An Alternate Day Dosing Strategy for Lenalidomide in Multiple Myeloma Improves Cost-Effectiveness Whilst Maintaining Efficacy

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Introduction

- Lenalidomide & dexamethasone is approved by NICE at second or subsequent relapse
- NICE appraisal process based on cost-effectiveness analysis
- This incorporated a patient access scheme whereby costs after 26 cycles are met by the manufacturer
- Whilst there is demonstrated efficacy at earlier stages of the disease unrestricted prescribing is currently limited by this guidance

Dimopoulos et al., Leukemia 2009
Stadtmauer et al.,Eur J haematol 2009
www.nice.org

Aims

- To investigate an alternate day dosing strategy initiated upon grade 3-4 haematological toxicity
- To assess efficacy of this schedule
- To calculate the treatment related costs
- To perform cost-effective analysis consistent with current NICE guidelines

Methods

- Retrospective single centre study
- All patients with normal renal function commenced treatment at lenalidomide 25mg daily (days 1-21 every 28 days)
- Upon grade 3-4 haematological toxicity, the alternate day schedule was followed instead of SPC schedule
- Response rates and TTP, PFS and OS determined by IMW response criteria & IMW consensus criteria

Durie et al., Leukemia 2006
Rajkumar et al., Blood 2011

Cost-effectiveness Analysis

- Actual drug costs calculated by capsules prescribed over treatment period
- Compared to predicted cost if SPC schedule followed
- Cost-effectiveness analysis as per ERG (NICE) preferred methods
- Comparator was high dose dexamethasone
- Mean TTP for lenalidomide modelled from actual Kaplan Meier plots using a Weibull model
- Mean TTP for dexamethasone was estimated as value was not available
- Utility values for both lenalidomide schedules was taken to be the same

Lenalidomide dose modification for Haematological Toxicity

If platelet count	Recommendation	If neutrophil count	Recommendation
Fall to <30,000/mcL	Interrupt lenalidomide treatment, follow CBC weekly	Fall to <1000/mcL	Interrupt lenalidomide treatment, add G-CSF, follow CBC weekly
Return to ≥30,000/mcL	Restart lenalidomide at dose level 1	Return to ≥1,000/mcL and neutropenia is the only toxicity	Resume lenalidomide at 25mg
For each subsequent drop <30,000/mcL	Interrupt lenalidomide treatment	Return to ≥1,000/mcL and if other toxicity	Resume lenalidomide at dose level 1
Return to ≥30,000/mcL	Resume lenalidomide at 5 mg less than the previous dose. Do not dose below 5 mg daily	For each subsequent drop <1000/mcl	Interrupt lenalidomide treatment until recovery. Resume at next lower dose level

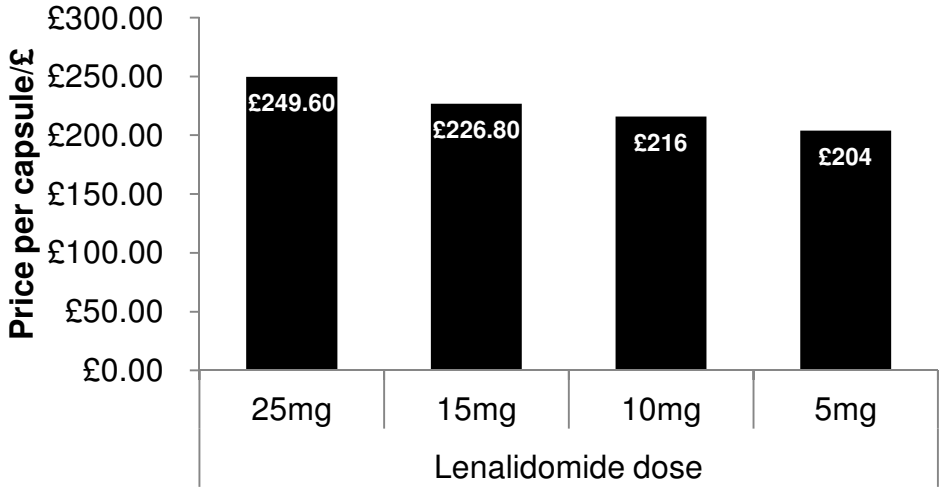
Summary of Product Characteristics (FDA Website)

Lenalidomide Dosing Schedule

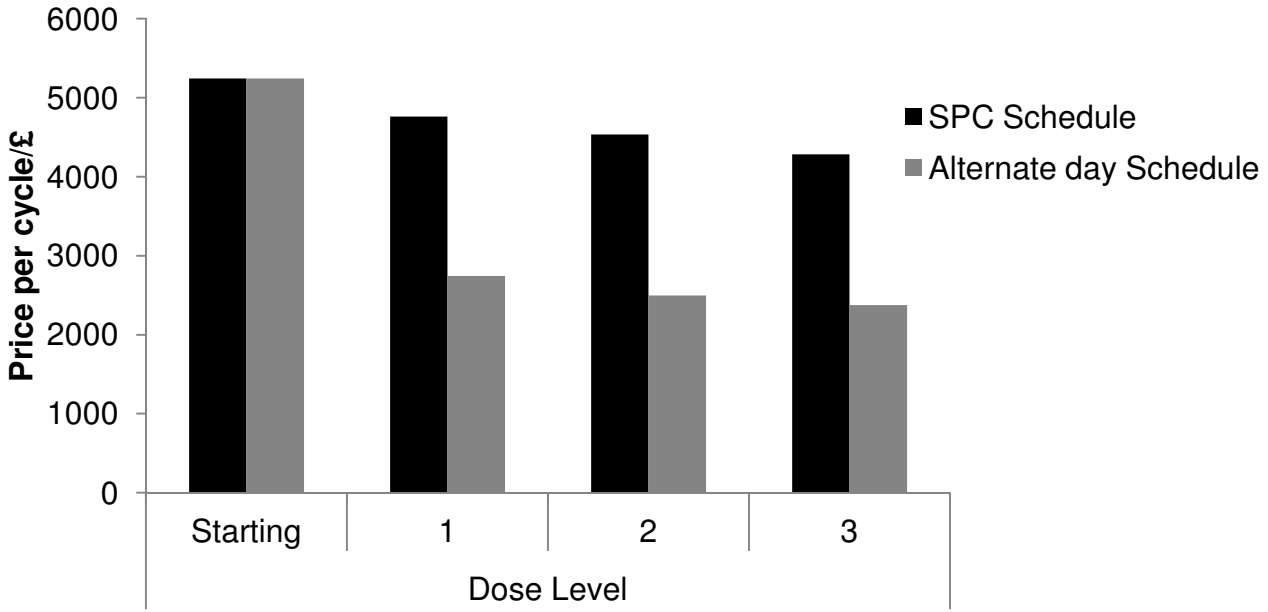
Dose Level	SPC Schedule	Number of capsules	Total Dose/ cycle	Alternate day schedule	Number of capsules	Total Dose/ cycle	% Difference SPC vs Alt day
Starting	25mg daily	21	525mg	25mg daily	21	525mg	0
1	15mg daily	21	315mg	25mg alt days	11	275mg	-13
2	10mg daily	21	210mg	15mg alt days	11	165mg	-21
3	5mg daily	21	105mg	10mg alt days	11	110mg	+1.05

All patients received lenalidomide for 3 weeks out of a 4 week cycle

Treatment Costs



Price from BNF + 20% VAT

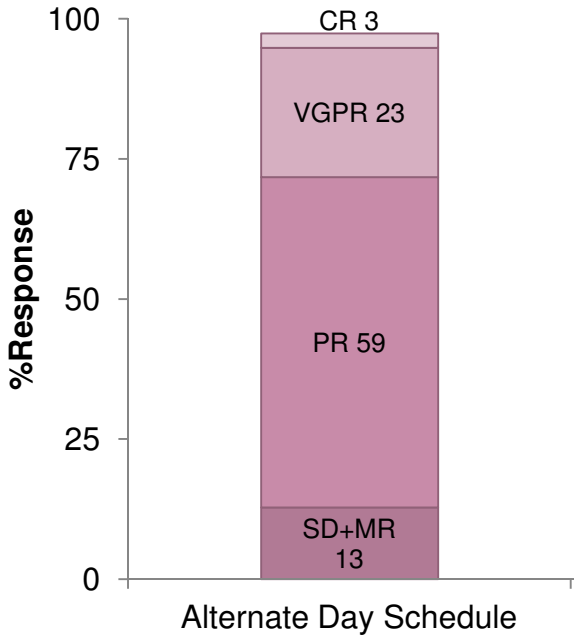


Demographics

	Alternate Dosing Schedule
Number of patients evaluable	39
Age, median (range)	68yrs (37-85)
1 Prior line of therapy, n (%)	3 (7.3%)
≥2 prior lines of therapy, n (%)	36 (87.8)
Median lines of therapy, n (range)	2 (1-8)
Median number of cycles, n (range)	6 (1-28)
Median duration of treatment/ months, n (range)	11.7 (1-31.1)
Patients requiring dose reductions, n (%)	24 (62%)

*Stadtmauer et al.,Eur J haematol 2009

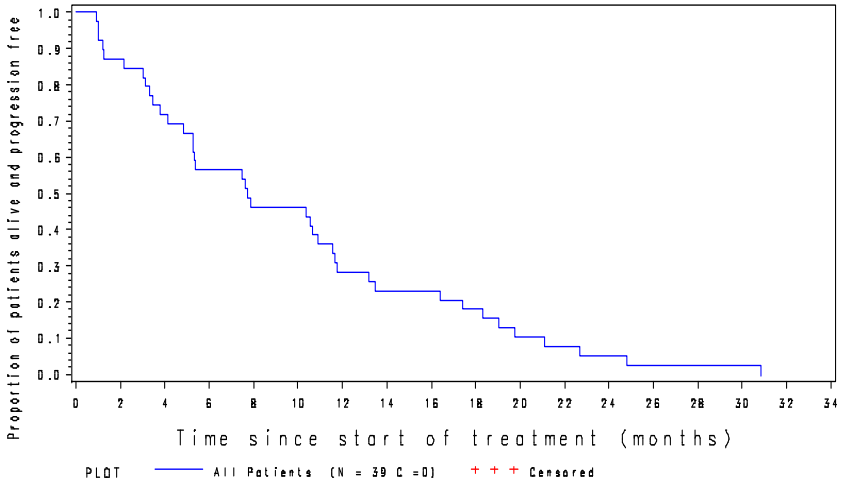
Efficacy



	Alternate Dosing Schedule
Response rate (≥PR)	85% (33)
Median duration of response/ months	7.1
Median follow-up/months	9.1

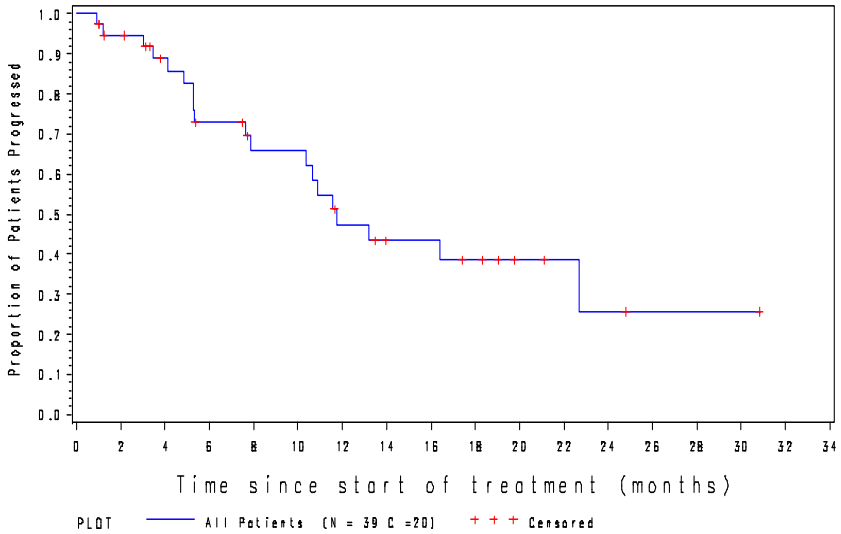
Efficacy

Progression Free Survival

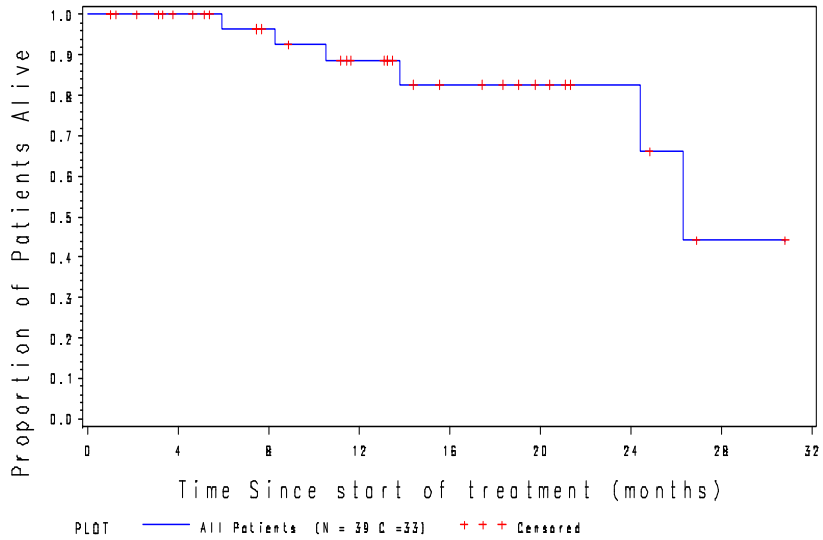


	Alternate Dosing Schedule
Median PFS/months	7.7 (4.9-11.6)
Median TTP/months	11.8 (7.9-NR)
Median OS/ months	26.3 (24.4-NR)

Time to Progression



Overall Survival

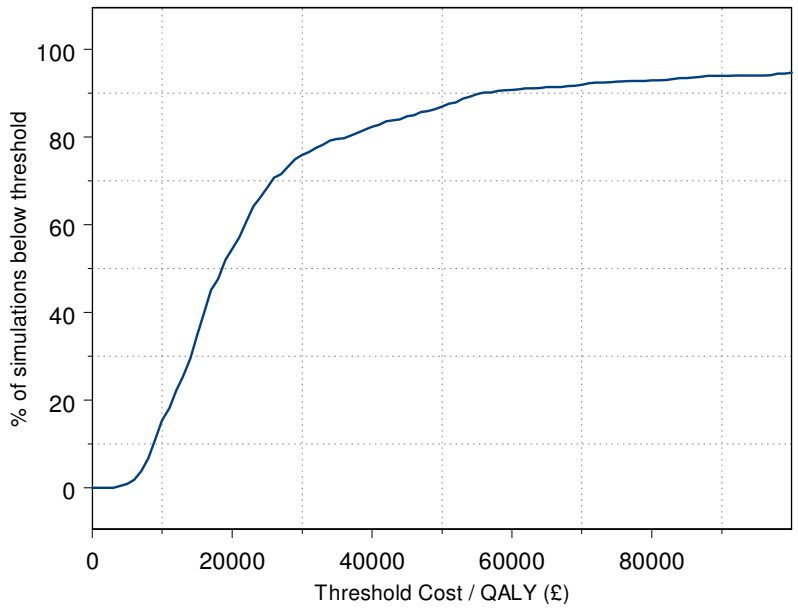


Cost-effectiveness

	SPC Schedule	Alternate day schedule	Cost Saving
All patients	£1,914,987.60	£1,450,665.60	**£464,322.00**
Per patient	£49,102.25	£37,196.55	**£11,905.69**

Incremental	SPC Schedule vs Dex	Alternate Day Schedule vs Dex
QALY	1.28	1.28
Costs	£51,705	£32,360
ICER (Cost/ QALY)	£40,394	£25,281

Cost-effectiveness Acceptability Analysis



	Mean	Range (Min - Max)
Base case ICER	£25281	
Incremental Cost (£)	£31110	£18698 - £42245
Incremental QALY	£1.29	0.026 - 7.6
ICER*	£24365	£3715 - > £100,000
Probability cost-effective at £30000 = 76%		Probability cost-effective at £40000 = 82%

One Way Sensitivity Analysis:

- Alter the following whilst all others fixed:
  - drug costs: +20%
  - mean TTP: -10% to +10%
  - utility values: -5%
- Impact on ICER:
  - range £23904 to £30047

* The ICER is very sensitive to incremental QALY. In some cases very small (as well as some very large) effects were possible which when divided by (incremental cost/ incremental QALY), yield very large ICERS. However, these cases were in < 2% of the simulations. Probability defined as the proportion of simulated ICERS < a given threshold divided by total number of simulations

Summary

- A limited retrospective study
- The alternate day dosing strategy of lenalidomide is likely to have equivalent efficacy to the standard schedule (MM009/010 trial patients at second relapse)
- Total saving of £464,322 equivalent to £11,905.69 per patient treated
- Cost effectiveness analysis estimated the Cost per QALY (ICER) to be £25281 compared to the original submission (as recalculated by ERG/ NICE) of >£47100
- This analysis did not include a price cap at 26 cycles or an increased QALY value for final years of life.

Conclusions

- The ICER for this schedule is below the upper threshold of £30,000 set by NICE for drugs to be approved within the UK.
- This schedule is likely to be cost-effective at earlier stages in disease
- Improved cost-effectiveness may lead to wider access to patients
- We recommend this schedule to be investigated prospectively

UK Myeloma Forum