ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 1

For new approaches to adjuvant therapy or new potentially curative therapies

Name of study:	Addition of Ifosfamide and Etoposide to Standard CHT for Ewing's Sarcoma				
Study medicine:	VDC/IE vs VDC	**Indication:**	First line		
First author:	Grier	**Year:**	2003	**Journal:**	NEJM
Name of evaluator:					

GRADE A	>5% improvement of survival at ≥3 years follow-up	✓
	Improvements in DFS alone (primary endpoint) (HR <0.65) in studies without mature survival data	
GRADE B	≥3% BUT ≤5% improvement at ≥3 years follow-up	
	Improvement in DFS alone (primary endpoint) (HR 0.65 - 0.8) without mature survival data	
	Non inferior OS or DFS with reduced treatment toxicity or improved QoL (with validated scales)	
	Non inferior OS or DFS with reduced treatment cost as reported study outcome (with equivalent outcomes and risks)	
GRADE C	<3% improvement of survival at ≥3 years follow-up	
	Improvement in DFS alone (primary endpoint) (HR >0.8) in studies without mature survival data	
	Improvements in pCR alone (primary endpoint) by ≥30% relative AND ≥15% absolute gain in studies without mature survival data	

Mark with √ if relevant

Magnitude of clinical benefit grade (highest grade scored)	**A**	**B**	**C**
	✓		

Curative setting grading - A and B indicates a substantial magnitude of clinical benefit.

DFS, disease-free survival; HR, hazard ratio; OS, overall survival; pCR, pathologic complete response/remission; QoL, quality of life.

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 1

For new approaches to adjuvant therapy or new potentially curative therapies

Name of study:	EE 2012				
Study medicine:	VDC/IE vs VIDE	**Indication:**	First line		
First author:	Wheatley	**Year:**	2019	**Journal:**	CTOS
Name of evaluator:					

GRADE A	>5% improvement of survival at ≥3 years follow-up	○
	Improvements in DFS alone (primary endpoint) (HR <0.65) in studies without mature survival data	○
GRADE B	≥3% BUT ≤5% improvement at ≥3 years follow-up	○
	Improvement in DFS alone (primary endpoint) (HR 0.65 - 0.8) without mature survival data	✓
	Non inferior OS or DFS with reduced treatment toxicity or improved QoL (with validated scales)	○
	Non inferior OS or DFS with reduced treatment cost as reported study outcome (with equivalent outcomes and risks)	○
GRADE C	<3% improvement of survival at ≥3 years follow-up	○
	Improvement in DFS alone (primary endpoint) (HR >0.8) in studies without mature survival data	○
	Improvements in pCR alone (primary endpoint) by ≥30% relative AND ≥15% absolute gain in studies without mature survival data	○

Mark with √ if relevant

Magnitude of clinical benefit grade (highest grade scored)	**A**	**B**	**C**
	☐	✓	☐

Curative setting grading - A and B indicates a substantial magnitude of clinical benefit.

DFS, disease-free survival; HR, hazard ratio; OS, overall survival; pCR, pathologic complete response/remission; QoL, quality of life.

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 1

For new approaches to adjuvant therapy or new potentially curative therapies

Name of study:	Randomized Comparison of Intensified Six-Drug Versus Standard Three-Drug CHT				
Study medicine:	IVA vs IVA+ Car-VP16-epi	**Indication:**	First line		
First author:	Oberlin et al	**Year:**	2012	**Journal:**	Lancet Onco
Name of evaluator:					

GRADE A	>5% improvement of survival at ≥3 years follow-up	○
	Improvements in DFS alone (primary endpoint) (HR <0.65) in studies without mature survival data	○
GRADE B	≥3% BUT ≤5% improvement at ≥3 years follow-up	○
	Improvement in DFS alone (primary endpoint) (HR 0.65 - 0.8) without mature survival data	○
	Non inferior OS or DFS with reduced treatment toxicity or improved QoL (with validated scales)	✓
	Non inferior OS or DFS with reduced treatment cost as reported study outcome (with equivalent outcomes and risks)	○
GRADE C	<3% improvement of survival at ≥3 years follow-up	○
	Improvement in DFS alone (primary endpoint) (HR >0.8) in studies without mature survival data	○
	Improvements in pCR alone (primary endpoint) by ≥30% relative AND ≥15% absolute gain in studies without mature survival data	○

Mark with √ if relevant

Magnitude of clinical benefit grade (highest grade scored)	**A**	**B**	**C**
	○	✓	○

Curative setting grading - A and B indicates a substantial magnitude of clinical benefit.

DFS, disease-free survival; HR, hazard ratio; OS, overall survival; pCR, pathologic complete response/remission; QoL, quality of life.

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 1

For new approaches to adjuvant therapy or new potentially curative therapies

Name of study:	Addition of dose-intensified doxorubicin to standard chemotherapy for rhabdomyo				
Study medicine:	IVA vs IVADo	**Indication:**	First line		
First author:	Bisogno G et al	**Year:**	2018	**Journal:**	Lancet Onco
Name of evaluator:					

GRADE A	>5% improvement of survival at ≥3 years follow-up	☐
	Improvements in DFS alone (primary endpoint) (HR <0.65) in studies without mature survival data	☐
GRADE B	≥3% BUT ≤5% improvement at ≥3 years follow-up	☐
	Improvement in DFS alone (primary endpoint) (HR 0.65 - 0.8) without mature survival data	☐
	Non inferior OS or DFS with reduced treatment toxicity or improved QoL (with validated scales)	✓
	Non inferior OS or DFS with reduced treatment cost as reported study outcome (with equivalent outcomes and risks)	☐
GRADE C	<3% improvement of survival at ≥3 years follow-up	☐
	Improvement in DFS alone (primary endpoint) (HR >0.8) in studies without mature survival data	☐
	Improvements in pCR alone (primary endpoint) by ≥30% relative AND ≥15% absolute gain in studies without mature survival data	☐

Mark with √ if relevant

Magnitude of clinical benefit grade (highest grade scored)	**A**	**B**	**C**
	☐	✓	☐

Curative setting grading - A and B indicates a substantial magnitude of clinical benefit.

DFS, disease-free survival; HR, hazard ratio; OS, overall survival; pCR, pathologic complete response/remission; QoL, quality of life.

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 1

For new approaches to adjuvant therapy or new potentially curative therapies

Name of study:	Adjuvant Chemotherapy for Adult Soft Tissue Sarcomas of the Extremities				
Study medicine:	EI vs follow-up	**Indication:**	Adjuvant		
First author:	Frustaci et al	**Year:**	2001	**Journal:**	JCO
Name of evaluator:					

GRADE A	>5% improvement of survival at ≥3 years follow-up	✓
	Improvements in DFS alone (primary endpoint) (HR <0.65) in studies without mature survival data	
GRADE B	≥3% BUT ≤5% improvement at ≥3 years follow-up	
	Improvement in DFS alone (primary endpoint) (HR 0.65 - 0.8) without mature survival data	
	Non inferior OS or DFS with reduced treatment toxicity or improved QoL (with validated scales)	
	Non inferior OS or DFS with reduced treatment cost as reported study outcome (with equivalent outcomes and risks)	
GRADE C	<3% improvement of survival at ≥3 years follow-up	
	Improvement in DFS alone (primary endpoint) (HR >0.8) in studies without mature survival data	
	Improvements in pCR alone (primary endpoint) by ≥30% relative AND ≥15% absolute gain in studies without mature survival data	

Mark with √ if relevant

Magnitude of clinical benefit grade (highest grade scored)	**A**	**B**	**C**
	✓		

Curative setting grading - A and B indicates a substantial magnitude of clinical benefit.

DFS, disease-free survival; HR, hazard ratio; OS, overall survival; pCR, pathologic complete response/remission; QoL, quality of life.

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 1

For new approaches to adjuvant therapy or new potentially curative therapies

Name of study:	Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy…				
Study medicine:	EI vs histotype-tailored	**Indication:**	Neoadjuvant		
First author:	Gronchi et al	**Year:**	2017	**Journal:**	Lancet Onco
Name of evaluator:					

GRADE A	>5% improvement of survival at ≥3 years follow-up	○
	Improvements in DFS alone (primary endpoint) (HR <0.65) in studies without mature survival data	✓
GRADE B	≥3% BUT ≤5% improvement at ≥3 years follow-up	○
	Improvement in DFS alone (primary endpoint) (HR 0.65 - 0.8) without mature survival data	○
	Non inferior OS or DFS with reduced treatment toxicity or improved QoL (with validated scales)	○
	Non inferior OS or DFS with reduced treatment cost as reported study outcome (with equivalent outcomes and risks)	○
GRADE C	<3% improvement of survival at ≥3 years follow-up	○
	Improvement in DFS alone (primary endpoint) (HR >0.8) in studies without mature survival data	○
	Improvements in pCR alone (primary endpoint) by ≥30% relative AND ≥15% absolute gain in studies without mature survival data	○

Mark with √ if relevant

Magnitude of clinical benefit grade (highest grade scored)	**A**	**B**	**C**
	✓		

Curative setting grading - A and B indicates a substantial magnitude of clinical benefit.

DFS, disease-free survival; HR, hazard ratio; OS, overall survival; pCR, pathologic complete response/remission; QoL, quality of life.

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 1

For new approaches to adjuvant therapy or new potentially curative therapies

Name of study:	Neoadjuvant Chemotherapy in high-risk STS: final results				
Study medicine:	EI vs histotype tailored	**Indication:**	Neoadjuvant		
First author:	Gronchi et al	**Year:**	2019	**Journal:**	ASCO
Name of evaluator:					

GRADE A	>5% improvement of survival at ≥3 years follow-up	✓
	Improvements in DFS alone (primary endpoint) (HR <0.65) in studies without mature survival data	
GRADE B	≥3% BUT ≤5% improvement at ≥3 years follow-up	
	Improvement in DFS alone (primary endpoint) (HR 0.65 - 0.8) without mature survival data	
	Non inferior OS or DFS with reduced treatment toxicity or improved QoL (with validated scales)	
	Non inferior OS or DFS with reduced treatment cost as reported study outcome (with equivalent outcomes and risks)	
GRADE C	<3% improvement of survival at ≥3 years follow-up	
	Improvement in DFS alone (primary endpoint) (HR >0.8) in studies without mature survival data	
	Improvements in pCR alone (primary endpoint) by ≥30% relative AND ≥15% absolute gain in studies without mature survival data	

Mark with √ if relevant

Magnitude of clinical benefit grade (highest grade scored)	**A**	**B**	**C**
	✓		

Curative setting grading - A and B indicates a substantial magnitude of clinical benefit.

DFS, disease-free survival; HR, hazard ratio; OS, overall survival; pCR, pathologic complete response/remission; QoL, quality of life.

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 2A

For therapies that are not likely to be curative with primary endpoint of OS

Name of study:	Eribulin versus dacarbazine in previously treated patients with advanced liposarc				
Study medicine:	Eribuline vs DTIC	**Indication:**	Second-line L sarcomas		
First author:	Schöffski, Patrick	**Year:**	2016	**Journal:**	Lancet Onc
Name of evaluator:					

If median OS with the standard treatment is ≤12 months

GRADE 4	HR ≤0.65 AND gain ≥3 months	✓
	Increase in 2 year survival ≥10%	
GRADE 3	HR ≤0.65 AND gain ≥2.0-<3 months	
GRADE 2	HR ≤0.65 AND gain ≥1.5-<2.0	
	HR >0.65-0.70 AND gain ≥1.5 months	
GRADE 1	HR >0.70 OR gain <1.5 months	

Mark with √ if relevant

Preliminary magnitude of clinical benefit grade (highest grade scored)	**4**	**3**	**2**	**1**
	✓			

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

HR, hazard ratio; OS, overall survival

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

Quality of life/Grade 3-4 toxicities* assessment

Does secondary endpoint QoL show improvement?	○
Are there statistically significantly less grade 3-4 toxicities impacting on daily well-being?*	○

*This does not include alopecia, myelosuppression, but rather chronic nausea,diarrhoea, fatigue, etc.

Mark with √ if relevant

Adjustments

01. Upgrade 1 level if improved QoL and/or less grade 3-4 toxicities impacting daily well-being are shown

02. If there is a long term plateau in the survival curve, and OS advantage continues to be observed at 5 years, also score according to form 1 (treatments with curative potential) and present both scores i.e. A/4.

Final adjusted magnitude of clinical benefit grade	5	4	3	2	1
	☐	✓	☐	☐	☐

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

OS, overall survival; QoL, quality of Life

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 2A

For therapies that are not likely to be curative with primary endpoint of OS

Name of study:	Eribulin versus dacarbazine in previously treated patients with advanced liposarc				
Study medicine:	Eribuline vs DTIC	**Indication:**	Second-line L sarcomas		
First author:	Schöffski, Patrick	**Year:**	2016	**Journal:**	Lancet Onc
Name of evaluator:					

If median OS with the standard treatment is ≤12 months

GRADE 4	HR ≤0.65 AND gain ≥3 months	☐
	Increase in 2 year survival ≥10%	☐
GRADE 3	HR ≤0.65 AND gain ≥2.0-<3 months	✓
GRADE 2	HR ≤0.65 AND gain ≥1.5-<2.0	☐
	HR >0.65-0.70 AND gain ≥1.5 months	☐
GRADE 1	HR >0.70 OR gain <1.5 months	☐

Mark with √ if relevant

Preliminary magnitude of clinical benefit grade (highest grade scored)	4	3	2	1
	☐	✓	☐	☐

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

HR, hazard ratio; OS, overall survival

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

Quality of life/Grade 3-4 toxicities* assessment

Does secondary endpoint QoL show improvement?	○
Are there statistically significantly less grade 3-4 toxicities impacting on daily well-being?*	○

*This does not include alopecia, myelosuppression, but rather chronic nausea,diarrhoea, fatigue, etc.

Mark with √ if relevant

Adjustments

01. Upgrade 1 level if improved QoL and/or less grade 3-4 toxicities impacting daily well-being are shown

02. If there is a long term plateau in the survival curve, and OS advantage continues to be observed at 5 years, also score according to form 1 (treatments with curative potential) and present both scores i.e. A/4.

Final adjusted magnitude of clinical benefit grade	5	4	3	2	1
	☐	☐	✓	☐	☐

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

OS, overall survival; QoL, quality of Life

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 2B

For therapies that are not likely to be curative with primary endpoint of PFS

Name of study:	Efficacy and Safety ofTrabectedin or Dacarbazine for Metastatic Liposarcoma				
Study medicine:	Trabectedin vs DTIC	**Indication:**	L-sarcoma		
First author:	Demetri G et al	**Year:**	2015	**Journal:**	JCO
Name of evaluator:					

If median PFS with standard treatment ≤6 months

GRADE 3	HR ≤0.65 AND gain ≥1.5 months	✓
GRADE 2	HR ≤0.65 BUT gain <1.5 months	
GRADE 1	HR >0.65	

Mark with √ if relevant

Preliminary magnitude of clinical benefit grade (highest grade scored)	**3**	**2**	**1**
	✓		

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

HR, hazard ratio; PFS, progression-free survival

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

Early stopping or crossover

Did the study have an early stopping rule based on interim analysis of survival?	○
Was the randomization terminated early based on the detection of overall survival advantage at interim analysis?	○

If the answer to both is "yes", then see letter "E" in the adjustment section below

Mark with √ if relevant

Toxicity assessment

Is the new treatment associated with a statistically significant incremental rate of:

«Toxic» death >2%	✓
Cardiovascular ischemia >2%	○
Hospitalisation for «toxicity» >10%	○
Excess rate of severe CHF >4%	○
Grade 3 neurotoxicity >10%	○
Severe other irreversible or long lasting toxicity >2% please specify:	○

(Incremental rate refers to the comparison versus standard therapy in the control arm)

Mark with √ if relevant

Quality of life/Grade 3-4 toxicities* assessment

Was QoL evaluated as secondary outcome?	○
Does secondary endpoint QoL show improvement?	○
Are there statistically significantly less grade 3-4 toxicities impacting on daily well-being?*	○

*This does not include alopecia, myelosuppression, but rather chronic nausea, diarrhoea, fatigue, etc.

Mark with √ if relevant

CHF, congestive heart failure; QoL, quality of Life

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

Adjustments

A When OS as secondary endpoint shows improvement, it will prevail and the new scoring will be done according to form 2a.

B Downgrade 1 level if there is one or more of the above incremental toxicities associated with the new medicine.

C Downgrade 1 level if the medicine ONLY leads to improved PFS (mature data shows no OS advantage) and QoL assessment does not demonstrate improved QoL.

D Upgrade 1 level if improved QoL or if less grade 3-4 toxicities that bother patients are demonstrated.

E Upgrade 1 level if study had early crossover because of early stopping or crossover based on detection of survival advantage at interim analysis.

F Upgrade 1 level if there is a long-term plateau in the PFS curve, and there is >10% improvement in PFS at 1 year.

Final, toxicity and QoL adjusted, magnitude of clinical benefit grade	4	3	2	1
	☐	✓	☐	☐

Highest magnitude clinic benefit grade that can be achieved grade 4.

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

PFS, progression-free survival; OS, overall survival; QoL, quality of life

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 2B

For therapies that are not likely to be curative with primary endpoint of PFS

Name of study:	Trabectedin monotherapy after standard chemotherapy versus BSC				
Study medicine:	Trabectedin	**Indication:**	TRS		
First author:	Kawai A et al	**Year:**	2015	**Journal:**	Lancet Onco
Name of evaluator:					

If median PFS with standard treatment ≤6 months

GRADE 3	HR ≤0.65 AND gain ≥1.5 months	✓
GRADE 2	HR ≤0.65 BUT gain <1.5 months	
GRADE 1	HR >0.65	

Mark with √ if relevant

Preliminary magnitude of clinical benefit grade (highest grade scored)	**3**	**2**	**1**
	✓		

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

HR, hazard ratio; PFS, progression-free survival

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

Early stopping or crossover

Did the study have an early stopping rule based on interim analysis of survival?	○
Was the randomization terminated early based on the detection of overall survival advantage at interim analysis?	○

If the answer to both is "yes", then see letter "E" in the adjustment section below

Mark with √ if relevant

Toxicity assessment

Is the new treatment associated with a statistically significant incremental rate of:

«Toxic» death >2%	○
Cardiovascular ischemia >2%	○
Hospitalisation for «toxicity» >10%	○
Excess rate of severe CHF >4%	○
Grade 3 neurotoxicity >10%	○
Severe other irreversible or long lasting toxicity >2% please specify:	○

(Incremental rate refers to the comparison versus standard therapy in the control arm)

Mark with √ if relevant

Quality of life/Grade 3-4 toxicities* assessment

Was QoL evaluated as secondary outcome?	○
Does secondary endpoint QoL show improvement?	○
Are there statistically significantly less grade 3-4 toxicities impacting on daily well-being?*	○

*This does not include alopecia, myelosuppression, but rather chronic nausea, diarrhoea, fatigue, etc.

Mark with √ if relevant

CHF, congestive heart failure; QoL, quality of Life

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

Adjustments

A When OS as secondary endpoint shows improvement, it will prevail and the new scoring will be done according to form 2a.

B Downgrade 1 level if there is one or more of the above incremental toxicities associated with the new medicine.

C Downgrade 1 level if the medicine ONLY leads to improved PFS (mature data shows no OS advantage) and QoL assessment does not demonstrate improved QoL.

D Upgrade 1 level if improved QoL or if less grade 3-4 toxicities that bother patients are demonstrated.

E Upgrade 1 level if study had early crossover because of early stopping or crossover based on detection of survival advantage at interim analysis.

F Upgrade 1 level if there is a long-term plateau in the PFS curve, and there is >10% improvement in PFS at 1 year.

Final, toxicity and QoL adjusted, magnitude of clinical benefit grade	4	3	2	1
	✓			

Highest magnitude clinic benefit grade that can be achieved grade 4.

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

PFS, progression-free survival; OS, overall survival; QoL, quality of life

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 2A

For therapies that are not likely to be curative with primary endpoint of OS

Name of study:	Trabectedin monotherapy after standard chemotherapy versus BSC				
Study medicine:	Trabectedin vs BSC	**Indication:**	Translocation-related sarcoma		
First author:	Kawai A et al	**Year:**	2015	**Journal:**	Lancet Onc
Name of evaluator:					

If median OS with the standard treatment is ≤12 months

GRADE 4	HR ≤0.65 AND gain ≥3 months	✓
	Increase in 2 year survival ≥10%	
GRADE 3	HR ≤0.65 AND gain ≥2.0-<3 months	
GRADE 2	HR ≤0.65 AND gain ≥1.5-<2.0	
	HR >0.65-0.70 AND gain ≥1.5 months	
GRADE 1	HR >0.70 OR gain <1.5 months	

Mark with √ if relevant

Preliminary magnitude of clinical benefit grade (highest grade scored)	**4**	**3**	**2**	**1**
	✓			

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

HR, hazard ratio; OS, overall survival

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

Quality of life/Grade 3-4 toxicities* assessment

Does secondary endpoint QoL show improvement?	○
Are there statistically significantly less grade 3-4 toxicities impacting on daily well-being?*	○

*This does not include alopecia, myelosuppression, but rather chronic nausea,diarrhoea, fatigue, etc.

Mark with √ if relevant

Adjustments

01. Upgrade 1 level if improved QoL and/or less grade 3-4 toxicities impacting daily well-being are shown

02. If there is a long term plateau in the survival curve, and OS advantage continues to be observed at 5 years, also score according to form 1 (treatments with curative potential) and present both scores i.e. A/4.

Final adjusted magnitude of clinical benefit grade	5	4	3	2	1
	☐	✓	☐	☐	☐

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

OS, overall survival; QoL, quality of Life

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 2B

For therapies that are not likely to be curative with primary endpoint of PFS

Name of study:	Pazopanib for metastatic soft-tissue sarcoma (PALETTE)				
Study medicine:	Pazopanib vs placebo	**Indication:**	Pretreated STS (except lipo)		
First author:	van der Graaf	**Year:**	2012	**Journal:**	Lancet Onco
Name of evaluator:					

If median PFS with standard treatment ≤6 months

GRADE 3	HR ≤0.65 AND gain ≥1.5 months	✓
GRADE 2	HR ≤0.65 BUT gain <1.5 months	
GRADE 1	HR >0.65	

Mark with √ if relevant

Preliminary magnitude of clinical benefit grade (highest grade scored)	**3**	**2**	**1**
	✓		

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

HR, hazard ratio; PFS, progression-free survival

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

Early stopping or crossover

Did the study have an early stopping rule based on interim analysis of survival?	○
Was the randomization terminated early based on the detection of overall survival advantage at interim analysis?	○

If the answer to both is "yes", then see letter "E" in the adjustment section below

Mark with √ if relevant

Toxicity assessment

Is the new treatment associated with a statistically significant incremental rate of:

«Toxic» death >2%	○
Cardiovascular ischemia >2%	○
Hospitalisation for «toxicity» >10%	○
Excess rate of severe CHF >4%	○
Grade 3 neurotoxicity >10%	○
Severe other irreversible or long lasting toxicity >2% please specify:	○

(Incremental rate refers to the comparison versus standard therapy in the control arm)

Mark with √ if relevant

Quality of life/Grade 3-4 toxicities* assessment

Was QoL evaluated as secondary outcome?	✓
Does secondary endpoint QoL show improvement?	○
Are there statistically significantly less grade 3-4 toxicities impacting on daily well-being?*	○

*This does not include alopecia, myelosuppression, but rather chronic nausea, diarrhoea, fatigue, etc.

Mark with √ if relevant

CHF, congestive heart failure; QoL, quality of Life

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

Adjustments

A When OS as secondary endpoint shows improvement, it will prevail and the new scoring will be done according to form 2a.

B Downgrade 1 level if there is one or more of the above incremental toxicities associated with the new medicine.

C Downgrade 1 level if the medicine ONLY leads to improved PFS (mature data shows no OS advantage) and QoL assessment does not demonstrate improved QoL.

D Upgrade 1 level if improved QoL or if less grade 3-4 toxicities that bother patients are demonstrated.

E Upgrade 1 level if study had early crossover because of early stopping or crossover based on detection of survival advantage at interim analysis.

F Upgrade 1 level if there is a long-term plateau in the PFS curve, and there is >10% improvement in PFS at 1 year.

Final, toxicity and QoL adjusted, magnitude of clinical benefit grade	4	3	2	1
	☐	✓	☐	☐

Highest magnitude clinic benefit grade that can be achieved grade 4.

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

PFS, progression-free survival; OS, overall survival; QoL, quality of life

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 2A

For therapies that are not likely to be curative with primary endpoint of OS

Name of study:	Randomized Phase II Study Comparing Gemcitabine Plus DTIC vs DTIC				
Study medicine:	Gem-DTIC vs DTIC	**Indication:**	Pretreated STS		
First author:	García del Muro et al	**Year:**	2011	**Journal:**	JCO
Name of evaluator:					

If median OS with the standard treatment is ≤12 months

GRADE 4	HR ≤0.65 AND gain ≥3 months	✓
	Increase in 2 year survival ≥10%	
GRADE 3	HR ≤0.65 AND gain ≥2.0-<3 months	
GRADE 2	HR ≤0.65 AND gain ≥1.5-<2.0	
	HR >0.65-0.70 AND gain ≥1.5 months	
GRADE 1	HR >0.70 OR gain <1.5 months	

Mark with √ if relevant

Preliminary magnitude of clinical benefit grade (highest grade scored)	**4**	**3**	**2**	**1**
	✓			

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

HR, hazard ratio; OS, overall survival

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

Quality of life/Grade 3-4 toxicities* assessment

Does secondary endpoint QoL show improvement?	○
Are there statistically significantly less grade 3-4 toxicities impacting on daily well-being?*	○

*This does not include alopecia, myelosuppression, but rather chronic nausea,diarrhoea, fatigue, etc.

Mark with √ if relevant

Adjustments

01. Upgrade 1 level if improved QoL and/or less grade 3-4 toxicities impacting daily well-being are shown

02. If there is a long term plateau in the survival curve, and OS advantage continues to be observed at 5 years, also score according to form 1 (treatments with curative potential) and present both scores i.e. A/4.

Final adjusted magnitude of clinical benefit grade	5	4	3	2	1
	☐	✓	☐	☐	☐

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

OS, overall survival; QoL, quality of Life

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 2C

For therapies that are not likely to be curative with primary endpoint other than OS or PFS or equivalence studies

Name of study:	Randomized Phase II Study of Gemcitabine and Docetaxel vs Gemcitabine alone				
Study medicine:	Gem vs Gem-Docetaxel	**Indication:**	Advanced STS		
First author:	Maki R et al	**Year:**	2007	**Journal:**	JCO
Name of evaluator:					

Primary outcome is Toxicity or Quality of Life AND Non-Inferiority Studies

GRADE 4	Reduced toxicity or improved QoL (using a validated scale) with evidence for statistical non-inferiority or superiority in PFS/OS	○
GRADE 3	Improvement in some symptoms (using a validated scale) BUT without evidence of improved overall QoL	○

Primary outcome is Response Rate

GRADE 2	RR is increased ≥20% but no improvement in toxicity/QoL/PFS/OS	○
GRADE 1	RR is increased <20% but no improvement in toxicity/QoL/PFS/OS	✓

Mark with √ if relevant

Final magnitude of clinical benefit grade	4	3	2	1
	☐	☐	☐	✓

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

PFS, progression-free survival; OS, overall survival; QoL, quality of life; RR, response rate

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 2C

For therapies that are not likely to be curative with primary endpoint other than OS or PFS or equivalence studies

Name of study:	TAXOGEM study				
Study medicine:	Gem vs Gem-Docetaxel	**Indication:**	Advanced Leimyosarcoma		
First author:	Pautier P et al	**Year:**	2012	**Journal:**	Oncologist
Name of evaluator:					

Primary outcome is Toxicity or Quality of Life AND Non-Inferiority Studies

GRADE 4	Reduced toxicity or improved QoL (using a validated scale) with evidence for statistical non-inferiority or superiority in PFS/OS	○
GRADE 3	Improvement in some symptoms (using a validated scale) BUT without evidence of improved overall QoL	○

Primary outcome is Response Rate

GRADE 2	RR is increased ≥20% but no improvement in toxicity/QoL/PFS/OS	○
GRADE 1	RR is increased <20% but no improvement in toxicity/QoL/PFS/OS	✓

Mark with √ if relevant

Final magnitude of clinical benefit grade	**4**	**3**	**2**	**1**
	☐	☐	☐	✓

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

PFS, progression-free survival; OS, overall survival; QoL, quality of life; RR, response rate

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 3

For single-arm studies in "orphan diseases" and for diseases with "high unmet need" when primary outcome is PFS or ORR

Name of study:	Phase II trial of first-line high-dose ifosfamide in advanced STS				
Study medicine:	Ifosfamide	**Indication:**	Advanced STS		
First author:	Buesa JM et al	**Year:**	1998	**Journal:**	Ann Oncol
Name of evaluator:					

GRADE 3	PFS ≥6 months	✓
	ORR (PR+CR) ≥60%	
	ORR (PR+CR) ≥20-<60% AND DoR ≥9 months	
GRADE 2	PFS ≥3-<6 months	
	ORR (PR+CR) ≥40-<60%	
	ORR (PR+CR) ≥20-<40% AND DoR ≥6-<9 months	
GRADE 1	PFS 2-<3 months	
	ORR(PR+CR) ≥20-<40% AND DoR <6 months	
	ORR (PR+CR) >10-<20% AND DoR ≥6 months	

Mark with √ if relevant

Preliminary magnitude of clinical benefit grade (highest grade scored)	**3**	**2**	**1**
	✓		

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

CR, complete response; DoR, duration of response; ORR, overall response rate; PFS, progression-free survival; PR, partial response

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

Quality of life/Grade 3-4 toxicities* assessment

Was QoL evaluated as secondary outcome?	○
Does secondary endpoint QoL show improvement?	○
Are there ≥30% grade 3-4 toxicities impacting on daily well-being?*	○

*This does not include alopecia, myelosuppression, but rather chronic nausea, diarrhoea, fatigue, etc.

Mark with √ if relevant

Adjustments

A Downgrade 1 level if there are ≥30% grade 3-4 toxicities impacting on daily well-being*

B Upgrade 1 level if improved QoL

C Upgrade 1 level for confirmatory, adequately sized, phase 4 experience

Final adjusted magnitude of clinical benefit grade	4	3	2	1
	✓			

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

QoL, quality of life

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 3

For single-arm studies in "orphan diseases" and for diseases with "high unmet need" when primary outcome is PFS or ORR

Name of study:	Adriamycin: a new effective agent in the therapy of disseminated sarcomas				
Study medicine:	Adriamycin	**Indication:**	Advanced STS		
First author:	Benjamin	**Year:**	1975	**Journal:**	Med Pediatr
Name of evaluator:					

GRADE 3	PFS ≥6 months	○
	ORR (PR+CR) ≥60%	○
	ORR (PR+CR) ≥20-<60% AND DoR ≥9 months	✓
GRADE 2	PFS ≥3-<6 months	○
	ORR (PR+CR) ≥40-<60%	○
	ORR (PR+CR) ≥20-<40% AND DoR ≥6-<9 months	○
GRADE 1	PFS 2-<3 months	○
	ORR(PR+CR) ≥20-<40% AND DoR <6 months	○
	ORR (PR+CR) >10-<20% AND DoR ≥6 months	○

Mark with √ if relevant

Preliminary magnitude of clinical benefit grade (highest grade scored)	**3**	**2**	**1**
	✓		

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

CR, complete response; DoR, duration of response; ORR, overall response rate; PFS, progression-free survival; PR, partial response

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

Quality of life/Grade 3-4 toxicities* assessment

Was QoL evaluated as secondary outcome?	○
Does secondary endpoint QoL show improvement?	○
Are there ≥30% grade 3-4 toxicities impacting on daily well-being?*	○

*This does not include alopecia, myelosuppression, but rather chronic nausea, diarrhoea, fatigue, etc.

Mark with √ if relevant

Adjustments

A Downgrade 1 level if there are ≥30% grade 3-4 toxicities impacting on daily well-being*

B Upgrade 1 level if improved QoL

C Upgrade 1 level for confirmatory, adequately sized, phase 4 experience

Final adjusted magnitude of clinical benefit grade	4	3	2	1
	✓			

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

QoL, quality of life

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 1

For new approaches to adjuvant therapy or new potentially curative therapies

Name of study:	Long-Term Results (>25 Years) of a Randomized, Prospective Clinical Trial OS				
Study medicine:	CHT vs FU	**Indication:**	Adjuvant		
First author:	Bernthal et al	**Year:**	2012	**Journal:**	Cancer
Name of evaluator:					

GRADE A	>5% improvement of survival at ≥3 years follow-up	✓
	Improvements in DFS alone (primary endpoint) (HR <0.65) in studies without mature survival data	
GRADE B	≥3% BUT ≤5% improvement at ≥3 years follow-up	
	Improvement in DFS alone (primary endpoint) (HR 0.65 - 0.8) without mature survival data	
	Non inferior OS or DFS with reduced treatment toxicity or improved QoL (with validated scales)	
	Non inferior OS or DFS with reduced treatment cost as reported study outcome (with equivalent outcomes and risks)	
GRADE C	<3% improvement of survival at ≥3 years follow-up	
	Improvement in DFS alone (primary endpoint) (HR >0.8) in studies without mature survival data	
	Improvements in pCR alone (primary endpoint) by ≥30% relative AND ≥15% absolute gain in studies without mature survival data	

Mark with √ if relevant

Magnitude of clinical benefit grade (highest grade scored)	**A**	**B**	**C**
	✓		

Curative setting grading - A and B indicates a substantial magnitude of clinical benefit.

DFS, disease-free survival; HR, hazard ratio; OS, overall survival; pCR, pathologic complete response/remission; QoL, quality of life.

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 1

For new approaches to adjuvant therapy or new potentially curative therapies

Name of study:	Osteosarcoma: The Addition of Muramyl Tripeptide to CHT improves OS				
Study medicine:	MAP vs MAP-Mifamurtid	**Indication:**	Adjuvant (OS)		
First author:	Meyers et al	**Year:**	2007	**Journal:**	JCO
Name of evaluator:					

GRADE A	>5% improvement of survival at ≥3 years follow-up	✓
	Improvements in DFS alone (primary endpoint) (HR <0.65) in studies without mature survival data	
GRADE B	≥3% BUT ≤5% improvement at ≥3 years follow-up	
	Improvement in DFS alone (primary endpoint) (HR 0.65 - 0.8) without mature survival data	
	Non inferior OS or DFS with reduced treatment toxicity or improved QoL (with validated scales)	
	Non inferior OS or DFS with reduced treatment cost as reported study outcome (with equivalent outcomes and risks)	
GRADE C	<3% improvement of survival at ≥3 years follow-up	
	Improvement in DFS alone (primary endpoint) (HR >0.8) in studies without mature survival data	
	Improvements in pCR alone (primary endpoint) by ≥30% relative AND ≥15% absolute gain in studies without mature survival data	

Mark with √ if relevant

Magnitude of clinical benefit grade (highest grade scored)	**A**	**B**	**C**
	✓		

Curative setting grading - A and B indicates a substantial magnitude of clinical benefit.

DFS, disease-free survival; HR, hazard ratio; OS, overall survival; pCR, pathologic complete response/remission; QoL, quality of life.

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 3

For single-arm studies in "orphan diseases" and for diseases with "high unmet need" when primary outcome is PFS or ORR

Name of study:	cis-Dichlorodiammineplatinum (II) in Advanced Osteogenic Sarcoma				
Study medicine:	Cisplatin	**Indication:**	Advanced osteosarcoma		
First author:	Ochs JJ	**Year:**	1978	**Journal:**	Cancer Tre
Name of evaluator:					

GRADE 3	PFS ≥6 months	○
	ORR (PR+CR) ≥60%	✓
	ORR (PR+CR) ≥20-<60% AND DoR ≥9 months	○
GRADE 2	PFS ≥3-<6 months	○
	ORR (PR+CR) ≥40-<60%	○
	ORR (PR+CR) ≥20-<40% AND DoR ≥6-<9 months	○
GRADE 1	PFS 2-<3 months	○
	ORR(PR+CR) ≥20-<40% AND DoR <6 months	○
	ORR (PR+CR) >10-<20% AND DoR ≥6 months	○

Mark with √ if relevant

Preliminary magnitude of clinical benefit grade (highest grade scored)	**3**	**2**	**1**
	✓		

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

CR, complete response; DoR, duration of response; ORR, overall response rate; PFS, progression-free survival; PR, partial response

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

Quality of life/Grade 3-4 toxicities* assessment

Was QoL evaluated as secondary outcome?	○
Does secondary endpoint QoL show improvement?	○
Are there ≥30% grade 3-4 toxicities impacting on daily well-being?*	✓

*This does not include alopecia, myelosuppression, but rather chronic nausea, diarrhoea, fatigue, etc.

Mark with √ if relevant

Adjustments

A Downgrade 1 level if there are ≥30% grade 3-4 toxicities impacting on daily well-being*

B Upgrade 1 level if improved QoL

C Upgrade 1 level for confirmatory, adequately sized, phase 4 experience

Final adjusted magnitude of clinical benefit grade	4	3	2	1
	☐	✓	☐	☐

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

QoL, quality of life

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 3

For single-arm studies in "orphan diseases" and for diseases with "high unmet need" when primary outcome is PFS or ORR

Name of study:	Phase II study of CDDP, Ifo and doxo in operable primary, axial and metastatic OS				
Study medicine:	CDDP, Ifo and doxo	**Indication:**	Localized and advanced osteosarcoma		
First author:	Voute	**Year:**	1999	**Journal:**	Ann Oncol
Name of evaluator:					

GRADE 3	PFS ≥6 months	○
	ORR (PR+CR) ≥60%	○
	ORR (PR+CR) ≥20-<60% AND DoR ≥9 months	✓
GRADE 2	PFS ≥3-<6 months	○
	ORR (PR+CR) ≥40-<60%	○
	ORR (PR+CR) ≥20-<40% AND DoR ≥6-<9 months	○
GRADE 1	PFS 2-<3 months	○
	ORR(PR+CR) ≥20-<40% AND DoR <6 months	○
	ORR (PR+CR) >10-<20% AND DoR ≥6 months	○

Mark with √ if relevant

Preliminary magnitude of clinical benefit grade (highest grade scored)	**3**	**2**	**1**
	✓		

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

CR, complete response; DoR, duration of response; ORR, overall response rate; PFS, progression-free survival; PR, partial response

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

Quality of life/Grade 3-4 toxicities* assessment

Was QoL evaluated as secondary outcome?	○
Does secondary endpoint QoL show improvement?	○
Are there ≥30% grade 3-4 toxicities impacting on daily well-being?*	○

*This does not include alopecia, myelosuppression, but rather chronic nausea, diarrhoea, fatigue, etc.

Mark with √ if relevant

Adjustments

A Downgrade 1 level if there are ≥30% grade 3-4 toxicities impacting on daily well-being*

B Upgrade 1 level if improved QoL

C Upgrade 1 level for confirmatory, adequately sized, phase 4 experience

Final adjusted magnitude of clinical benefit grade	4	3	2	1
	✓			

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

QoL, quality of life

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 3

For single-arm studies in "orphan diseases" and for diseases with "high unmet need" when primary outcome is PFS or ORR

Name of study:	Ifosfamide and Etoposide in Childhood OS. A Phase II Study of the Frech Society				
Study medicine:	Ifo-VP16	**Indication:**	Advanced osteosarcoma		
First author:	Gentet et al	**Year:**	1997	**Journal:**	Eur J Cance
Name of evaluator:					

GRADE 3	PFS ≥6 months	○
	ORR (PR+CR) ≥60%	○
	ORR (PR+CR) ≥20-<60% AND DoR ≥9 months	○
GRADE 2	PFS ≥3-<6 months	○
	ORR (PR+CR) ≥40-<60%	✓
	ORR (PR+CR) ≥20-<40% AND DoR ≥6-<9 months	○
GRADE 1	PFS 2-<3 months	○
	ORR(PR+CR) ≥20-<40% AND DoR <6 months	○
	ORR (PR+CR) >10-<20% AND DoR ≥6 months	○

Mark with √ if relevant

Preliminary magnitude of clinical benefit grade (highest grade scored)	**3**	**2**	**1**
	○	✓	○

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

CR, complete response; DoR, duration of response; ORR, overall response rate; PFS, progression-free survival; PR, partial response

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

Quality of life/Grade 3-4 toxicities* assessment

Was QoL evaluated as secondary outcome?	○
Does secondary endpoint QoL show improvement?	○
Are there ≥30% grade 3-4 toxicities impacting on daily well-being?*	○

*This does not include alopecia, myelosuppression, but rather chronic nausea, diarrhoea, fatigue, etc.

Mark with √ if relevant

Adjustments

A Downgrade 1 level if there are ≥30% grade 3-4 toxicities impacting on daily well-being*

B Upgrade 1 level if improved QoL

C Upgrade 1 level for confirmatory, adequately sized, phase 4 experience

Final adjusted magnitude of clinical benefit grade	4	3	2	1
	☐	✓	☐	☐

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

QoL, quality of life

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 3

For single-arm studies in "orphan diseases" and for diseases with "high unmet need" when primary outcome is PFS or ORR

Name of study:	HDIFO in Relapsed Pediatric OS: Therapeutic Effects and Renal Toxicity				
Study medicine:	HDIFO	**Indication:**	Advanced osteosarcoma		
First author:	Berrak	**Year:**	2005	**Journal:**	Pediatr Bloo
Name of evaluator:					

GRADE 3	PFS ≥6 months	○
	ORR (PR+CR) ≥60%	✓
	ORR (PR+CR) ≥20-<60% AND DoR ≥9 months	○
GRADE 2	PFS ≥3-<6 months	○
	ORR (PR+CR) ≥40-<60%	○
	ORR (PR+CR) ≥20-<40% AND DoR ≥6-<9 months	○
GRADE 1	PFS 2-<3 months	○
	ORR(PR+CR) ≥20-<40% AND DoR <6 months	○
	ORR (PR+CR) >10-<20% AND DoR ≥6 months	○

Mark with √ if relevant

Preliminary magnitude of clinical benefit grade (highest grade scored)	**3**	**2**	**1**
	✓		

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

CR, complete response; DoR, duration of response; ORR, overall response rate; PFS, progression-free survival; PR, partial response

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

Quality of life/Grade 3-4 toxicities* assessment

Was QoL evaluated as secondary outcome?	○
Does secondary endpoint QoL show improvement?	○
Are there ≥30% grade 3-4 toxicities impacting on daily well-being?*	○

*This does not include alopecia, myelosuppression, but rather chronic nausea, diarrhoea, fatigue, etc.

Mark with √ if relevant

Adjustments

A Downgrade 1 level if there are ≥30% grade 3-4 toxicities impacting on daily well-being*

B Upgrade 1 level if improved QoL

C Upgrade 1 level for confirmatory, adequately sized, phase 4 experience

Final adjusted magnitude of clinical benefit grade	4	3	2	1
	✓			

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

QoL, quality of life

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 3

For single-arm studies in "orphan diseases" and for diseases with "high unmet need" when primary outcome is PFS or ORR

Name of study:	Sorafenib and everolimus for patients with unresectable high-grade osteosarcoma				
Study medicine:	Sorafenib+everolimus	**Indication:**	Advanced osteosarcoma		
First author:	Grignani	**Year:**	2015	**Journal:**	Lancet Onco
Name of evaluator:					

GRADE 3	PFS ≥6 months	○
	ORR (PR+CR) ≥60%	○
	ORR (PR+CR) ≥20-<60% AND DoR ≥9 months	○
GRADE 2	PFS ≥3-<6 months	✓
	ORR (PR+CR) ≥40-<60%	○
	ORR (PR+CR) ≥20-<40% AND DoR ≥6-<9 months	○
GRADE 1	PFS 2-<3 months	○
	ORR(PR+CR) ≥20-<40% AND DoR <6 months	○
	ORR (PR+CR) >10-<20% AND DoR ≥6 months	○

Mark with √ if relevant

Preliminary magnitude of clinical benefit grade (highest grade scored)	**3**	**2**	**1**
	☐	✓	☐

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

CR, complete response; DoR, duration of response; ORR, overall response rate; PFS, progression-free survival; PR, partial response

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

Quality of life/Grade 3-4 toxicities* assessment

Was QoL evaluated as secondary outcome?	○
Does secondary endpoint QoL show improvement?	○
Are there ≥30% grade 3-4 toxicities impacting on daily well-being?*	○

*This does not include alopecia, myelosuppression, but rather chronic nausea, diarrhoea, fatigue, etc.

Mark with √ if relevant

Adjustments

A Downgrade 1 level if there are ≥30% grade 3-4 toxicities impacting on daily well-being*

B Upgrade 1 level if improved QoL

C Upgrade 1 level for confirmatory, adequately sized, phase 4 experience

Final adjusted magnitude of clinical benefit grade	4	3	2	1
	☐	☐	✓	☐

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

QoL, quality of life

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 3

For single-arm studies in "orphan diseases" and for diseases with "high unmet need" when primary outcome is PFS or ORR

Name of study:	Efficacy and safety of regorafenib in adult patients with metastatic OS-REGOBONE				
Study medicine:	Regorafenib	**Indication:**	Advanced osteosarcoma		
First author:	Duffaud et al	**Year:**	2019	**Journal:**	Lancet Onco
Name of evaluator:					

GRADE 3	PFS ≥6 months	○
	ORR (PR+CR) ≥60%	○
	ORR (PR+CR) ≥20-<60% AND DoR ≥9 months	○
GRADE 2	PFS ≥3-<6 months	✓
	ORR (PR+CR) ≥40-<60%	○
	ORR (PR+CR) ≥20-<40% AND DoR ≥6-<9 months	○
GRADE 1	PFS 2-<3 months	○
	ORR(PR+CR) ≥20-<40% AND DoR <6 months	○
	ORR (PR+CR) >10-<20% AND DoR ≥6 months	○

Mark with √ if relevant

Preliminary magnitude of clinical benefit grade (highest grade scored)	**3**	**2**	**1**
	☐	✓	☐

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

CR, complete response; DoR, duration of response; ORR, overall response rate; PFS, progression-free survival; PR, partial response

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

Quality of life/Grade 3-4 toxicities* assessment

Was QoL evaluated as secondary outcome?	○
Does secondary endpoint QoL show improvement?	○
Are there ≥30% grade 3-4 toxicities impacting on daily well-being?*	○

*This does not include alopecia, myelosuppression, but rather chronic nausea, diarrhoea, fatigue, etc.

Mark with √ if relevant

Adjustments

A Downgrade 1 level if there are ≥30% grade 3-4 toxicities impacting on daily well-being*

B Upgrade 1 level if improved QoL

C Upgrade 1 level for confirmatory, adequately sized, phase 4 experience

Final adjusted magnitude of clinical benefit grade	4	3	2	1
	☐	☐	✓	☐

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

QoL, quality of life

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 3

For single-arm studies in "orphan diseases" and for diseases with "high unmet need" when primary outcome is PFS or ORR

Name of study:	rEECur (Gemcitabine-docetaxel)				
Study medicine:	Gem-Doc	**Indication:**	Advanced Ewing		
First author:	McCabe	**Year:**	2019	**Journal:**	ASCO
Name of evaluator:					

GRADE 3	PFS ≥6 months	○
	ORR (PR+CR) ≥60%	○
	ORR (PR+CR) ≥20-<60% AND DoR ≥9 months	○
GRADE 2	PFS ≥3-<6 months	✓
	ORR (PR+CR) ≥40-<60%	○
	ORR (PR+CR) ≥20-<40% AND DoR ≥6-<9 months	○
GRADE 1	PFS 2-<3 months	○
	ORR(PR+CR) ≥20-<40% AND DoR <6 months	○
	ORR (PR+CR) >10-<20% AND DoR ≥6 months	○

Mark with √ if relevant

Preliminary magnitude of clinical benefit grade (highest grade scored)	**3**	**2**	**1**
	☐	✓	☐

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

CR, complete response; DoR, duration of response; ORR, overall response rate; PFS, progression-free survival; PR, partial response

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

Quality of life/Grade 3-4 toxicities* assessment

Was QoL evaluated as secondary outcome?	○
Does secondary endpoint QoL show improvement?	○
Are there ≥30% grade 3-4 toxicities impacting on daily well-being?*	○

*This does not include alopecia, myelosuppression, but rather chronic nausea, diarrhoea, fatigue, etc.

Mark with √ if relevant

Adjustments

A Downgrade 1 level if there are ≥30% grade 3-4 toxicities impacting on daily well-being*

B Upgrade 1 level if improved QoL

C Upgrade 1 level for confirmatory, adequately sized, phase 4 experience

Final adjusted magnitude of clinical benefit grade	4	3	2	1
	☐	☐	✓	☐

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

QoL, quality of life

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 3

For single-arm studies in "orphan diseases" and for diseases with "high unmet need" when primary outcome is PFS or ORR

Name of study:	GEIS 21				
Study medicine:	Gem-Doc (window)	**Indication:**	Newly diagnosed ES(axial and 23%M)		
First author:	Mora J	**Year:**	2017	**Journal:**	BJC
Name of evaluator:					

GRADE 3	PFS ≥6 months	○
	ORR (PR+CR) ≥60%	○
	ORR (PR+CR) ≥20-<60% AND DoR ≥9 months	○
GRADE 2	PFS ≥3-<6 months	○
	ORR (PR+CR) ≥40-<60%	✓
	ORR (PR+CR) ≥20-<40% AND DoR ≥6-<9 months	○
GRADE 1	PFS 2-<3 months	○
	ORR(PR+CR) ≥20-<40% AND DoR <6 months	○
	ORR (PR+CR) >10-<20% AND DoR ≥6 months	○

Mark with √ if relevant

Preliminary magnitude of clinical benefit grade (highest grade scored)	**3**	**2**	**1**
	☐	✓	☐

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

CR, complete response; DoR, duration of response; ORR, overall response rate; PFS, progression-free survival; PR, partial response

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

Quality of life/Grade 3-4 toxicities* assessment

Was QoL evaluated as secondary outcome?	○
Does secondary endpoint QoL show improvement?	○
Are there ≥30% grade 3-4 toxicities impacting on daily well-being?*	○

*This does not include alopecia, myelosuppression, but rather chronic nausea, diarrhoea, fatigue, etc.

Mark with √ if relevant

Adjustments

A Downgrade 1 level if there are ≥30% grade 3-4 toxicities impacting on daily well-being*

B Upgrade 1 level if improved QoL

C Upgrade 1 level for confirmatory, adequately sized, phase 4 experience

Final adjusted magnitude of clinical benefit grade	4	3	2	1
	☐	☐	✓	☐

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

QoL, quality of life

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 3

For single-arm studies in "orphan diseases" and for diseases with "high unmet need" when primary outcome is PFS or ORR

Name of study:	Prolonged 14-Day Continuous Infusion of High-Dose Ifosfamide				
Study medicine:	HDIFO	**Indication:**	Refractory sarcoma		
First author:	Meazza	**Year:**	2010	**Journal:**	Ped Blood C
Name of evaluator:					

GRADE 3	PFS ≥6 months	○
	ORR (PR+CR) ≥60%	✓
	ORR (PR+CR) ≥20-<60% AND DoR ≥9 months	○
GRADE 2	PFS ≥3-<6 months	○
	ORR (PR+CR) ≥40-<60%	○
	ORR (PR+CR) ≥20-<40% AND DoR ≥6-<9 months	○
GRADE 1	PFS 2-<3 months	○
	ORR(PR+CR) ≥20-<40% AND DoR <6 months	○
	ORR (PR+CR) >10-<20% AND DoR ≥6 months	○

Mark with √ if relevant

Preliminary magnitude of clinical benefit grade (highest grade scored)	**3**	**2**	**1**
	✓		

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

CR, complete response; DoR, duration of response; ORR, overall response rate; PFS, progression-free survival; PR, partial response

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

Quality of life/Grade 3-4 toxicities* assessment

Was QoL evaluated as secondary outcome?	○
Does secondary endpoint QoL show improvement?	○
Are there ≥30% grade 3-4 toxicities impacting on daily well-being?*	○

*This does not include alopecia, myelosuppression, but rather chronic nausea, diarrhoea, fatigue, etc.

Mark with √ if relevant

Adjustments

A Downgrade 1 level if there are ≥30% grade 3-4 toxicities impacting on daily well-being*

B Upgrade 1 level if improved QoL

C Upgrade 1 level for confirmatory, adequately sized, phase 4 experience

Final adjusted magnitude of clinical benefit grade	4	3	2	1
	☐	✓	☐	☐

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

QoL, quality of life

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 1

For new approaches to adjuvant therapy or new potentially curative therapies

Name of study:	One vs Three Years of Adjuvant Imatinib for Operable GIST				
Study medicine:	Imatinib 1 vs 3 y	**Indication:**	Adjuvant		
First author:	Joensuu	**Year:**	2012	**Journal:**	JAMA
Name of evaluator:					

GRADE A	>5% improvement of survival at ≥3 years follow-up	✓
	Improvements in DFS alone (primary endpoint) (HR <0.65) in studies without mature survival data	
GRADE B	≥3% BUT ≤5% improvement at ≥3 years follow-up	
	Improvement in DFS alone (primary endpoint) (HR 0.65 - 0.8) without mature survival data	
	Non inferior OS or DFS with reduced treatment toxicity or improved QoL (with validated scales)	
	Non inferior OS or DFS with reduced treatment cost as reported study outcome (with equivalent outcomes and risks)	
GRADE C	<3% improvement of survival at ≥3 years follow-up	
	Improvement in DFS alone (primary endpoint) (HR >0.8) in studies without mature survival data	
	Improvements in pCR alone (primary endpoint) by ≥30% relative AND ≥15% absolute gain in studies without mature survival data	

Mark with √ if relevant

Magnitude of clinical benefit grade (highest grade scored)	**A**	**B**	**C**
	✓		

Curative setting grading - A and B indicates a substantial magnitude of clinical benefit.

DFS, disease-free survival; HR, hazard ratio; OS, overall survival; pCR, pathologic complete response/remission; QoL, quality of life.

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 3

For single-arm studies in "orphan diseases" and for diseases with "high unmet need" when primary outcome is PFS or ORR

Name of study:	Safety and efficacy of imatinib (STI571) in metastatic GIST				
Study medicine:	Imatinib	**Indication:**	Advanced GIST		
First author:	van Oosterom	**Year:**	2001	**Journal:**	Lancet
Name of evaluator:					

GRADE 3	PFS ≥6 months	✓
	ORR (PR+CR) ≥60%	
	ORR (PR+CR) ≥20-<60% AND DoR ≥9 months	
GRADE 2	PFS ≥3-<6 months	
	ORR (PR+CR) ≥40-<60%	
	ORR (PR+CR) ≥20-<40% AND DoR ≥6-<9 months	
GRADE 1	PFS 2-<3 months	
	ORR(PR+CR) ≥20-<40% AND DoR <6 months	
	ORR (PR+CR) >10-<20% AND DoR ≥6 months	

Mark with √ if relevant

Preliminary magnitude of clinical benefit grade (highest grade scored)	**3**	**2**	**1**
	✓		

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

CR, complete response; DoR, duration of response; ORR, overall response rate; PFS, progression-free survival; PR, partial response

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

Quality of life/Grade 3-4 toxicities* assessment

Was QoL evaluated as secondary outcome?	○
Does secondary endpoint QoL show improvement?	○
Are there ≥30% grade 3-4 toxicities impacting on daily well-being?*	○

*This does not include alopecia, myelosuppression, but rather chronic nausea, diarrhoea, fatigue, etc.

Mark with √ if relevant

Adjustments

A Downgrade 1 level if there are ≥30% grade 3-4 toxicities impacting on daily well-being*

B Upgrade 1 level if improved QoL

C Upgrade 1 level for confirmatory, adequately sized, phase 4 experience

Final adjusted magnitude of clinical benefit grade	4	3	2	1
	✓			

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

QoL, quality of life

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 2B

For therapies that are not likely to be curative with primary endpoint of PFS

Name of study:	Efficacy and safety of sunitinib in patients with advanced GIST				
Study medicine:	Sunitinib vs placebo	**Indication:**	Pretreated GIST		
First author:	Demetri et al	**Year:**	2006	**Journal:**	Lancet
Name of evaluator:					

If median PFS with standard treatment ≤6 months

GRADE 3	HR ≤0.65 AND gain ≥1.5 months	✓
GRADE 2	HR ≤0.65 BUT gain <1.5 months	
GRADE 1	HR >0.65	

Mark with √ if relevant

Preliminary magnitude of clinical benefit grade (highest grade scored)	**3**	**2**	**1**
	✓		

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

HR, hazard ratio; PFS, progression-free survival

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

Early stopping or crossover

Did the study have an early stopping rule based on interim analysis of survival?	✓
Was the randomization terminated early based on the detection of overall survival advantage at interim analysis?	

If the answer to both is "yes", then see letter "E" in the adjustment section below

Mark with √ if relevant

Toxicity assessment

Is the new treatment associated with a statistically significant incremental rate of:

«Toxic» death >2%	
Cardiovascular ischemia >2%	
Hospitalisation for «toxicity» >10%	
Excess rate of severe CHF >4%	
Grade 3 neurotoxicity >10%	
Severe other irreversible or long lasting toxicity >2% please specify:	

(Incremental rate refers to the comparison versus standard therapy in the control arm)

Mark with √ if relevant

Quality of life/Grade 3-4 toxicities* assessment

Was QoL evaluated as secondary outcome?	
Does secondary endpoint QoL show improvement?	
Are there statistically significantly less grade 3-4 toxicities impacting on daily well-being?*	

*This does not include alopecia, myelosuppression, but rather chronic nausea, diarrhoea, fatigue, etc.

Mark with √ if relevant

CHF, congestive heart failure; QoL, quality of Life

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

Adjustments

A When OS as secondary endpoint shows improvement, it will prevail and the new scoring will be done according to form 2a.

B Downgrade 1 level if there is one or more of the above incremental toxicities associated with the new medicine.

C Downgrade 1 level if the medicine ONLY leads to improved PFS (mature data shows no OS advantage) and QoL assessment does not demonstrate improved QoL.

D Upgrade 1 level if improved QoL or if less grade 3-4 toxicities that bother patients are demonstrated.

E Upgrade 1 level if study had early crossover because of early stopping or crossover based on detection of survival advantage at interim analysis.

F Upgrade 1 level if there is a long-term plateau in the PFS curve, and there is >10% improvement in PFS at 1 year.

Final, toxicity and QoL adjusted, magnitude of clinical benefit grade	4	3	2	1
	✓			

Highest magnitude clinic benefit grade that can be achieved grade 4.

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

PFS, progression-free survival; OS, overall survival; QoL, quality of life

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 2A

For therapies that are not likely to be curative with primary endpoint of OS

Name of study:	Complete Longitudinal Analyses of the Randomized, Placebo-Controlled…				
Study medicine:	Sunitinib vs placebo	**Indication:**	Advanced GIST after imatinib		
First author:	Demetri G	**Year:**	2012	**Journal:**	Clin Can Re
Name of evaluator:					

If median OS with the standard treatment is ≤12 months

GRADE 4	HR ≤0.65 AND gain ≥3 months	✓
	Increase in 2 year survival ≥10%	
GRADE 3	HR ≤0.65 AND gain ≥2.0-<3 months	
GRADE 2	HR ≤0.65 AND gain ≥1.5-<2.0	
	HR >0.65-0.70 AND gain ≥1.5 months	
GRADE 1	HR >0.70 OR gain <1.5 months	

Mark with √ if relevant

Preliminary magnitude of clinical benefit grade (highest grade scored)	**4**	**3**	**2**	**1**
	✓			

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

HR, hazard ratio; OS, overall survival

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

Quality of life/Grade 3-4 toxicities* assessment

Does secondary endpoint QoL show improvement?	○
Are there statistically significantly less grade 3-4 toxicities impacting on daily well-being?*	○

*This does not include alopecia, myelosuppression, but rather chronic nausea,diarrhoea, fatigue, etc.

Mark with √ if relevant

Adjustments

01. Upgrade 1 level if improved QoL and/or less grade 3-4 toxicities impacting daily well-being are shown

02. If there is a long term plateau in the survival curve, and OS advantage continues to be observed at 5 years, also score according to form 1 (treatments with curative potential) and present both scores i.e. A/4.

Final adjusted magnitude of clinical benefit grade	5	4	3	2	1
	☐	✓	☐	☐	☐

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

OS, overall survival; QoL, quality of Life

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 2B

For therapies that are not likely to be curative with primary endpoint of PFS

Name of study:	Efficacy and safety of regorafenib for advanced GIST (GRID)				
Study medicine:	Regorafenib vs placebo	**Indication:**	Pretreated GIST		
First author:	Demetri et al	**Year:**	2013	**Journal:**	Lancet Onco
Name of evaluator:					

If median PFS with standard treatment ≤6 months

GRADE 3	HR ≤0.65 AND gain ≥1.5 months	✓
GRADE 2	HR ≤0.65 BUT gain <1.5 months	
GRADE 1	HR >0.65	

Mark with √ if relevant

Preliminary magnitude of clinical benefit grade (highest grade scored)	**3**	**2**	**1**
	✓		

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

HR, hazard ratio; PFS, progression-free survival

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

Early stopping or crossover

Did the study have an early stopping rule based on interim analysis of survival?	○
Was the randomization terminated early based on the detection of overall survival advantage at interim analysis?	○

If the answer to both is "yes", then see letter "E" in the adjustment section below

Mark with √ if relevant

Toxicity assessment

Is the new treatment associated with a statistically significant incremental rate of:

«Toxic» death >2%	○
Cardiovascular ischemia >2%	○
Hospitalisation for «toxicity» >10%	○
Excess rate of severe CHF >4%	○
Grade 3 neurotoxicity >10%	○
Severe other irreversible or long lasting toxicity >2% please specify:	○

(Incremental rate refers to the comparison versus standard therapy in the control arm)

Mark with √ if relevant

Quality of life/Grade 3-4 toxicities* assessment

Was QoL evaluated as secondary outcome?	✓
Does secondary endpoint QoL show improvement?	○
Are there statistically significantly less grade 3-4 toxicities impacting on daily well-being?*	○

*This does not include alopecia, myelosuppression, but rather chronic nausea, diarrhoea, fatigue, etc.

Mark with √ if relevant

CHF, congestive heart failure; QoL, quality of Life

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

Adjustments

A When OS as secondary endpoint shows improvement, it will prevail and the new scoring will be done according to form 2a.

B Downgrade 1 level if there is one or more of the above incremental toxicities associated with the new medicine.

C Downgrade 1 level if the medicine ONLY leads to improved PFS (mature data shows no OS advantage) and QoL assessment does not demonstrate improved QoL.

D Upgrade 1 level if improved QoL or if less grade 3-4 toxicities that bother patients are demonstrated.

E Upgrade 1 level if study had early crossover because of early stopping or crossover based on detection of survival advantage at interim analysis.

F Upgrade 1 level if there is a long-term plateau in the PFS curve, and there is >10% improvement in PFS at 1 year.

Final, toxicity and QoL adjusted, magnitude of clinical benefit grade	4	3	2	1
	☐	✓	☐	☐

Highest magnitude clinic benefit grade that can be achieved grade 4.

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

PFS, progression-free survival; OS, overall survival; QoL, quality of life

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 2B

For therapies that are not likely to be curative with primary endpoint of PFS

Name of study:	INVICTUS				
Study medicine:	Ripretinib vs placebo	**Indication:**	Pretreated GIST		
First author:	Von Mehren et al	**Year:**	2019	**Journal:**	ESMO
Name of evaluator:					

If median PFS with standard treatment ≤6 months

GRADE 3	HR ≤0.65 AND gain ≥1.5 months	✓
GRADE 2	HR ≤0.65 BUT gain <1.5 months	
GRADE 1	HR >0.65	

Mark with √ if relevant

Preliminary magnitude of clinical benefit grade (highest grade scored)	**3**	**2**	**1**
	✓		

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

HR, hazard ratio; PFS, progression-free survival

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

Early stopping or crossover

Did the study have an early stopping rule based on interim analysis of survival?	○
Was the randomization terminated early based on the detection of overall survival advantage at interim analysis?	○

If the answer to both is "yes", then see letter "E" in the adjustment section below

Mark with √ if relevant

Toxicity assessment

Is the new treatment associated with a statistically significant incremental rate of:

«Toxic» death >2%	○
Cardiovascular ischemia >2%	○
Hospitalisation for «toxicity» >10%	○
Excess rate of severe CHF >4%	○
Grade 3 neurotoxicity >10%	○
Severe other irreversible or long lasting toxicity >2% please specify:	○

(Incremental rate refers to the comparison versus standard therapy in the control arm)

Mark with √ if relevant

Quality of life/Grade 3-4 toxicities* assessment

Was QoL evaluated as secondary outcome?	✓
Does secondary endpoint QoL show improvement?	○
Are there statistically significantly less grade 3-4 toxicities impacting on daily well-being?*	○

*This does not include alopecia, myelosuppression, but rather chronic nausea, diarrhoea, fatigue, etc.

Mark with √ if relevant

CHF, congestive heart failure; QoL, quality of Life

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

Adjustments

A When OS as secondary endpoint shows improvement, it will prevail and the new scoring will be done according to form 2a.

B Downgrade 1 level if there is one or more of the above incremental toxicities associated with the new medicine.

C Downgrade 1 level if the medicine ONLY leads to improved PFS (mature data shows no OS advantage) and QoL assessment does not demonstrate improved QoL.

D Upgrade 1 level if improved QoL or if less grade 3-4 toxicities that bother patients are demonstrated.

E Upgrade 1 level if study had early crossover because of early stopping or crossover based on detection of survival advantage at interim analysis.

F Upgrade 1 level if there is a long-term plateau in the PFS curve, and there is >10% improvement in PFS at 1 year.

Final, toxicity and QoL adjusted, magnitude of clinical benefit grade	4	3	2	1
	✓			

Highest magnitude clinic benefit grade that can be achieved grade 4.

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

PFS, progression-free survival; OS, overall survival; QoL, quality of life

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 EVALUATION FORM 2A

For therapies that are not likely to be curative with primary endpoint of OS

Name of study:	INVICTUS				
Study medicine:	Ripretinib vs placebo	**Indication:**	Pretreated GIST		
First author:	Von Mehren et al	**Year:**	2019	**Journal:**	ESMO
Name of evaluator:					

If median OS with the standard treatment is ≤12 months

GRADE 4	HR ≤0.65 AND gain ≥3 months	✓
	Increase in 2 year survival ≥10%	
GRADE 3	HR ≤0.65 AND gain ≥2.0-<3 months	
GRADE 2	HR ≤0.65 AND gain ≥1.5-<2.0	
	HR >0.65-0.70 AND gain ≥1.5 months	
GRADE 1	HR >0.70 OR gain <1.5 months	

Mark with √ if relevant

Preliminary magnitude of clinical benefit grade (highest grade scored)	4	3	2	1
	✓			

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

HR, hazard ratio; OS, overall survival

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

Quality of life/Grade 3-4 toxicities* assessment

Does secondary endpoint QoL show improvement?	○
Are there statistically significantly less grade 3-4 toxicities impacting on daily well-being?*	✓

*This does not include alopecia, myelosuppression, but rather chronic nausea,diarrhoea, fatigue, etc.

Mark with √ if relevant

Adjustments

01. Upgrade 1 level if improved QoL and/or less grade 3-4 toxicities impacting daily well-being are shown

02. If there is a long term plateau in the survival curve, and OS advantage continues to be observed at 5 years, also score according to form 1 (treatments with curative potential) and present both scores i.e. A/4.

Final adjusted magnitude of clinical benefit grade	**5**	**4**	**3**	**2**	**1**
	✓				

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

OS, overall survival; QoL, quality of Life