations: CAILS = composite assessment of index lesion severity, mSWAT = modified severity weighted assessment tool

Advanced stage (stage IIB+) not included

NICE

* These values were used in the model

Study 201 results for chlormethine gel: ITT including NYU population

	CAILS response	mSWAT response
Response n (%)	Chlormethine gel n=130	Chlormethine gel n=130
OR	76 (58.5)	61 (46.9)
CR	18 (13.8)	[redacted]
PR	58 (44.6)	[redacted]

Abbreviations: CAILS = Composite Assessment of Index Lesion Severity, mSWAT = modified Severity Weighted Assessment Tool, ITT = intention to treat, NYU = New York University, OR = overall response, CR = complete response, PR = partial response.

Data from trial has been used to inform the following parameters in the model:

- the extent of skin involvement
- dosage of chlormethine gel per application
- transition probabilities for chlormethine gel

For modelling, mSWAT, which incorporates skin burden, has been used (**not** CAILS).

Results from comparator chlormethine ointment not presented as no longer in use.

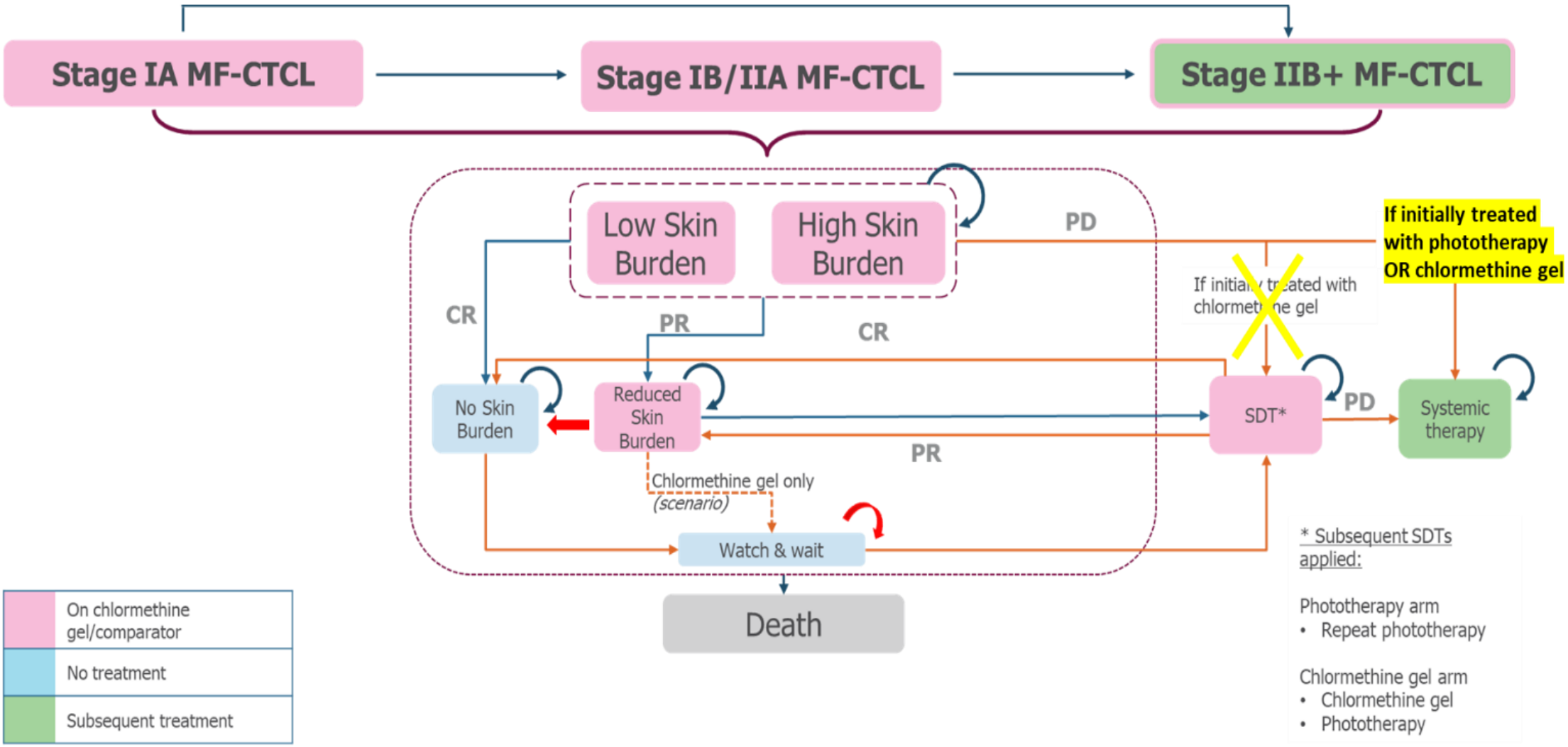
Committee considerations

- Current treatment is usually **based on the level of skin involvement** rather than stage of disease but results from the evidence on chlormethine gel is not separated by the level of skin burden.
- People with low skin burden have a particular clinical need for alternative options.
- Chlormethine gel addresses symptoms and improve quality of life but is not a cure.
- Chlormethine gel is likely to be used for early disease amongst a battery of skin directed treatments. People will cycle through these treatments until symptoms no longer respond. In advanced disease, it may be used in combination with systemic therapies.
- The main trial (study 201) includes people with early stage disease (IA, IB, IIA) only and is not generalisable to advanced disease (stage IIB+).

Committee considerations

- The main trial (study 201) includes a comparator (chlormethine ointment) that is no longer used.
- Phototherapy: comparator in the company submission but the **relative effectiveness is not known** (no head-to-head evidence or a connected network for an indirect comparison).
- The true clinical effectiveness of phototherapy is uncertain; all sources have limitations but committee prefer using a consistent data source for all clinical effectiveness parameters (Phan et al. 2019 meta-analysis of 7 observational studies was preferred for all outcomes, rather than using Whittaker et al. 2012 RCT for duration of complete response).

Model structure for ACM2 with ERG amendments



ERG amendments in yellow. Abbreviations: CR: complete response; MF-CTCL: mycosis fungoides cutaneous T-cell lymphoma; PD: progressive disease; PR: partial response; SDT: skin-directed therapy. (arrows: blue - old transitions, orange - new transitions, red - added by the ERG to represent model)

- In ERG model amendments, people who enter systemic therapy state with progressed disease/ refractory to chlormethine gel treatment, have a round of phototherapy before starting systemic therapies.

Committee considerations

- Clinical practice is better represented in the company's updated model than the original, simplified model.
- Treatment sequencing for refractory skin symptoms in clinical practice is not reflected in the updated model.
- Treatment sequencing for disease that relapses after initial response is not reflected in the updated model - the committee preferred the ERG's updated model structure but did not accept the ERG's assumption of reduced efficacy of treatment second time.
- The phototherapy effectiveness parameters used in the model are highly uncertain. Although the committee did not consider that any data source was robust, it preferred the ERG's approach of using 1 data source for all outcome measures.
- Mean daily dose of chlormethine gel is uncertain (ERG used 2.8g from SPC but company used a smaller value, [redacted]). Committee preferred 2.8g.
- The committee would have preferred utility values derived from patient-reported outcomes.

Company's base case at ACM2 and cumulative impact of ERG's preferred assumptions on the ICER (with original PAS)

	Incremental costs	Incremental QALYs	ICER (£/QALY)
Company's ACM2 base case	[redacted]	0.33	[redacted]
1) Phan et al used for phototherapy effectiveness data (duration of CR & PR)	[redacted]	0.14	[redacted]
2) Allow patients refractory to chlormethine gel to progress straight into systemic therapy	[redacted]	0.07	[redacted]
3) Reduced effectiveness for 2nd and further rounds of skin directed therapy for patients who respond but relapse	[redacted]	0.22	[redacted]
4) Reduced effectiveness of phototherapy for patients with progressed disease after chlormethine in the systemic therapy state	[redacted]	0.21	[redacted]
5) ERG preferred base case*	[redacted]	0.21	[redacted]

NICE

*used mean daily chlormethine gel dose from Valchlor® SmPC by disease stage ([redacted] for stage I and [redacted] for stage IB/IIA)

Committee considerations

- No reliable cost-effectiveness estimates, and those that included its preferred assumptions were above the acceptable range.
- The company does not present any cost-effectiveness analyses by subgroups who may benefit more from chlormethine gel

ACD preliminary recommendation

- Chlormethine gel is not recommended for treating MF-CTCL

ACD2 consultation responses

- Consultee comments on ACD2 from:
  - UK Cutaneous Lymphoma Group (UKCLG)
  - Company (Recordati Rare Diseases/Helsinn Healthcare SA)

UKCLG comments (1)

- Not recommending contributes to overall discrimination in rare cancer; while not ‘unlawful’ discrimination has significant impact on patients’ lives.
- Patients disadvantaged at all stages:
  - **Recognition:** GPs usually unfamiliar with condition
  - **Referral:** no 2-week wait referral like other cancers; may be reluctance to refer and given ineffective topical treatment; long waiting times
  - **Diagnosis:** often not straight-forward, requiring multiple biopsies & specialist pathology. Only 10 supra-regional UK teams experienced in CTCL – may not be referred to one of these. Quality of life affected by diagnosis delay and ineffective treatment.
  - **Treatment:** few licensed treatments for CTCL, paucity of RCT data due to rarity of disease, existing guidelines rely on low quality evidence based on retrospective data, particularly in early stage disease.
  - **UK disparity:** chlormethine gel a rare licensed treatment for early stage. Nitrogen mustard used extensively historically with evidence from retrospective studies; clear advantages to using chlormethine gel compared to nitrogen mustard.

UKCLG comments (2)

Theme	Comments
Trial comparator	• Trial discounted unfairly based on comparator (ointment) no longer used since it is no longer available.

Evidence on ointment relevant to gel	• Reasonable to extrapolate from evidence on ointment to gel (non-inferior in trial).
	• Ointment:
	  • more effective in early stage – same expectation for chlormethine gel.
	  • shown to result in remission longer than 8 years; could suggest CTCL might be 'cured'.
	  • may have unique effect on MF-CTCL immunopathogenesis.
	  • benefit in stage IB disease, sites missed by other skin-directed therapies.

Current practice	• No 'gold standard', depends on: skin burden or stage, therapy availability, clinician speciality, location and personal experience, and patient preference. • Patients cycle through treatments with periods of active monitoring (watch and wait) between therapies. • Skin-directed treatments for early disease aim to relieve symptoms – improving quality of life; using all available topical therapies for as long as possible reduces systemic treatment use (which are more expensive and toxic)

UKCLG comments (3)

Theme	Comments
Relevant comparator (s)	• Limited options for early stage: usually topical steroids, rarely clears symptoms and has side effects and risks over time. • Phototherapy inconvenient with finite cumulative dose because carcinogenic, not suitable for the young. Expensive and requires hospital treatment • Efficacy of phototherapy overestimated: Whittaker et al. (2012) more directly applicable to the UK, with much lower rates than Phan et al. • Effect of COVID-19 pandemic; will take years for services to resolve.
Patient choice not taking into account	• Full costs for the patient not fully considered (travel, loss of work and income) or loss over autonomy with hospital based therapy. • Patients often anxious at the end of treatment course. Chlormethine gel gives control back because can be used long-term.
Estimated gel usage overestimated	• No robust evidence for ERG's preferred 2.8g estimate of gel usage over the company's estimate; highly likely gel used will be less than trial as will be recommended for lesions only, rather than whole or regional body as was advocated in trial.

UKCLG comments (4)

Theme	Comments
Length of benefit	• Assumption that chlormethine gel only used for 4-6 months or up to 12 months not necessarily correct. • 12 months median time to complete response in Kim 2003 but many used for longer. Trial extension shows use for 7 months with further response. • Benefit longer than 12 months with nitrogen mustard ointment (experience).
Cost saving	• Difficult to determine on paper because reduces burden of patient from hospital and allows patients to return to work with less days off. • Overall costs to NHS small since MF-CTCL is rare. (annual incidence 332 for all CTCL and 182 for MF-CTCL; compared 50,000/year for breast cancer)
Potential of chlormethine gel	• Potential to offer long-term remission, reduce risk of disease progression or delay the need for systemic therapy in some early stage IA patients should not be dismissed given the evidence provided by historical data for nitrogen mustard.

Company response – summary

- Committee adopt pessimistic view when faced with uncertainty; resulting ICER is ‘worst case’.
- Company’s approach to modelling subsequent phototherapy after progressive disease with chlormethine gel is more aligned with clinical practice.
- A degree of uncertainty should be accepted in modelling approach given rare disease with poor evidence base for existing treatments.
- Updated cost-effectiveness results:
  - incorporated the committee’s preferences, despite disagreeing – provided scenarios with company’s preferences
  - unable to model by skin burden but company present 2 models by disease stage
  - no longer seeking approval for advanced stage disease (stage IIB+), despite being licensed in all stages (though no trial data in this population)
  - new commercial arrangement submitted and accepted by NHSE.

Company: ERG and committee preferences 'worst case'

- Committee adopt pessimistic view when faced with uncertainty, including:
  - dosing from Valchor summary of product characteristics (vs study 201 individual patient data)
  - Phan et al (2019) for all phototherapy estimates (vs Whittaker et al 2012 for duration of response or PROCLIPI for complete/partial response)
  - patients in the model who are refractory to treatment were assumed to receive only one course of phototherapy before systemic therapy (treatment distribution of bexarotene 44.65%, interferon-α 44.65% and phototherapy 10.71%).
- However, company incorporate all of the above committee preferences in updated model, providing scenarios of company preferred assumptions.

Company: ERG approach to modelling one course of phototherapy after chlormethine gel not aligned with clinical practice

- **Underestimate number of courses of phototherapy** for people after chlormethine gel. Clinical experts: number of courses depends on type of phototherapy and duration of response (2-4 courses if short duration or 1-2 for longer duration).
- **Does not capture range of responses to phototherapy** – company approach (maintaining skin-directed therapy (SDT) state for those refractory to chlormethine gel) allows people to enter 'watch and wait' if complete response to phototherapy, enter 'reduced skin burden' if partial response.
- **Advantage for chlormethine gel appropriate and reflects clinical practice**, with chlormethine gel delaying need for systemic therapy. Consistent with clinical expert advice that patients refractory to chlormethine gel would try phototherapy before systemic therapy while those refractory to phototherapy would go straight to systemic therapy.
- Company acknowledge utility overestimate in patients when having phototherapy when refractory to chlormethine gel (company model gives same utility to people entering SDT state when relapse). Conduct scenarios looking at differing utility rates for those who have refractory disease vs those who have relapsed disease.

Company: degree of uncertainty should be accepted given rare disease

- MF CTCL is rare disease with complex treatment pathway and very limited robust data for comparator therapies. Developing a model is challenging with available data.
- NICE ongoing methods review acknowledges these contexts and proposes ‘a greater degree of uncertainty and risk should be accepted in defined circumstances, including conditions for which it is recognised that evidence generation is complex and difficult, such as rare diseases’.
- Company agreed updated commercial agreement with NHSE in light of this uncertainty; level of discount differs depending on the population modelled, based on expected patient numbers:
  - Unable to model by skin burden (committee preferred) due to restrictions in model structure.
  - Instead company present 2 models by disease stage: stage IA and ‘early stage’ disease (stage IA, IB, IIA).
- No longer seeking approval for advanced stage disease (stage IIB+), despite being licensed in all stages.

Company updated model(s)

- Incorporates committee preferences.
- Two models by disease stage

Stage 1A

Low skin burden only but excludes those with low skin burden in stage IIA*

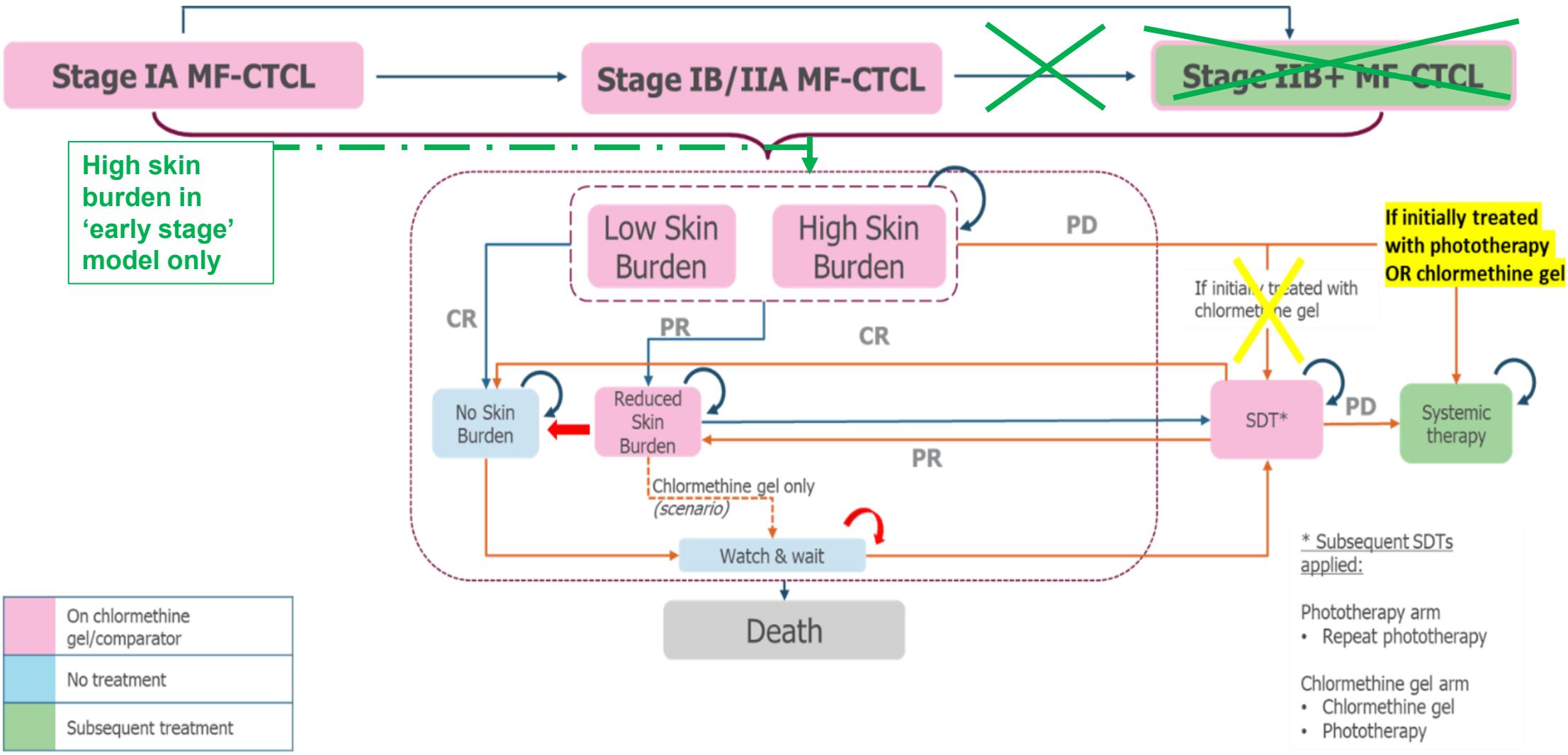
Early stage (stage IA, IB, IIA)

Mixed skin burden. Assumes high skin burden in all with stage IIA, despite some have low skin burden*

- Company prefer 'early stage' model – includes low skin burden in stages other than stage IA and skin burden is not only factor influencing disease stage.
- Company consider 'early stage' model conservative – includes people with higher burden who would have greater usage and therefore higher costs.
- Transitions probabilities for underlying disease removed so patients in stage IA model do not progress beyond stage IA and no transition into stage IIB+ for early stage model. This was due to complexity of model but probability of disease progression is low at early stages and is modelled as independent of treatment in the model (does not favour either treatment).

* Company report [redacted] of people with stage IIA disease have low skin burden (PROCLIPI registry). *(figure corrected by company during committee meeting as an error in company consultation response)*

Updated model structure and ERG amendments



ERG amendments in yellow. Abbreviations: CR: complete response; MF-CTCL: mycosis fungoides cutaneous T-cell lymphoma; PD: progressive disease; PR: partial response; SDT: skin-directed therapy. (arrows: blue - old transitions, orange - new transitions, red - added by the ERG to represent model)

ERG critique (1)

- Note that ‘early stage’ model applies to people with both low- and high-skin burden within these stages.
- Not clear if ‘early stage’ model conservative – differential treatment effect and therefore costs of low vs high skin burden unknown.
- Combined state of stage IB / IIA assumes all have high skin burden.
- ERG agree model not easily amended to represent low skin burden based on current structure and difficulty populating required transition probabilities.
- Decision based on disease stage is more robust given model structure; assessment based on skin burden cannot necessarily be verified with the model and difficult to implement in current practice.

ERG critique (2)

- Removal of transition probabilities for underlying disease:
  - ERG consider* it is more clinically intuitive to allow for underlying disease progression and current approach could misrepresent the numbers entering ‘death’ state over time; however, consider if any biases resulting from this exist, they are likely to be small.

- Overall:
  - Company have implemented the committee’s preferred assumptions.
  - Modelling approach based on stage is best approach given the model limitations and difficulties populating transition probabilities.
  - No further ERG analyses and no major concerns outstanding.

(factual accuracy corrected after committee meeting)

Key issues

- Are the two updated models, based on specific populations, appropriate for decision making?
  - Stage IA only – low skin burden
  - Early disease (stages IA, IB, IIA) – mixed low and high skin burden

- Is the treatment considered clinically and cost effective for either of these groups, taking into account new confidential pricing?

As all the cost effectiveness results are marked as confidential due to updated commercial arrangements, they will only be presented in Part 2 of the meeting.