Chair's presentation

Ixazomib with lenalidomide and dexamethasone for relapsed or refractory multiple myeloma

3rd Appraisal Committee meeting

Committee D

Lead team: David Bowen, Malcolm Oswald, Paula Ghaneh

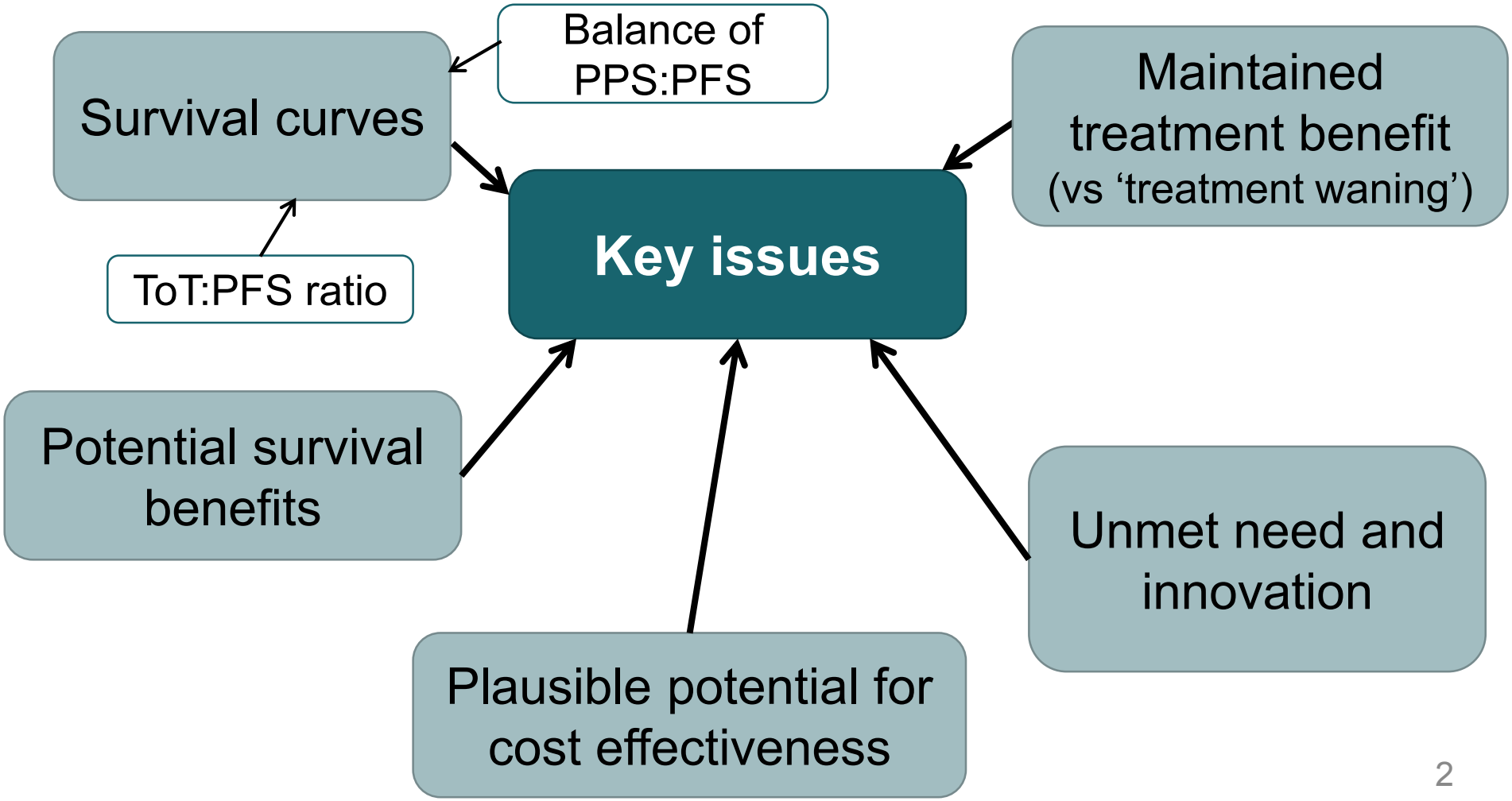
ERG: Warwick Evidence

NICE technical team: Sophie Cooper, Raisa Sidhu

Company: Takeda

26 October 2017

Company seeks recommendation for CDF and has proposed an improved commercial offer



ACD2: recommendations

Ixazomib, with lenalidomide and dexamethasone, is not recommended within its marketing authorisation for treating multiple myeloma in adults who have already had at least 1 therapy

- Survival benefit uncertain, median OS not reached in TMM1
- ICER after 2 or 3 therapies, with patient access scheme (PAS): £125,000–£274,000/QALY vs. len+dex
- End of life criteria not met – estimates not sufficiently robust
  - Modelled OS with len+dex = 3.9 years
  - Modelled benefit with ixa+len+dex uncertain because mostly in extrapolated phase and uncertainty in how to extrapolate:
    - Δ OS = 1.56 years
    - Δ QALY = 0.88–0.98 QALYs
- No benefits not captured in QALY

ACD2: CDF considerations

Ixazomib is not suitable for the Cancer Drugs Fund (CDF)

- Data collection has potential to reduce uncertainty re. OS
- No plausible potential to satisfy end of life criteria
  - extension to life of 1.56 years does not represent an exceptional proportional gain
- No plausible potential for cost-effectiveness under the proposed commercial offer

ACD2: treatment waning

- Proportional hazards proven for the 23-month median trial follow-up period only (relative benefit of ixazomib is constant for 23 months)
- Unlikely that relative benefit of ixazomib (when added to len+dex) would be maintained undiminished over a patient's lifetime
- Expert input: "relative benefit likely to be maintained for ≥1–2 relapses, diminishing over 2 years"
- Committee used experience appraising other immunomodulatory cancer drugs

CONCLUSION: relative survival benefit wanes to zero between 32 months (longest duration of trial follow up) and 5 years

ACD2: uncertainty about survival curves

Heard ERG's critique of options for extrapolating OS:

- AIC and BIC similar for exponential, Weibull and gompertz
- Weibull → implausible proportion of ixazomib's net OS gain occurs after progression (one third)
- Gompertz predicts higher mortality than Weibull

COMMITTEE CONCLUSION: mortality with gompertz is plausible but would be pessimistic to use gompertz AND apply treatment waning

Heard ERG's critique of options for extrapolating PFS:

- Gamma → more un-progressed patients alive than total number patients alive (PFS curve crosses OS curve)
- Weibull more plausible, but increases proportion of ixazomib's OS gain achieved post-progression, unless use Gompertz for OS

COMMITTEE CONCLUSION: accept company curves (Weibull OS, gamma PFS, exponential ToT) as long as treatment waning applied

ACD2: other key conclusions

Utilities

- Calculation of pre-progression utility values inappropriate: mixed contemporaneous response data and best overall response data
- ERG alternative base-case analysis could only partly correct this

COMMITTEE CONCLUSION: consider results from both the company's base case and the ERG's alternative base case

Treatment costs

- Model overestimates difference between ToT & PFS compared with trial
  - people treated for 62% (IXA) or 69% (LEN) of time spent in PFS, compared with 92% (IXA) and 97% (LEN) in trial
- Error in company's weekly costing of post-progression treatment
  - Partly corrected in ERG base case (little impact on ICER)

COMMITTEE CONCLUSION: true ICER for ixazomib is somewhere between the estimate based on ToT and the estimate based on PFS

ACD2 consultation responses

- Consultee comments from:
  - Takeda (including additional evidence)
  - Myeloma UK
  - UK Myeloma Forum (UKMF)

- Web comments from:
  - 30 NHS professionals
    - Mostly consultant haematologists
    - 1 professor of Haematology
    - 1 cancer pharmacist/myeloma clinic prescriber
  - 1 patient

Company comments: treatment waning

- Not applied in appraisal of lenalidomide or any other myeloma drug
- Not appropriate to use assumptions from other immunomodulators
  - Different drug mechanism of action and natural disease history
  - Assumption was applied differently in other TAs
    - Other TAs: waning explored only in scenarios where no-one on treatment (2-year stopping rule), and was not part of base case
    - Ixazomib ACM2: ~30% of IXA patients still on treatment at 32 months, implying that 30% of patients start losing benefit whilst on treatment
- Shouldn't be part of base case because not evidence based
- Explore in scenarios, with the following amendments:
  - benefit of treatment should wane at same rate in both arms
  - starting from 42.5 months (IXA) or 35.5 months (len+dex) to reflect expert opinion that relative benefit maintained for ≥1–2 relapses
    - 42.5 and 35.5 = mean ToT from model + median PFS of subsequent treatments (panobinostat and pomalidomide)

Company comments: survival curves

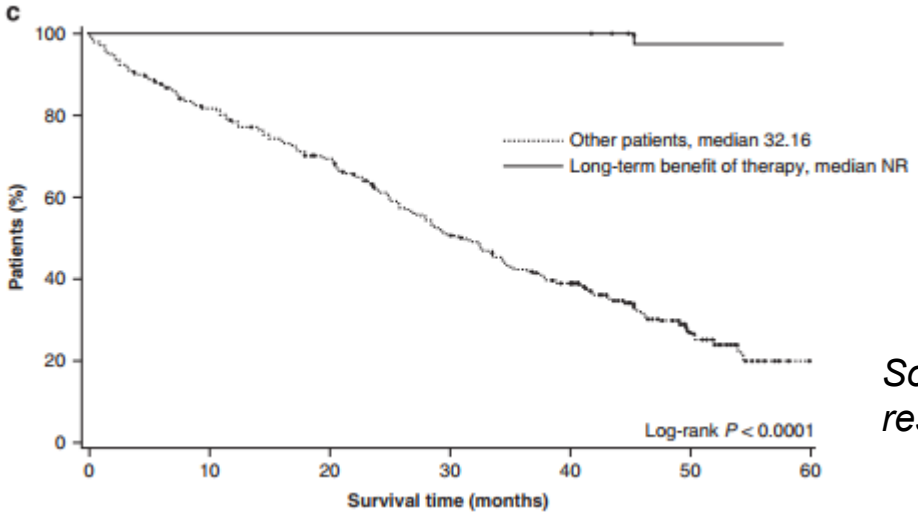
- Not appropriate to use gompertz for modelling overall survival (OS)
  - Worst AIC and BIC statistics
  - Too pessimistic
  - Not enough of a tail to reflect long term OS of a subgroup of patients

- Should use Weibull for OS, PFS and ToT
  - PFS doesn't cross OS curve
  - ToT:PFS ratio better reflects TMM1 when Weibull used for all curves
    - Model: 92% (IXA) and 100% (LEN)
    - TMM1: 97% (IXA) and 92% (LEN)
  - Advisory board of 6 clinical experts support Weibull for OS

Gompertz OS model is too pessimistic: evidence from company and other C&C's

- Gompertz curve predicts 3% of len+dex patients alive at 8 years, with effectively no patients (0.3%) surviving beyond 10 years
- Cancer Research UK data shows 1 in 3 patients survive >10 years
  - ERG consider irrelevant because relates to survival from diagnosis
- Lenalidomide trials (MM-009 & MM-010) show 5-year survival of ~20%
- Long term follow of bortezomib trials show 8-year survival rates of 10%

Figure: Kaplan-Meier plot for OS from MM-009/10 trials of len+dex



Source: figure 1 company response to ACD

Company comments: CDF

- Overall survival is main driver of ICER; mature data will improve ICER
  - Final OS analysis due in 2019 and third interim analysis Q2 2018
  - OS endpoint may be reached at the third interim analysis
- Highly likely that a significant OS benefit will be observed, based on:
  - Interim analysis from TMM1: HR 0.645, 95% CI 0.409 to 1.017
  - Final analysis from China continuation study (not previously presented to committee for people with 2–3 previous therapies):
    - Median OS: 25.8 for ixazomib versus 11.2 months for len+dex
    - Hazard ratio 0.302 (95% CI 0.150 to 0.605, p=0.0004)

China continuation study (n=115): regional extension of TMM1, with identical study design including stratification according to prior therapies (1 vs. 2 or 3 prior lines)

Other consultee and web comments

OS curves	Gompertz not realistic
Treatment waning	• Apply to both arms • No evidence for waning at all • No evidence for appropriate time period for waning • Not appropriate to compare with other immune drugs
Potential for OS benefit	• Promising OS results, good PFS, supported by RW data • OS results from China continuation study should be used in model – represent UK practice
Unmet need and innovation	Benefits not adequately represented in ACD • Quality of life, very well tolerated, very convenient • Triple therapy = standard of care • Bone remodelling • Lenalidomide-associated cytopenias can allow for at least a myeloma drug to continue
Subgroup	More cost effective in subgroups with high risk cytogenetics? *NB cost effectiveness evidence not provided for this group*

New evidence from company

Company new evidence

Updated economic model:

- used Weibull to extrapolate PFS, ToT and OS
- ToT extrapolation for costings (because new curves rectify ToT:PFS ratio)
- treatment waning NOT included
- updated utilities to avoid mixing BoR and contemporaneous data, using IA2: applied ORR distribution to ORR regression data
  - reflects ERG's suggested approach for ACM2
- updated post-progression treatment costs (reflects ERG base case approach for ACM2):
  - same one-off cost for active post-progression treatment in each arm (£78,607), plus arm-specific weekly off-treatment costs

Key scenario analyses explored:

- treatment waning, but applied to BOTH treatment arms
- reduced dose cap on lenalidomide (from 26 to 22 cycles)
- improved HR for overall survival (from 0.69 to 0.67)

Updated company results (with PAS)

Deterministic base case (people who have had 2–3 therapies)

Treatment	Total costs	Total QALYs	Δ costs	Δ QALYs	ICER/QALY
LEN+DEX	£[redacted]	2.70			
IXA+LEN+DEX	£[redacted]	3.68	£121,062	0.97	£124,242

Scenario analyses

	Δ costs	Δ QALYs	ICER/QALY
Treatment waning in both arms, over 5 years			
32 month cut off in both arms	£117,913	0.80	£146,853
42.5 month cut off in both arms	£119,060	0.83	£144,031
42.5 month (IXA) / 35.5 (LEN) cut off	£118,990	0.85	£139,883
Reduced dose cap for LEN (22 cycles)	£119,088	0.97	£122,217
Reduced dose cap for LEN (20 cycles)	£118,113	0.97	£121,216

ERG critique

ERG critique: survival curves (company used Weibull for OS, PFS & ToT)

Trials of len+dex (MM-009/010) and pomalidomide (MM-003 and STRATUS MM-010) provide useful data in comparable population

5- and 10-year survival rates

- MM-009/010 suggest 5- and 10-year survival of 30–35% and 5–10%
- Support using Weibull for OS: 5- & 10-year survival 30% and 5%
- Gompertz OS too pessimistic: 5- & 10-year survival 24% and 0.3%

Ratio of post-progression survival to pre-progression survival (PPS:PFS)

- 52–58% of net survival gain is in PPS in len+dex and pomalidomide trials
- Support using Weibull for all 3 outcomes: 47% in PPS (61% len+dex, 57% ixa)
- Gamma for PFS less plausible: 32% in PPS (42% len+dex, 39% ixa)

Absolute post-progression survival (PPS) gain

- PPS gain is 1.61 years in pomalidomide trials
- Supports gamma PFS (1.63 years PPS); Weibull less plausible (2.37 years PPS)

ERG prefer Weibull for OS but no clear preference for PFS (Weibull or gamma)
NB Weibull for PFS gives a more plausible ToT:PFS ratio than gamma

ERG critique: treatment waning

- Company's application of treatment waning did not reflect committee's preferred assumption in ACM2
  - company approach meant that the relative benefit of adding ixazomib to len+dex was maintained over the patient's lifetime
  - from the cut off point of 32, 35.5 or 45.5 months:
    - ixa+len+dex arm: a linear decline is applied to the 0.37 treatment effect causing it to fall to 0.00 after 5 years
    - len+dex arm: a linear decline is applied to the 0.00 treatment effect causing it to fall to -0.37 after 5 years
    - treatment effect for ixa+len+dex relative to len+dex is maintained at 0.37 throughout
- ERG explored an adaptation of the company implementation:
  - linear decline in treatment effect in both arms
  - faster waning for ixa+len+dex relative treatment effect such that it falls to the same value as len+dex treatment effect after 5 years (both to -0.37)

ERG critique: utilities and costs

Utilities

- Agree with company's revised base case approach
- Preferred company base case (ORR) over its scenario (BoR)
- Utility for progressed disease (0.751) higher than:
  - UK population norms for this age group (0.729–0.782)
  - previous appraisals in myeloma (0.610–0.640)

Costs

- Cost of active post-progression treatment does not differ by model arm
  - implies that post-progression treatment is unaffected by duration of PPS (which is 26 weeks longer for IXA)
  - ERG consider that increased PPS → increased # of treatment
- ERG explored this in a scenario analysis (also presented at ACM2), but acknowledge that the resulting ICER is pessimistic

ERG exploratory analyses (with PAS)

	Δ costs	Δ QALYs	ICER/QALY
Company base case: no waning	£121k	0.97	£124k
Company scenario: waning in both arms, from 32 months in both arms	£118k	0.80	£147k
Company scenario: waning in both arms, from 42.5 month (IXA) / 35.5 (LEN)	£119k	0.85	£140k
ERG scenario from ACM2: waning in IXA arm ('ERG SA01')			
from 32 months	£119k	0.68	£176k
from 42.5 months	£121k	0.75	£161k
ERG new scenario: mixed waning method ('ERG SA03')			
from 32 months in both arms	£117k	0.60	£194k
from 42.5 month (IXA) / 35.5 (LEN)	£119k	0.70	£170k
Equal PPS weekly costs ('ERG SA07') *(pessimistic)*	£136k	0.97	£139k
Results based on Weibulls for all curves (OS, PFS and ToT), costing based on ToT Source: table 13 ERG addendum post-ACD2 & table 13 ERG additional 5 year waning analyses			

Key issues for discussion

1. Suitable candidate for CDF?
   - Plausible potential to be cost effective? Depends on:
     - questions 2 & 3
     - discussion of commercial offer in part 2
   - Could data collection reduce uncertainty?
   - Will ongoing studies provide useful data?
   - Is CDF data collection feasible?

2. Survival curves
   - Accept company extrapolations of OS, PFS & ToT? (Weibull)

3. Maintained treatment benefit versus treatment waning
   - What evidence is there, for and against?
   - Prefer company or ERG approach?

Committee decision-making for CDF