# Appendix B

Summary: This document contains certainty of evidence assessment using the GRADE Approach.

Addition of daratumumab to multiple myeloma backbone regimens: A systematic review and meta-analysis of randomised controlled trials

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### Patient or population: newly diagnosed multiple myeloma

Relative effect

(95% CI)

OR 3.61

(2.33 to 5.61)

OR 2.29

(1.49 to 3.51)

OR 2.14

(1.66 to 2.75)

HR 0.47

(0.39 to 0.57)

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be

close to the estimate of the effect, but there is a possibility that it is substantially different

Anticipated absolute effects

Risk with backbone

therapy

226 per 1 000

157 per 1 000

266 per 1 000

394 per 1 000

Risk difference

with

daratumumab + backbone therapy

287 more per

1 000

(179 more to 395

more)

142 more per

1 000

(60 more to 238 more)

171 more per

1 000

(110 more to 233

more)

184 fewer per

1 000

(216 fewer to 146 fewer)

**Intervention:** daratumumab + backbone therapy

the evidence

(GRADE)

 $\Theta\ThetaOO$ 

LOW

 $\Theta\ThetaOO$ 

LOW

 $\Theta\ThetaOO$ 

LOW

 $\Theta \Phi \Phi \Theta$ 

**MODERATE** 

the comparison group and the relative effect of the intervention (and its 95% CI).

Comparis	son: k	oackbo	one tl	herapy

ii. Daeiibe	ine therapy

**Outcomes** 

minimal residual

disease negativity

(MRD negativity)

stringent complete

response (sCR)

complete response

or better (CR or

better)

death or disease

progression

Comparison: backbone therapy										
	№ of	Certainty of								

participants

(studies)

2735

(4 RCTs)

2735

(4 RCTs)

2735

(4 RCTs)

2528

(3 RCTs)

**GRADE** Working Group grades of evidence

different from the estimate of the effect

substantially different from the estimate of effect

CI: Confidence interval; OR: Odds ratio; HR: Hazard Ratio

Patient or population: newly diagnosed multiple myeloma Intervention: daratumumab + backbone therapy

 $\Theta\ThetaOO$ 

LOW

ФООО

**VERY LOW** 

 $\Theta \oplus \Theta \bigcirc$ 

**MODERATE** 

 $\Theta \Phi \Phi \Theta$ 

**MODERATE** 

 $\Theta\ThetaOO$ 

LOW

 $\Theta\ThetaOO$ 

LOW

ФООО

**VERY LOW** 

comparison group and the relative effect of the intervention (and its 95% CI).

Relative effect

(95% CI)

OR 1.20

(0.76 to 1.88)

OR 1.27

(0.77 to 2.09)

OR 1.49

(1.17 to 1.89)

OR 1.60

(1.21 to 2.11)

OR 1.63

(1.06 to 2.49)

OR 1.76

(1.20 to 2.59)

OR 1.39

(0.61 to 3.13)

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: The true

Comparison: backbone therapy

1998

(3 RCTs)

1998

(3 RCTs)

2021

(3 RCTs)

2021

(3 RCTs)

2735

(4 RCTs)

2735

(4 RCTs)

1650

(3 RCTs)

**GRADE** Working Group grades of evidence

CI: Confidence interval; OR: Odds ratio; HR: Hazard Ratio

effect is likely to be substantially different from the estimate of effect

№ of **Outcomes** participants evidence

all grade

thrombocytopenia

grade 3-4

thrombocytopenia

all grade

lymphopenia

grade 3-4

lymphopenia

all grade

neutropenia

grade 3-4

neutropenia

all grade anaemia

Certainty of the (studies) (GRADE)

> 55 more per (20 more to 95 56 more per (20 more to 98

Anticipated absolute effects

Risk with

backbone therapy

299 per 1 000

184 per 1 000

139 per 1 000

112 per 1 000

339 per 1 000

271 per 1 000

336 per 1 000

Risk difference

with

daratumumab +

backbone therapy

40 more per

1 000

(54 fewer to 146 more) 39 more per

1 000

(36 fewer to 136 more)

1 000

more)

1 000

more)

1 000

more)

1 000

more) 77 more per

1 000

(100 fewer to 277 more)

116 more per

(13 more to 222 124 more per

(37 more to 219

Patient or population: newly diagnosed multiple myeloma

evidence

(GRADE)

**Ф**ООО

**VERY LOW** 

 $\Theta \Phi \Phi \Theta$ 

**MODERATE** 

ФООО

**VERY LOW** 

ФООО

VERY LOW

comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; OR: Odds ratio; HR: Hazard Ratio

Relative effect

(95% CI)

OR 0.77

(0.49 to 1.23)

OR 0.76

(0.63 to 0.92)

OR 0.8

(0.4 to 1.6)

OR 0.88

(0.54 to 1.45)

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be

close to the estimate of the effect, but there is a possibility that it is substantially different

Anticipated absolute effects

Risk difference with

daratumumab +

backbone therapy

35 fewer per 1 000

(83 fewer to 33

more)

69 fewer per 1 000

(115 fewer to 21

fewer)

12 fewer per 1 000

(37 fewer to 35

more)

3 fewer per 1 000

(12 fewer to 12

more)

Risk with

backbone

therapy

180 per 1 000

535 per 1 000

64 per 1 000

27 per 1 000

**Intervention:** daratumumab + backbone therapy

Comparison: backbone therapy

_	_ ·

participants

(studies)

1650

(3 RCTs)

1998

(3 RCTs)

1998

(3 RCTs)

2528

(3 RCTs)

**GRADE** Working Group grades of evidence

different from the estimate of the effect

substantially different from the estimate of effect

Outcomes

grade 3-4

anaemia

all grade

peripheral

neuropathy

grade 3-4

peripheral

neuropathy

second

primary

cancer

	— ·
№ of	Certainty of the
312 01	Certainty of the

### Patient or population: newly diagnosed multiple myeloma

**Intervention:** daratumumab + backbone therapy

Comparison: backbone therapy

				Anticipated	absolute effects
Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Risk with backbone therapy	Risk difference with daratumumab + backbone therapy

All grade Not reported.

hypertension

Grade 3-4 Not reported. hypertension

Not reported.

Acute heart failure

**Ischemic** Not reported. heart disease Renal failure Not reported.

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the

comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; OR: Odds ratio; HR: Hazard Ratio **GRADE** Working Group grades of evidence High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

# Patient or population: <u>newly diagnosed multiple myeloma</u>

392/1365

(28.7%)

597/1365

(43.7%)

318/1261

(25.2%)

324/997

(32.5%)

198/997

(19.9%)

195/1011

(19.3%)

169/1011

(16.7%)

215/1370

(15.7%)

364/1370

(26.6%)

499/1267

(39.4%)

299/1001

(29.9%)

183/1001

(18.3%)

140/1010

(13.9%)

113/1010

(11.2%)

Certainty

 $\Theta\Theta \cap \cap$ 

 $\Theta\ThetaOO$ 

LOW

 $\Theta\ThetaOO$ 

LOW

 $\Theta\Theta\Theta\Theta$ 

MODERATE

 $\Theta\ThetaOO$ 

LOW

**Ф**ООО

VERY LOW

 $\Theta \Phi \Phi O$ 

MODERATE

 $\Theta \Phi \Phi O$ 

MODERATE

Absolute

(95% CI)

287 more

142 more

per 1 000

(from 60 more to 238 more)

171 more

per 1 000

(from 110 more to 233 more)

1 000 (from 216 fewer to 146 fewer)

40 more

per 1 000

(from 54 fewer to 146 more)

39 more

per 1 000

(from 36 fewer to 136 more)

per 1 000

(from 20 more to 95 more)

56 more

per 1 000

(from 20 more to 98 more)

.61) per 1 000 (from 179 more to 395 more)

OR 2.29

(1.49 to 3.51)

OR 2.14

(1.66 to 2.75)

HR 0.47

OR 1.20

(0.76 to 1.88)

OR 1.27

(0.77 to 2.09)

OR 1.49

(1.17 to 1.89)

OR 1.60

(1.21 to 2.11)

(0.39 to 0.57) fewer per

Importance

IMPORTANT

IMPORTANT

IMPORTANT

CRITICAL

**IMPORTANT** 

IMPORTANT

IMPORTANT

IMPORTANT

#### Intervention: daratumumab + backbone therapy

#### Comparison: backbone therapy

serious

not serious

serious

serious

not serious

not serious

serious

serious

serious

serious

stringent complete response

d trials

Complete response or better

d trials

Death or disease progression

randomise

All grade thrombocytopenia

d trials

Grade 3-4 thrombocytopenia

All grade lymphopenia

3 randomise no

Grade 3-4 lymphopenia

d trials

randomise not serious

d trials

randomise not serious

randomise not serious

not serious

d trials

not serious

randomise not serious

randomise not serious

	Comparison: backbone therapy											
Certainty assessment							№ of p	atients	Effec	et		
№ of studies	Study design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other considerations	daratumuma b + backbone therapy	backbone therapy	Relative (95% CI)	A (9		
minimal	l residual di	isease negati	vity									
4	randomise d trials	not serious	serious	serious	not serious	none	587/1365 (43.0%)	309/1370 (22.6%)	OR 3.61 (2.33 to 5.61)	28 pe		

not serious

not serious

not serious

not serious

serious

not serious

not serious

none

none

none

none

### Patient or population: newly diagnosed multiple myeloma

#### Intervention: daratumumab + backbone therapy

#### Comparison: backbone therapy

Grade 3-4 neutropenia

All grade anaemia randomis

Grade 3-4 anaemia

randomis

ed trials

All grade peripheral neuropathy

Grade 3-4 peripheral neuropathy randomis

ed trials

Second primary cancer randomis

ed trials

randomis

ed trials

randomis

ed trials

ed trials

not serious

not serious

not serious

not serious

not serious

serious

serious

serious

not serious

serious

serious

serious

serious

serious

serious

serious

not serious

serious

serious

not serious

serious

none

Certainty assessment

№ of studies	Study design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Other considerations	daratumuma b + backbone therapy	backbone therapy	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
All grad	e neutroper	nia										
4	randomis ed trials	not serious	serious	serious	not serious	none	595/1365 (43.6%)	465/1370 (33.9%)	OR 1.63 (1.06 to 2.49)	116 more per 1 000 (from 13 more to 222 more)	ФФО LOW	IMPORTANT

none

none

510/1365

(37.4%)

351/822

(42.7%)

112/822

(13.6%)

473/997

(47.4%)

57/997

(5.7%)

30/1261

(2.4%)

All grade hypertension, grade 3-4 hypertension, acute heart failure, ischemic heart failure, and renal failure were not reported.

368/1370

(26.9%)

278/828

(33.6%)

148/828

(17.9%)

536/1001

(53.5%)

64/1001

(6.4%)

34/1267

(2.7%)

OR 1.76

(1.20 to

2.59)

OR 1.39

(0.61 to

3.13)

OR 0.77

(0.49 to

1.23)

OR 0.76

(0.63 to

0.92)

OR 0.8

(0.4 to 1.6)

OR 0.88

(0.54 to

1.45)

124 more

per 1 000

(from 37 more to 219 more)

per 1 000

(from 100 fewer to 277 more)

35 fewer

per 1 000

(from 83 fewer to 33 more)

69 fewer

per 1 000

(from 115 fewer to 21 fewer)

12 fewer

per 1 000

(from 37 fewer to 35 more)

3 fewer

per 1 000

(from 12 fewer to 12 more)

 $\Theta\ThetaOO$ 

LOW

 $\oplus$ 

VERY LOW

**Ф**ООО

VERY LOW

 $\Theta\Theta\Theta$ 

MODERATE

 $\Theta$ OOO

VERY LOW

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VERY LOW

IMPORTANT

IMPORTANT

IMPORTANT

IMPORTANT

IMPORTANT

IMPORTANT

№ of patients

**Effect** 

Patient or population: newly diagnosed multiple myeloma with standard cytogenetic risk

**Intervention:** daratumumab + backbone therapy

Comparison: backbone therapy

1982

(3 RCTs)

165

(1 RCT)

677

(2 RCTs)

518

(1 RCT)

death or disease

progression

minimal residual

disease negativity

(MRD negativity)

stringent

complete

response (sCR)

complete

response or

better (CR or

better)

				Anticipated abso	lute effects
Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Risk with backbone therapy	Risk difference with daratumuma b+

 $\Theta\ThetaOO$ 

LOW

 $\Theta\ThetaOO$ 

LOW

 $\Theta\ThetaOO$ 

LOW

 $\Theta\ThetaOO$ 

LOW

comparison group and the relative effect of the intervention (and its 95% CI).

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be

close to the estimate of the effect, but there is a possibility that it is substantially different

HR 0.43

(0.35 to 0.53)

OR 4.72

(2.37 to 9.40)

OR 2.51

(1.72 to 3.65)

OR 2.70

(1.86 to 3.91)

b +backbone therapy 153 fewer per 1 000

(178 fewer

to 124 fewer)

344 more

per 1 000

(174 more

to 503 more)

158 more

per 1 000

(83 more to

243 more)

226 more

per 1 000

(134 more

to 318

more)

291 per 1 000

205 per 1 000

151 per 1 000

257 per 1 000

CI: Confidence interval; HR: Hazard Ratio; OR: Odds ratio

substantially different from the estimate of effect

**GRADE** Working Group grades of evidence

different from the estimate of the effect

Patient or population: newly diagnosed multiple myeloma with standard cytogenetic risk

Comparison: backbone therapy										
				Anticipated abs						
Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Risk with backbone thera						

thrombocytopenia - not

reported Grade 3-4 thrombocytopenia - not

reported All grade lymphopenia -

not reported

Grade 3-4 lymphopenia -

not reported

All grade neutropenia -

not reported

Grade 3-4 neutropenia -

not reported

All grade anaemia - not

reported

Grade 3-4 anaemia - not

reported

All grade peripheral

neuropathy - not reported

Grade 3-4 peripheral

neuropathy - not reported

All grade hypertension -

not reported

Grade 3-4 hypertension -

not reported

Acute cardiac failure - not

reported

Ischaemic heart diease -

not reported

Renal failure - not

reported

intervention (and its 95% CI).

GRADE Working Group grades of evidence

possibility that it is substantially different

CI: Confidence interval; HR: Hazard Ratio; OR: Odds ratio

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

				Anticipated absolute effect	ite effects
Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Risk with backbone therapy	Risk difference with daratumumab + backbone therapy
All grade					

Not reported.

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

				Anticipated absolu	ite eff
Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Risk with backbone therapy	Ris with

ntervention: darat	umumab + backbon	e therapy	
Comparison: backb	one therapy		

# Patient or population: newly diagnosed multiple myeloma with standard cytogenetic risk

Other

consider

ations

none

none

none

none

All grade thrombocytopenia, grade 3-4 thrombocytopenia, all grade lymphopenia, grade 3-4 lymphopenia, all grade neutropenia, grade 3-4

neutropenia, all grade anaemia, grade 3-4 anaemia, all grade peripheral neuropathy, grade 3-4 peripheral neuropathy, all grade hypertension, grade 3-4 hypertension, acute cardiac failure, ischaemic heart failure, and renal failure were not reported.

umab +

backbon

e

therapy

992

45/82

(54.9%)

105/340

(30.9%)

126/261

(48.3%)

backbon

therapy

990

17/83

(20.5%)

51/337

(15.1%)

66/257

(25.7%)

Relative

(95%

CI)

HR 0.43

(0.35 to)

0.53)

OR 4.72

(2.37 to

9.40)

OR 2.51

(1.72 to

3.65)

OR 2.70

(1.86 to

3.91)

Absolute

(95%

CI)

153

fewer per

1 000

(from 178 fewer to 124 fewer)

344 more

per 1 000

(from 174 more to 503 more)

158 more

per 1 000

(from 83 more to 243 more)

226 more

per 1 000

(from 134 more to 318 more)

Importa

nce

**CRITIC** 

AL

**IMPORT** 

ANT

**IMPORT** 

ANT

**IMPORT** 

ANT

Certainty

 $\Theta\ThetaOO$ 

LOW

 $\Theta\ThetaOO$ 

LOW

 $\Theta\ThetaOO$ 

LOW

 $\Theta\ThetaOO$ 

LOW

Inter	venti	om: ua	aratu.		av + i	Dacku	one t	пегај	y		
Comparison: backbone therapy											
Certainty assessment № of patients Effect											
											1

Imprecis

ion

serious

serious

serious

serious

Com	Comparison: backbone therapy								
Certainty assessment						№ of p	atients		
							daratum		

Indirectn

ess

serious

not

serious

not

serious

not

serious

№ of

studies

3

Study

design

death or disease progression

randomis

ed trials

Minimal residual disease negativity

randomis

ed trials

Stringent complete response

randomis

ed trials

Complete response or better randomis

ed trials

2

Risk of

bias

not

serious

serious

serious

serious

Inconsist

ency

not

serious

not

serious

not

serious

not

nterv	ention	: dara	atumu	mab +	- back	kbone t	therapy

ntervention:	daratumuma	b + backbon	e therapy

Patient or population: newly diagnosed multiple myeloma with high cytogenetic risk

Relative effect

(95% CI)

HR 0.76

(0.53 to 1.10)

OR 2.19

(0.92 to 5.25)

Certainty of the

evidence

(GRADE)

 $\Theta\ThetaOO$ 

LOW

 $\Theta\ThetaOO$ 

LOW

comparison group and the relative effect of the intervention (and its 95% CI).

Anticipated absolute effects

Risk with

backbone therapy

331 per 1 000

244 per 1 000

Risk difference

with

daratumumab

+ backbone therapy

68 fewer per 1 000

(139 fewer to

170 more per

1 000

(15 fewer to

385 more)

**Intervention:** daratumumab + backbone therapy

Comparison: backbone therapy

**Outcomes** 

death or disease

progression

complete

response or

better (CR or

better)

№ of participants

(studies)

358

(3 RCTs)

98

(1 RCT)

18	(====,		(0.000.000.00)		26 more)
minimal residual disease negativity (MRD negativity)	30	⊕○○○ VERY LOW	OR 1.50 (0.32 to 6.99)	286 per 1 000	89 more per 1 000 (172 fewer to 451 more)
stringent complete response (sCR)	312 (2 RCTs)	⊕○○○ VERY LOW	OR 1.63 (0.91 to 2.92)	148 per 1 000	73 more per 1 000 (11 fewer to 188 more)

CI: Confidence interval; HR: Hazard Ratio; OR: Odds ratio

**GRADE** Working Group grades of evidence

substantially different from the estimate of effect

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the

Patient or population: newly diagnosed multiple myeloma with high cytogenetic risk Intervention: daratumumab + backbone therapy

**Comparison:** backbone therapy

not reported

Grade 3-4 lymphopenia -

not reported

All grade neutropenia -

not reported

Grade 3-4 neutropenia -

not reported

All grade anaemia - not

reported

Grade 3-4 anaemia - not

reported

All grade peripheral

neuropathy - not reported

Grade 3-4 peripheral

neuropathy - not reported

All grade hypertension -

not reported

Grade 3-4 hypertension -

not reported

Acute cardiac failure - not

reported

Ischaemic heart diease -

not reported

Renal failure - not

reported

intervention (and its 95% CI).

GRADE Working Group grades of evidence

possibility that it is substantially different

CI: Confidence interval; HR: Hazard Ratio; OR: Odds ratio

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Risk with backbone therapy	Risk difference with daratumumab + backbone therapy
All grade thrombocytopenia - not reported			Not reported.		
Grade 3-4					

thrombocytopenia - not reported All grade lymphopenia -

Not reported. Not reported.

Not reported.

Not reported.

Not reported.

Not reported.

Not reported.

Not reported.

Not reported.

Not reported.

Not reported.

Not reported.

Not reported.

Not reported.

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Anticipated absolute effects

Patient or population: newly diagnosed multiple myeloma with high

Intervention: daratumumab + backb	one therap	ру	
Comparison: backbone therapy			
Certainty assessment	№ of patients	Effect	

Inter	Intervention: daratumumab + backbone therapy										
Com	Comparison: backbone therapy										
	Certainty assessment № of patients Effect										
							daratum				Importa

Other

consider

ations

none

none

none

none

All grade thrombocytopenia, grade 3-4 thrombocytopenia, all grade lymphopenia, grade 3-4 lymphopenia, all grade neutropenia, grade 3-4 neutropenia, all grade anaemia, grade 3-4 anaemia, all grade peripheral neuropathy, grade 3-4 peripheral neuropathy, all grade hypertension, grade 3-4 hypertension, acute cardiac failure, ischaemic heart failure, and renal failure were not reported.

Imprecis

ion

serious

very

serious

very

serious

very

serious

Indirectn

ess

serious

not

serious

serious

not

serious

№ of

studies

Study

design

death or disease progression

randomis

ed trials

minimal residual disease negativity

randomis

ed trials

stringent complete response

randomis

ed trials

complete response or better

randomis

ed trials

2

Risk of

bias

not

serious

serious

not

serious

not

serious

Inconsist

ency

not

serious

not

serious

not

serious

not

serious

umab +

backbon

e

therapy

183

6/16

(37.5%)

30/136

(22.1%)

22/53

(41.5%)

backbon

therapy

175

4/14

(28.6%)

26/176

(14.8%)

11/45

(24.4%)

Relative

(95%

CI)

HR 0.76

(0.53 to)

1.10)

OR 1.50

(0.32 to

6.99)

OR 1.63

(0.91 to

2.92)

OR 2.19

(0.92 to

5.25)

Absolute

(95%

CI)

68 fewer

per 1 000

(from 139 fewer to 26 more)

89 more

per 1 000

(from 172 fewer to 451 more)

73 more

per 1 000

(from 11 fewer to 188 more)

170 more

per 1 000

(from 15 fewer to 385 more)

**Importa** 

nce

**CRITIC** 

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**IMPORT** 

ANT

**IMPORT** 

ANT

**IMPORT** 

ANT

Certainty

 $\Theta\ThetaOO$ 

LOW

**Φ**000

**VERY LOW** 

**Ф**ООО

**VERY LOW** 

 $\Theta\ThetaOO$ 

LOW

<u>cytogenetic risk</u>			
Intervention: daratumumab + backl	one therap	<b>y</b>	
Comparison: backbone therapy			
Certainty assessment	№ of patients	Effect	

Tations of populations are will aligned and to be any crossing with angu-
<u>cytogenetic risk</u>
Intervention: daratumumab + backbone therapy
Comparison: backbone therapy

### Patient or population: relapsed/refractory multiple myeloma

evidence

(GRADE)

 $\Theta \oplus \Theta \bigcirc$ 

**MODERATE** 

 $\Theta \Phi \Phi \Theta$ 

**MODERATE** 

 $\Theta \Phi \Phi \Theta$ 

MODERATE

 $\Theta\ThetaOO$ 

LOW

comparison group and the relative effect of the intervention (and its 95% CI).

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be

close to the estimate of the effect, but there is a possibility that it is substantially different

Relative effect

(95% CI)

OR 5.43

(2.76 to 10.66)

OR 3.08

(2.00 to 4.76)

OR 3.50

(2.33 to 5.25)

HR 0.50

(0.37 to 0.67)

Anticipated absolute effects

Risk with

backbone therapy

27 per 1 000

40 per 1 000

117 per 1 000

559 per 1 000

Risk difference

with

daratumuma

h +backbone therapy

104 more

per 1 000

(44 more to 201 more)

74 more per 1 000

(37 more to 126 more)

199 more

per 1 000

(119 more

to 293 more)

223 fewer per 1 000

(298 fewer

to 137 fewer)

Intervention: daratumumab + backbone therapy

Comparison	: backbone i	inerapy

**Outcomes** 

minimal residual

disease negativity

stringent

complete respone

complete

response or

better

death or disease

progression

# Certainty of the № of participants

(studies)

970

(3 RCTs)

1571

(4 RCTs)

1571

(4 RCTs)

2048

(5 RCTs)

CI: Confidence interval; OR: Odds ratio; HR: Hazard Ratio

**GRADE Working Group grades of evidence** 

different from the estimate of the effect

substantially different from the estimate of effect

# Patient or population: relapsed/refractory multiple myeloma

(GRADE)

 $\Theta\ThetaOO$ 

LOW

 $\Theta \Phi \Phi \Theta$ 

**MODERATE** 

ФООО

**VERY LOW** 

 $\Theta\ThetaOO$ 

LOW

 $\Theta \oplus \Theta \bigcirc$ 

**MODERATE** 

 $\Theta\ThetaOO$ 

LOW

comparison group and the relative effect of the intervention (and its 95% CI).

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the

**Intervention:** daratumumab + backbone therapy

Comparison: backbone therapy

Outcomes	№ of participants (studies)	Certainty of the evidence

1743

(4 RCTs)

**GRADE** Working Group grades of evidence

CI: Confidence interval; OR: Odds ratio; HR: Hazard Ratio

effect is likely to be substantially different from the estimate of effect

all grade

thrombocytopeni

grade 3-4

thrombocytopeni

a

all grade

lymphopenia

grade 3-4

lymphopenia

all grade

neutropenia

grade 3-4

neutropenia

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: The true

Anticipated absolute effects

Risk with

backbone therapy

366 per 1 000

220 per 1 000

94 per 1 000

62 per 1 000

232 per 1 000

168 per 1 000

Relative effect

(95% CI)

OR 1.58

(1.03 to 2.43)

OR 1.47

(1.10 to 1.98)

OR 1.54

(0.89 to 2.66)

OR 1.75

(1.02 to 2.99)

OR 1.98

(1.56 to 2.52)

OR 1.84

(0.98 to 3.46)

Risk difference

with

daratumuma

b +backbone therapy 111 more

per 1 000

(7 more to 218 more)

73 more per

1 000

(17 more to

138 more)

44 more per

1 000

(9 fewer to 122 more) 42 more per

1 000

(1 more to 103 more) 142 more

per 1 000

(88 more to 200 more)

102 more

per 1 000

(3 fewer to 244 more)

# **Intervention: daratumumab + backbone therapy**

Patient or population: relapsed/refractory multiple myeloma

Anticipated absolute effects

Risk with

backbone therapy

362 per 1 000

170 per 1 000

113 per 1 000

51 per 1 000

262 per 1 000

41 per 1 000

Risk difference

with

daratumuma

b +backbone therapy 26 fewer per

1 000

(72 fewer to 22 more)

13 fewer per

1 000

(57 fewer to 45 more) 106 more

per 1 000

(8 fewer to 289 more) 96 more per

1 000

(1 fewer to 312 more)

44 more per

1 000

(14 fewer to 107 more)

21 fewer per

1 000

(32 fewer to 2 more)

Comparison: backbone therapy

Outcomes	№ of participants (studies)	Certainty evider (GRA)

1743

(4 RCTs)

1743

(4 RCTs)

1174

(3 RCTs)

1174

(3 RCTs)

941

(2 RCTs)

941

(2 RCTs)

effect is likely to be substantially different from the estimate of effect

all grade anaemia

grade 3-4

anaemia

all grade

hypertension

grade 3-4

hypertension

all grade

neuropathy

grade 3-4

neuropathy

OR: Odds ratio; HR: Hazard Ratio

**GRADE** Working Group grades of evidence

### y of the ence DE)

 $\Theta \Phi \Phi \Theta$ 

**MODERATE** 

ФООО

**VERY LOW** 

 $\Theta\ThetaOO$ 

LOW

 $\Theta\ThetaOO$ 

LOW

 $\Theta\ThetaOO$ 

LOW

 $\Theta\ThetaOO$ 

LOW

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval;

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: The true

Relative effect

(95% CI)

OR 0.89

(0.72 to 1.10)

OR 0.91

(0.62 to 1.34)

OR 2.21

(0.92 to 5.29)

OR 3.21

(0.97 to 10.61)

OR 1.24

(0.93 to 1.65)

OR 0.48

(0.22 to 1.04)

#### Patient or population: relapsed/refractory multiple myeloma

evidence

(GRADE)

 $\Theta\ThetaOO$ 

LOW

 $\Theta\ThetaOO$ 

LOW

 $\Theta\ThetaOO$ 

LOW

 $\Theta\ThetaOO$ 

LOW

comparison group and the relative effect of the intervention (and its 95% CI).

The true effect is likely to be substantially different from the estimate of effect

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be

certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate:

close to the estimate of the effect, but there is a possibility that it is substantially different. Low

Relative effect

(95% CI)

OR 1.26

(0.57 to 2.80)

OR 0.69

(0.35 to 1.35)

OR 1.30

(0.46 to 3.73)

OR 0.73

(0.34 to 1.56)

with

daratumuma

h +backbone therapy

5 more per

1 000

(9 fewer to 36 more)

30 fewer

per 1 000

(65 fewer to

32 more)

9 more per

1 000

(17 fewer to 79 more)

20 fewer

per 1 000

(50 fewer to

39 more)

Risk with

backbone therapy

21 per 1 000

105 per 1 000

33 per 1 000

78 per 1 000

**Intervention:** daratumumab + backbone therapy

№ of participants

(studies)

461

(1 RCT)

461

(1 RCT)

461

(1 RCT)

CI: Confidence interval; OR: Odds ratio; HR: Hazard Ratio

**GRADE** Working Group grades of evidence

Comparison	: backbone (	therapy		
			Anticipated abso	lute effects
	<b>3</b> 5 6 (: : : )	Certainty of the		Risk difference

second primary cancer	1048 (2 RCTs)	

Outcomes

acute cardiac

failure

ischaemic heart

disease

renal failure

# Patient or population: relapsed/refractory multiple myeloma **Intervention:** daratumumab + backbone therapy Comparison: backbone therapy

Imprecisi

on

not

serious

not

serious

serious

not

serious

not

serious

not

serious

Effect

Absolute

(95% CI)

104 more

per 1 000

(from 44 more to 201 more)

74 more

per 1 000

(from 37 more to 126 more)

199 more

per 1 000

(from 119 more to 293 more)

223 fewer

per 1 000

(from 298 fewer to 137 fewer)

111 more

per 1 000

(from 7 more to 218 more)

74 more

per 1 000

(from 17 more to 140 more)

Relative

(95% CI)

OR 5.43

(2.76 to)

10.66)

OR 3.08

(2.00 to)

4.76)

OR 3.50

(2.33 to)5.25)

HR 0.50

(0.37 to)

0.67)

OR 1.58

(1.03 to

2.43)

OR 1.47

(1.10 to

1.98)

daratumu

mab +

backbone

therapy

87/600

(14.5%)

98/825

(11.9%)

249/825

(30.2%)

476/1141

(41.7%)

461/989

(46.6%)

293/989

(29.6%)

backbone

therapy

10/370

(2.7%)

30/746

(4.0%)

87/746

(11.7%)

507/907

(55.9%)

276/752

(36.7%)

166/754

(22.0%)

Other

considerat

ions

none

none

none

none

none

none

**Importan** 

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Certainty

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**MODERATE** 

 $\Theta \Phi \Phi \Theta$ 

**MODERATE** 

 $\Theta \Phi \Phi \Theta$ 

**MODERATE** 

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LOW

**0000** 

LOW

 $\Theta \Phi \Phi \Theta$ 

**MODERATE** 

# № of patients

Indirectne

SS

serious

serious

serious

serious

serious

serious

	Cert	ainty assessi	ment		
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Inconsiste

ncy

serious

not

serious

not

serious

serious

serious

not

serious

№ of

studies

Study

design

minimal residual disease negativity randomise

d trials

stringent complete respone

complete response or better

death or disease progression

all grade thrombocytopenia

grade 3-4 thrombocytopenia

randomise

d trials

Risk of

bias

serious

not

serious

serious

not

serious

not

serious

not

# Patient or population: relapsed/refractory multiple myeloma **Intervention:** daratumumab + backbone therapy

Imprecisi

serious

not

serious

not

serious

not

serious

not

serious

serious

Effect

Absolute

(95% CI)

44 more

per 1 000

(from 10 fewer to 123 more)

43 more per 1 000

(from 1 more to 105 more)

142 more

per 1 000

(from 88 more to 200 more)

104 more

per 1 000

(from 3 fewer to 246 more)

26 fewer

per 1 000

(from 72 fewer to 22 more)

13 fewer

per 1 000

(from 58 fewer to 46 more)

Relative

(95% CI)

OR 1.54

(0.89 to

2.66)

OR 1.75

(1.02 to

2.99)

OR 1.98

(1.56 to

2.52)

OR 1.84

(0.98 to)

3.46)

OR 0.89

(0.72 to

1.10)

OR 0.91

(0.62 to

1.34)

daratumu

mab +

backbone

therapy

156/989

(15.8%)

120/989

(12.1%)

322/989

(32.6%)

227/989

(23.0%)

361/989

(36.5%)

156/989

(15.8%)

backbone

therapy

71/754

(9.4%)

47/754

(6.2%)

175/754

(23.3%)

127/754

(16.8%)

273/754

(36.3%)

128/754

(17.0%)

Other

considerat

ions

none

none

none

none

none

none

**Importan** 

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ANT

Certainty

 $\Theta \cap \cap \cap \Theta$ 

VERY LOW

 $\Theta\ThetaOO$ 

LOW

 $\bigcirc$ 

MODERATE

 $\Theta\ThetaOO$ 

LOW

 $\Theta \Phi \Phi \Theta$ 

MODERATE

**@**000

**VERY LOW** 

# Comparison: backbone therapy

Comparison. backbone therapy		
Certainty assessment	№ of patients	

Indirectne

serious

serious

serious

serious

serious

serious

№ of

studies

Study

design

randomise

d trials

all grade lymphopenia

grade 3-4 lymphopenia

all grade neutropenia

grade 3-4 neutropenia

all grade anaemia

grade 3-4 anaemia

Risk of

bias

not

serious

not

serious

not

serious

not

serious

not

serious

not

serious

Inconsiste

ncy

serious

serious

not

serious

serious

not

serious

# Patient or population: relapsed/refractory multiple myeloma Intervention: daratumumab + backbone therapy

Imprecisi

on

serious

not

serious

serious

serious

daratumu

mab +

backbone

therapy

142/703

(20.2%)

87/703

(12.4%)

168/551

(30.5%)

11/551

(2.0%)

backbone

therapy

53/471

(11.3%)

24/471

(5.1%)

102/390

(26.2%)

16/390

(4.1%)

Other

considerat

ions

none

none

none

none

Effect

Absolute

(95% CI)

109 more

per 1 000

(from 8 fewer to 293 more)

98 more

per 1 000

(from 1 fewer to 317 more)

44 more per 1 000

(from 14 fewer to 107 more)

21 fewer

per 1 000

(from 32 fewer to 2 more)

Relative

(95% CI)

OR 2.21

(0.92 to

5.29)

OR 3.21

(0.97 to

10.61)

OR 1.24

(0.93 to

1.65)

OR 0.48

(0.22 to

1.04)

**Importan** 

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**IMPORT** 

ANT

Certainty

 $\Theta\ThetaOO$ 

LOW

 $\Theta\ThetaOO$ 

LOW

 $\Theta\ThetaOO$ 

LOW

**ӨӨОО** 

LOW

Comparison: backbone therapy	

Comparison: backbone therapy		
Certainty assessment	№ of patients	

mparison: ba	ekbone therapy	
--------------	----------------	--

Indirectne

serious

serious

serious

serious

№ of

studies

Study

design

randomise

d trials

all grade hypertension

grade 3-4 hypertension

all grade neuropathy

grade 3-4 neuropathy

randomise

d trials

randomise

d trials

randomise

d trials

Risk of

bias

not

serious

not

serious

not

serious

serious

Inconsiste

ncy

serious

serious

not

serious

# Patient or population: relapsed/refractory multiple myeloma Intervention: daratumumab + backbone therapy

Comparison:	backbone therapy	

Campaniaan, baalabana thanany	
Comparison: backbone therapy	

Comparison:	backbone therapy	
	_ ·	

№ of patients

backbone

therapy

11/520

(2.1%)

16/153

(10.5%)

5/153

(3.3%)

12/153

(7.8%)

daratumu

mab +

backbone

therapy

14/528

(2.7%)

23/308

(7.5%)

13/308

(4.2%)

18/308

(5.8%)

Other

considerat

ions

none

none

none

none

Effect

Absolute

(95% CI)

5 more per

1 000

(from 9 fewer to 36 more)

30 fewer

per 1 000

(from 65 fewer to 32 more)

9 more per

1 000

(from 17 fewer to 79 more)

20 fewer

per 1 000

(from 50 fewer to 39 more)

Relative

(95% CI)

OR 1.26

(0.57 to

2.80)

OR 0.69

(0.35 to

1.35)

OR 1.30

(0.46 to

3.73)

OR 0.73

(0.34 to)

1.56)

**Importan** 

ce

**IMPORT** 

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IMPORT

ANT

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**IMPORT** 

ANT

Certainty

**ӨӨОО** 

LOW

 $\Theta\ThetaOO$ 

LOW

**ӨӨОО** 

LOW

 $\Theta\ThetaOO$ 

LOW

Comparison: back	bone therapy		
			_

Indirectne

serious

not

serious

not

serious

not

serious

Imprecisi

on

serious

very

serious

very

serious

very

serious

Certainty assessment

Inconsiste

ncy

serious

not

serious

not

serious

not

serious

Risk of

bias

serious

not

serious

not

serious

not

serious

№ of

studies

Study

design

randomise

d trials

randomise

d trials

second primary cancer

Acute cardiac failure

Ischaemic heart disease

Renal failure

randomise

d trials

randomise

d trials

Comparison: backbone therapy	
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om	pariso	on: bacl	kbone	therap	V		
					J		

Patient or population: relapsed/refractory multiple myeloma with standard cytogenetic risk

(GRADE)

ФООО

**VERY LOW** 

 $\Theta$ 

VERY LOW

ФООО

VERY LOW

 $\Theta\ThetaOO$ 

LOW

close to the estimate of the effect, but there is a possibility that it is substantially different

comparison group and the relative effect of the intervention (and its 95% CI).

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be

Relative effect

(95% CI)

OR 29.88

(4.04 to 220.78)

OR 3.12

(1.93 to 5.04)

OR 3.78

(2.63 to 5.43)

HR 0.38

(0.29 to 0.50)

Anticipated absolute effects

Risk with

backbone therapy

3 per 1 000

85 per 1 000

183 per 1 000

722 per 1 000

Risk difference

with

daratumuma

b +backbone therapy

86 more per

1 000

(10 more to

417 more)

140 more

per 1 000

(67 more to

234 more)

275 more

per 1 000

(188 more

to 366

more)

337 fewer per 1 000

(412 fewer

to 249 fewer)

Intervention: daratumumab + backbone therapy

Comparison: backbone therapy							

Outcomes	№ of participants	Certainty of the evidence

minimal residual

disease negativity

(MRD negativity)

stringent

complete

response (sCR)

complete

response or

better (CR or

better)

death or disease

progression

(studies)

631

(2 RCTs)

631

(2 RCTs)

631

(2 RCTs)

1076

(5 RCTs)

CI: Confidence interval; OR: Odds ratio; HR: Hazard Ratio

**GRADE** Working Group grades of evidence

different from the estimate of the effect

substantially different from the estimate of effect

standard cytogenetic risk **Intervention:** daratumumab + backbone therapy

Patient or population: relapsed/refractory multiple myeloma with

Comparison: backbone therapy

Outcomes	№ of participants (studies)	Certainty evider (GRAI
----------	-----------------------------	------------------------------

all grade

thrombocytopeni

grade 3-4

thrombocytopeni

a

all grade

lymphopenia

grade 3-4

neutropenia

# of the

nce DE)

641

(2 RCTs)

(2 RCTs)

641

(2 RCTs)

**GRADE Working Group grades of evidence** 

CI: Confidence interval; OR: Odds ratio; HR: Hazard Ratio

effect is likely to be substantially different from the estimate of effect

641  $\Theta\ThetaOO$ (2 RCTs) LOW  $\Theta\ThetaOO$ 641

 $\Theta\ThetaOO$ 

LOW

LOW

OR 1.32 (0.92 to 1.90)OR 1.06 (0.61 to 1.88)

OR 1.91

(1.36 to 2.69)

Relative effect

(95% CI)

OR 1.48

(1.07 to 2.04)

 $\Theta\ThetaOO$ grade 3-4 641 OR 2.16 lymphopenia (2 RCTs) LOW (1.01 to 4.65)all grade 641  $\Theta\ThetaOO$ OR 1.77 neutropenia (2 RCTs) LOW (1.28 to 2.45)

32 per 1 000

240 per 1 000

Anticipated absolute effects

Risk with

backbone therapy

333 per 1 000

221 per 1 000

80 per 1 000

Risk difference

with

daratumuma

b +backbone therapy 92 more per

1 000

(15 more to 172 more) 51 more per

1 000

(14 fewer to

129 more) 4 more per

1 000

(30 fewer to

61 more) 35 more per

1 000

(0 fewer to 101 more) 133 more

per 1 000

(55 more to 214 more) 136 more

per 1 000

(61 more to 219 more)

308 per 1 000

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the

 $\Theta\ThetaOO$ 

LOW

comparison group and the relative effect of the intervention (and its 95% CI).

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: The true

standard cytogenetic risk **Intervention:** daratumumab + backbone therapy

Patient or population: relapsed/refractory multiple myeloma with

(GRADE)

 $\Theta\ThetaOO$ 

LOW

 $\Theta\ThetaOO$ 

**LOW** 

 $\Theta\ThetaOO$ 

**LOW** 

 $\Theta\ThetaOO$ 

LOW

 $\Theta\ThetaOO$ 

LOW

 $\Theta\ThetaOO$ 

LOW

comparison group and the relative effect of the intervention (and its 95% CI).

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: The true

Relative effect

(95% CI)

OR 1.11

(0.80 to 1.53)

OR 0.96

(0.64 to 1.44)

OR 1.72

(1.06 to 2.80)

OR 0.48

(0.14 to 1.64)

OR 3.22

(1.14 to 9.13)

OR 4.58

(1.30 to 16.09)

Comparison: backbone therapy

Outcomes	№ of participants (studies)	Certainty evide

641

(2 RCTs)

641

(2 RCTs)

270

(1 RCT)

273

(1 RCT)

641

(2 RCTs)

641

(2 RCTs)

**GRADE** Working Group grades of evidence

CI: Confidence interval; OR: Odds ratio; HR: Hazard Ratio

effect is likely to be substantially different from the estimate of effect

all grade anaemia

grade 3-4

anaemia

all grade

peripheral

neuropathy

grade 3-4

peripheral

neuropathy

all grade

hypertension

grade 3-4

hypertension

v of the ence

> 6 fewer per 1 000 (56 fewer to 59 more) 132 more per 1 000 (14 more to 252 more) 30 fewer per 1 000

Anticipated absolute effects

Risk with

backbone therapy

330 per 1 000

176 per 1 000

368 per 1 000

59 per 1 000

42 per 1 000

10 per 1 000

Risk difference

with

daratumuma

b +backbone therapy 23 more per

1 000

(47 fewer to

100 more)

(50 fewer to 34 more)

81 more per 1 000 (6 more to 242 more)

33 more per

1 000

(3 more to 125 more) Patient or population: relapsed/refractory multiple myeloma with standard cytogenetic risk

Intervention: daratumumab + backbone therapy

Comparison: backbone therapy

				Anticipated abso	olute effects
Outcomes	№ of participants (studies)	Certainty of the evidence	Relative effect (95% CI)	Risk with	Risk difference with

(GRADE)

# (95% CI)

Not reported.

Not reported.

Not reported.

Not reported.

# backbone therapy

Risk fference with daratumuma b +backbone therapy

failure - not reported Ischaemic heart

Second primary

cancer

Acute cardiac

diease - not

reported

Renal failure not reported

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; HR: Hazard Ratio; OR: Odds ratio

different from the estimate of the effect

substantially different from the estimate of effect

**GRADE** Working Group grades of evidence

close to the estimate of the effect, but there is a possibility that it is substantially different

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be

# standard cytogenetic risk

Patient or population: relapsed/refractory multiple myeloma with

Other

considerat

ions

none

none

none

none

none

none

daratumu

mab +

backbone

therapy

29/325

(8.9%)

73/325

(22.5%)

149/325

(45.8%)

239/594

(40.2%)

140/329

(42.6%)

90/329

(27.4%)

backbone

therapy

1/306

(0.3%)

26/306

(8.5%)

56/306

(18.3%)

348/482

(72.2%)

104/312

(33.3%)

69/312

(22.1%)

Effect

Absolute

(95% CI)

86 more

per 1 000

(from 10 more to 417 more)

140 more

per 1 000

(from 67 more to 234 more)

275 more

per 1 000

(from 188 more to 366 more)

337 fewer

per 1 000

(from 412 fewer to 249 fewer)

92 more

per 1 000

(from 15

more to 172 more)

51 more

per 1 000

(from 14 fewer to 129 more)

Relative

(95% CI)

OR 29.88

(4.04 to

220.78)

OR 3.12

(1.93 to

5.04)

OR 3.78

(2.63 to)

5.43)

HR 0.38

(0.29 to

0.50)

OR 1.48

(1.07 to

2.04)

OR 1.32

(0.92 to

1.90)

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Certainty

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VERY LOW

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VERY LOW

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VERY LOW

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LOW

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LOW

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LOW

Comparison. Dackbone merapy	
Certainty assessment	№ of patients
Certainty assessment	1 312 of patients

Inconsiste

ncy

not

serious

not

serious

not

serious

serious

not

serious

not

serious

Risk of

bias

not

serious

not

serious

not

serious

not

serious

not

serious

not

serious

№ of

studies

Study

design

minimal residual disease negativity randomise

d trials

stringent complete response

complete response or better

death or disease progression

all grade thrombocytopenia

grade 3-4 thrombocytopenia

randomise

d trials

Intervention:	daratumumab +	backbone	thera

Indirectne

SS

serious

serious

serious

serious

serious

serious

Imprecisi

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very

serious

very

serious

very

serious

not

serious

serious

Interv	ention	: dara	itumum	nab + b	oackbone	therapy

Comparison: backbone therapy		
	1	

ntervention:	daratumumab	+ backbone	therapy

ntervention: daratumumab + backbone therapy	y
---	---

# standard cytogenetic risk

Patient or population: relapsed/refractory multiple myeloma with

Other

considerat

ions

none

none

none

none

none

none

№ of patients

backbone

therapy

25/312

(8.0%)

10/312

(3.2%)

96/312

(30.8%)

75/312

(24.0%)

103/312

(33.0%)

55/312

(17.6%)

daratumu

mab +

backbone

therapy

28/329

(8.5%)

22/329

(6.7%)

145/329

(44.1%)

124/329

(37.7%)

116/329

(35.3%)

56/329

(17.0%)

Effect

Absolute

(95% CI)

4 more per

1 000

(from 30 fewer to 61 more)

35 more

per 1 000

(from 0 fewer to 101 more)

133 more

per 1 000

(from 55 more to 214 more)

136 more

per 1 000

(from 61 more to 219 more)

23 more

per 1 000

(from 47 fewer to 100 more)

6 fewer per 1 000

(from 56 fewer to 59 more)

Relative

(95% CI)

OR 1.06

(0.61 to

1.88)

OR 2.16

(1.01 to

4.65)

OR 1.77

(1.28 to

2.45)

OR 1.91

(1.36 to

2.69)

OR 1.11

(0.80 to)

1.53)

OR 0.96

(0.64 to

1.44)

Importan

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Certainty

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Indirectne

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serious

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Imprecisi

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serious

BOIII BUCILB	one energy
Certainty asse	ssment

certainty assessment	Certainty assessment
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Risk of

bias

not

serious

not

serious

not

serious

not

serious

not

serious

not

serious

№ of

studies

Study

design

randomise

d trials

all grade lymphopenia

grade 3-4 lymphopenia

all grade neutropenia

grade 3-4 neutropenia

all grade anaemia

grade 3-4 anaemia

Comparison.	Duckbolic	unci ap
	Certainty assessment	

n	tervent	tion: c	darat	tumu	mab	+ ba	ackl	one	therap	Dy

					-1-7
omnarison.	hackbana	thorony			

<b>Comparison:</b>	backbone therapy

Inconsiste

ncy

not

serious

not

serious

not

serious

not

serious

not

serious

not

Comparison:	backbone	therapy

Intervention: daratumumab + backbone therapy										
Comparison: backbone therapy										
Certainty assessment	№ of patients	Effect								

Inter	ntervention: daratumumab + backbone therapy											
Comparison: backbone therapy												
Certainty assessment					№ of p	atients	Efi	fect				
						Other	daratumu				Certainty	Importan

Other

considerat

ions

none

none

none

none

Second primary cancer, acute cardiac failure, ischaemic heart failure, and renal failure were not reported.

mab +

backbone

therapy

67/134

(50.0%)

4/137

(2.9%)

27/329

(8.2%)

14/329

(4.3%)

backbone

therapy

50/136

(36.8%)

8/136

(5.9%)

13/312

(4.2%)

3/312

(1.0%)

Relative

(95% CI)

OR 1.72

(1.06 to

2.80)

OR 0.48

(0.14 to

1.64)

OR 3.22

(1.14 to

9.13)

OR 4.58

(1.30 to

16.09)

Absolute

(95% CI)

132 more

per 1 000

(from 14 more to 252 more)

30 fewer

per 1 000

(from 50 fewer to 34 more)

81 more

per 1 000

(from 6 more to 242 more)

33 more

per 1 000

(from 3 more to 125 more)  $\oplus \oplus \bigcirc \bigcirc$ 

LOW

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LOW

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LOW

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LOW

№ of

studies

Study

design

all grade peripheral neuropathy

randomise

d trials

grade 3-4 peripheral neuropathy

randomise

d trials

randomise

d trials

randomise

d trials

all grade hypertension

grade 3-4 hypertension

Risk of

bias

not

serious

serious

not

serious

not

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Inconsiste

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Indirectne

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Imprecisi

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**IMPORT** 

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standard cytogenetic risk			
Intervention: daratumumab + backb	one therap	y	
Comparison: backbone therapy			
Certainty assessment	№ of patients	Effect	

Patient or population: <u>relapsed/refractory multiple myeloma wit</u>	П
standard cytogenetic risk	
Intervention: daratumumab + backbone therapy	
Comparison: backbong therapy	

Patient or population: <u>relapsed/refractory multiple myeloma with</u>
standard cytogenetic risk
Intervention, deretumumen + beckhone thereny

Patient or population: relapsed/refractory multiple myeloma with high cytogenetic risk

Relative effect

(95% CI)

OR 18.48

(2.38 to 143.67)

OR 8.74

(0.45 to 168.00)

OR 6.29

(1.28 to 30.82)

HR 0.52

(0.35 to 0.76)

Intervention: daratumumab + backbone therapy

Comparison, backbone merapy			

Outcomes	№ of participants	Certain evid
Outcomes	(studies)	CVIU

142

(2 RCTs)

142

(2 RCTs)

73

(1 RCT)

366

(5 RCTs)

CI: Confidence interval; OR: Odds ratio; HR: Hazard Ratio

**GRADE** Working Group grades of evidence

minimal residual

disease negativity

(MRD negativity)

stringent

complete

response (sCR)

complete

response or

better (CR or

better)

death or disease

progression

# ity of the dence (GRADE)

**Ф**ООО

**VERY LOW** 

ФООО

**VERY LOW** 

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LOW

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**MODERATE** 

comparison group and the relative effect of the intervention (and its 95% CI).

The true effect is likely to be substantially different from the estimate of effect

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be

certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate:

close to the estimate of the effect, but there is a possibility that it is substantially different. Low

Risk difference with daratumuma

b +backbone therapy

0 fewer per

1 000

(0 fewer to

0 fewer)

101 more

per 1 000

(8 fewer to

700 more)

223 more

per 1 000

(15 more to

599 more)

236 fewer per 1 000

(363 fewer

to 100 fewer)

Anticipated absolute effects

Risk with

backbone therapy

0 per 1 000

15 per 1 000

59 per 1 000

734 per 1 000

high cytogenetic risk Intervention: daratumumab + backbone therapy

Comparison: backbone therapy

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)

143

(2 RCTs)

CI: Confidence interval; OR: Odds ratio; HR: Hazard Ratio

**GRADE** Working Group grades of evidence

different from the estimate of effect

comparison group and the relative effect of the intervention (and its 95% CI).

all grade

thrombocytopeni

grade 3-4

thrombocytopeni

a

all grade

lymphopenia

grade 3-4

lymphopenia

all grade

neutropenia

grade 3-4

neutropenia

# ty of the ence

Patient or population: relapsed/refractory multiple myeloma with

 $\Theta\ThetaOO$ 

LOW

 $\Theta\ThetaOO$ 

LOW

 $\Theta\ThetaOO$ 

**LOW** 

 $\Theta\ThetaOO$ 

LOW

 $\Theta\ThetaOO$ 

LOW

 $\Theta\ThetaOO$ 

LOW

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the

Relative effect (95% CI)

OR 1.23

(0.64 to 2.38)

OR 1.18

(0.59 to 2.35)

OR 1.18

(0.42 to 3.39)

OR 1.23

(0.41 to 3.78)

OR 1.58

(0.79 to 3.14)

OR 1.23

(0.59 to 2.55)

Risk with backbone therapy 441 per 1 000

324 per 1 000

103 per 1 000

88 per 1 000

309 per 1 000

265 per 1 000

Anticipated absolute effects

Risk difference

with

daratumuma

b +backbone therapy

51 more per 1 000 (106 fewer 37 more per (103 fewer 16 more per

to 211 more)

(57 fewer to 177 more) 18 more per (50 fewer to 180 more) 105 more per 1 000

(48 fewer to 275 more)

42 more per 1 000 (90 fewer to

214 more)

high cytogenetic risk Intervention: daratumumab + backbone therapy

Patient or population: relapsed/refractory multiple myeloma with

Comparison: backbone therapy

Outcomes	№ of participants	Certainty evide
	(studies)	(GRA

all grade anaemia

grade 3-4

anaemia

all grade

peripheral

neuropathy

grade 3-4

peripheral

neuropathy

all grade

hypertension

grade 3-4

hypertension

143

(2 RCTs)

143

(2 RCTs)

74

(1 RCT)

74

(1 RCT)

143

(2 RCTs)

143

(2 RCTs)

**GRADE** Working Group grades of evidence

CI: Confidence interval; OR: Odds ratio; HR: Hazard Ratio

effect is likely to be substantially different from the estimate of effect

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LOW

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LOW

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LOW

 $\Theta\ThetaOO$ 

LOW

ФООО

**VERY LOW** 

 $\Theta\ThetaOO$ 

LOW

comparison group and the relative effect of the intervention (and its 95% CI).

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be

(95% CI) OR 0.49

OR 0.56

(0.24 to 1.31)

OR 1.97

(0.78 to 5.01)

OR 0.39

(0.07 to 2.30)

OR 4.54

(1.23 to 16.71)

OR 12.81

(0.71 to 231.89)

Relative effect (0.24 to 0.99)

backbone therapy 426 per 1 000

Risk with

235 per 1 000

382 per 1 000

118 per 1 000

44 per 1 000

0 per 1 000

Anticipated absolute effects

therapy 159 fewer per 1 000 (275 fewer to 2 fewer) 88 fewer per (167 fewer to 52 more) 167 more per 1 000 (57 fewer to

Risk difference

with

daratumuma

b +backbone

374 more) 68 fewer per (108 fewer 129 more per 1 000 (10 more to

391 more)

0 fewer per 1 000

(0 fewer to 0 fewer)

Patient or population: relapsed/refractory multiple myeloma with high cytogenetic risk

**Intervention: daratumumab + backbone therapy** 

Comparison: backbone therapy

Second primary

cancer

Acute cardiac failure - not

reported

Ischaemic heart diease - not

reported

Renal failure -

not reported

				Anticipated abso	lute effects
Outcomes	№ of participants	Certainty of the evidence	Relative effect	Diele mide	Risk difference with

Not reported.

Not reported.

Not reported.

Not reported.

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be

close to the estimate of the effect, but there is a possibility that it is substantially different

comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; HR: Hazard Ratio; OR: Odds ratio

**GRADE** Working Group grades of evidence

different from the estimate of the effect

substantially different from the estimate of effect

# (studies) (95% CI) (GRADE)

# Risk with backbone therapy

daratumuma

b +backbone therapy

# high cytogenetic risk

Patient or population: relapsed/refractory multiple myeloma with

Other

considerat

ions

none

none

none

none

none

none

daratumu

mab +

backbone

therapy

4/74

(5.4%)

14/74

(18.9%)

11/39

(28.2%)

103/208

(49.5%)

37/75

(49.3%)

27/75

(36.0%)

backbone

therapy

0/68

(0.0%)

1/68

(1.5%)

2/34

(5.9%)

116/158

(73.4%)

30/68

(44.1%)

22/68

(32.4%)

Effect

Absolute

(95% CI)

0 fewer

per 1 000

(from 0 fewer to 0 fewer)

101 more

per 1 000

(from 8 fewer to 700 more)

223 more

per 1 000

(from 15 more to 599 more)

236 fewer

per 1 000

(from 363 fewer to 100 fewer)

51 more

per 1 000

(from 106 fewer to 211 more)

37 more

per 1 000

(from 103 fewer to 206 more)

Relative

(95% CI)

OR 18.48

(2.38 to

143.67)

OR 8.74

(0.45 to

168.00)

OR 6.29

(1.28 to

30.82)

HR 0.52

(0.35 to)

0.76)

OR 1.23

(0.64 to)

2.38)

OR 1.18

(0.59 to

2.35)

Importan

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Certainty

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VERY LOW

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VERY LOW

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LOW

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**MODERATE** 

**ӨӨОО** 

LOW

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LOW

# **Intervention:** daratumumab + backbone therapy

Comparison: bad	ekbone therapy	
Certain	nty assessment	<b>№</b> of patients

Indirectne

SS

serious

serious

not

serious

serious

serious

serious

Imprecisi

on

very

serious

very

serious

verv

serious

not

serious

serious

serious

№ of

studies

Study

design

minimal residual disease negativity randomise

d trials

stringent complete response

complete response or better

death or disease progression

all grade thrombocytopenia

grade 3-4 thrombocytopenia

randomise

d trials

Risk of

bias

not

serious

not

serious

not

serious

not

serious

not

serious

not

serious

Inconsiste

ncy

not

serious

not

serious

serious

not

serious

not

serious

not

### high cytogenetic risk Intervention: daratumumab + backbone therapy

Patient or population: relapsed/refractory multiple myeloma with

Other

considerat

ions

none

none

none

none

none

none

daratumu

mab +

backbone

therapy

9/75

(12.0%)

8/75

(10.7%)

31/75

(41.3%)

23/75

(30.7%)

20/75

(26.7%)

11/75

(14.7%)

Effect

Absolute

(95% CI)

16 more

per 1 000

(from 57 fewer to 177 more)

18 more

per 1 000

(from 50 fewer to 180 more)

105 more

per 1 000

(from 48 fewer to 275 more)

42 more

per 1 000

(from 90 fewer to 214 more)

159 fewer

per 1 000

(from 275 fewer to 2 fewer)

88 fewer

per 1 000

(from 167 fewer to 52 more)

Relative

(95% CI)

OR 1.18

(0.42 to

3.39)

OR 1.23

(0.41 to

3.78)

OR 1.58

(0.79 to

3.14)

OR 1.23

(0.59 to)

2.55)

OR 0.49

(0.24 to)

0.99)

OR 0.56

(0.24 to

1.31)

backbone

therapy

7/68

(10.3%)

6/68

(8.8%)

21/68

(30.9%)

18/68

(26.5%)

29/68

(42.6%)

16/68

(23.5%)

**Importan** 

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**IMPORT** 

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Certainty

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LOW

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LOW

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LOW

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LOW

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LOW

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LOW

Comparison.	backbone therapy
	Cartainty assassment

Inconsiste

ncy

not

serious

not

serious

not

serious

not

serious

not

serious

not

serious

Risk of

bias

not

serious

not

serious

not

serious

not

serious

not

serious

not

serious

№ of

studies

Study

design

randomise

d trials

all grade lymphopenia

grade 3-4 lymphopenia

all grade neutropenia

grade 3-4 neutropenia

all grade anaemia

grade 3-4 anaemia

Comparison, backbone therapy	
Certainty assessment	№ of patients

<sup>7</sup> omporicon•	haalzhana	thorony	

Indirectne

SS

serious

serious

serious

serious

serious

serious

Imprecisi

on

serious

serious

serious

serious

serious

IIICI	vention.	uai atumuman -	T Dackbone merap	Y
٧		haal-hana 4hana		

# Patient or population: relapsed/refractory multiple myeloma with

intervention: daratumuman + backbone therapy											
Comparison: backbone therapy											
Certainty assessment						№ of patients		Effect			
											1

Imprecisi

on

very

serious

very

serious

very

serious

serious

№ of

studies

Study

design

all grade peripheral neuropathy

randomise

d trials

grade 3-4 peripheral neuropathy

randomise

d trials

randomise

d trials

randomise

d trials

all grade hypertension

grade 3-4 hypertension

Risk of

bias

not

serious

serious

not

serious

not

serious

Inconsiste

ncy

not

serious

not

serious

not

serious

not

serious

Indirectne

SS

not

serious

not

serious

serious

serious

Intervention: daratumumab + backbone therapy											
Comparison: backbone therapy											
Certainty assessment					№ of patients		Effect				

Other

considerat

ions

none

none

none

none

Second primary cancer, acute cardiac failure, ischaemic heart failure, and renal failure were not reported.

daratumu

mab +

backbone

therapy

22/40

(55.0%)

2/40

(5.0%)

13/75

(17.3%)

6/75

(8.0%)

backbone

therapy

13/34

(38.2%)

4/34

(11.8%)

3/68

(4.4%)

0/68

(0.0%)

Relative

(95% CI)

OR 1.97

(0.78 to

5.01)

OR 0.39

(0.07 to

2.30)

OR 4.54

(1.23 to

16.71)

OR 12.81

(0.71 to

231.89)

Absolute

(95% CI)

167 more

per 1 000

(from 57 fewer to 374 more)

68 fewer

per 1 000

(from 108 fewer to 117 more)

129 more

per 1 000

(from 10 more to 391 more)

0 fewer

per 1 000

(from 0fewer to 0 fewer)

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Certainty

 $\Theta\ThetaOO$ 

LOW

**0000** 

LOW

 $\Theta \cap \cap \cap \Theta$ 

VERY LOW

 $\Theta\ThetaOO$ 

LOW

ingh cytogenetic risk			
Intervention: daratumumab + backb	one therap	y	
Comparison: backbone therapy			
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high cytogenetic risk		
Intervention: daratum	umab + backbone therapy	
Comparison: backbone	e therany	