Letter to Editor

Utilisation of the ESMO-MCBS in practice of HTA

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(Accepted for publication Annals of Oncology – Please keep Confidential).

Disclosure: The authors have declared no conflicts of interest.

It is highly appreciated that the European Society of Medical Oncology has developed a system to assess new oncologic compounds according to their value to patients. Consequently, offering decision-support to those who either want to use the new cancer therapies in clinical practice but cannot keep up-to-date with all therapy options or, alternatively, to those who have to decide whether or not to fund new oncology medicines or exclude from reimbursement due to their low value. This is particularly important with ever-rising prices for new oncology medicines which have increased up to ten fold in recent years.

Having established a horizon-scanning system for new oncology medicines for Austria [1] since 2009, we have extensive experience with the early assessment of newly approved therapies for patients with cancer (n=59). Until recently, these assessments have not included recommendations. We are now considering an adapted version of the ESMO-MCBS. With the aim of piloting and validating the ESMO-MCBS – as suggested by Hartmann [2] - we – 3 researchers, blinded to ESMO scores, blinded to each other´s scoring - rated drugs in 3 indications (colorectal carcinoma, melanoma and lung cancer) which had been assessed by the Austrian HSO programme as well as having been scored by ESMO (n=11) (Table 1).

Table 1: Adapted benefit assessment based on ESMO-MBSC

Active substance (Trial name)	Indication	Intention	PE (SE)	Form	MG standard treatment	Efficacy				Safety		Adjustments	HSO	ESMO
						MG (months)	*HR (95% CI)*	*Score calculation*	*PM*	*Toxicity*	*QoL*			
Aflibercept (VELOUR)	mCRC (2nd line)	Not curative	OS	2a	>1 year	1.44	0.817 (0.71-0.94)	HR > 0.75 OR OS < 1.5 m	1	+21% ≥ grade 3 AE; ~15% AEs lead to discontinuation (-1)	-	-1	**1 (0)**	**1**
Regorafenib (CORRECT)	mCRC	Not curative	OS	2a	≤1 year	1.4	0.77 (0.64-0.94)	HR > 0.75 OR OS < 1.5 m	1	+21% ≥ grade 3 AE; 76% dose reduction or interruption due to AE (-1)	NO impr.	-1	**1 (0)**	**1**
Nab-Paclitaxel (MPACT)	m adenocarcinoma of the pancreas (1st line)	Not curative	OS	2a	≤1 year	1.8	0.72 (0.62-0.83)	HR > 0.70 OR OS < 1.5 m HR > 0.65 OR OS < 1.5 - 2.4m	1-2	+ 1-16% ≥grade 3 AE; ~20% AEs lead to discontinuation (-1)	-	-1	**1**	**3**
Afatinib (LUX3)	locally advanced/ mNSCLC (1st line)	Not curative	PFS (OS)	2a[1]	>1 year	1.8	OS: 1.12 (0.73–1.73)	HR >0.70-0.75 OR OS 1.5-2.9 m	2	+1%≥grade 3 AE; +4% discontinuation	impr QoL: +1	+1	**3**	**4**
Afatinib (LUX6)	locally advanced/ mNSCLC (1st line)	Not curative	PFS (OS)	2b	≤6 months	5.4 **(-0.1)**	PFS: 0.28 (0.20–0.39)	HR ≤ 0.65 AND PFS ≥ 1.5m	3	grade5: -0.5; **-33,9% discontinuation** (+1)		+1/-1[2]	**3**	**4**
Crizotinib (Profile 1007)	NSCLC (ALK positiv) (>1 therapie)	Not curative	PFS (OS)	2b	≤6 months	4.7 (not reached)	PFS: 0.49 (0.37–0.64)	HR ≤ 0.65 AND PFS ≥ 1.5m	3	+1-14% ≥grade 3 AE; **+11% grade 5** (-1)	benef.f or interve ntion group +1	+1/-1	**3**	**4**
Erlotinib (OPTIMAL, CTONG-0802)	NSCLC (1st line)	Not curative	PFS (OS)	2b	>1 year	8.5 (not reached)	PFS:0.16 (0.10-0.26)	HR ≤ 0.65 AND PFS ≥ 1.5m	3	-12% SAE (+1)	improved QoL: +1	+1/-1[3]	**3**	**4**
Erlotinib (EURTAC)	NSCLC (1st line)	Not curative	PFS (OS)	2a[4]	>1 year	4.5 (4.1)	OS: 0.80 (0.47–1.37)	HR >0.70-0.75 OR OS ≥ 1.5-2.9m	3	+4% grade 5 -25% % ≥grade 3 AE (+1)	-	+1	**4**	**4**
Gefitinib (IPASS)	locally advanced/ m NSCLC (EGRF) (1st line)	Not curative	PFS (OS)	2a[5]	>6 months	3.2 **(-0.3)**	OS: HR 1.00 (0.76 - 1.33)	HR >0.70 OR gain <1.5m	1	+1,1% grade 5 -32.3% ≥grade 3 AE (+1)	improved QoL +1 -1/ OS	+1/-1[6]	**1-2**	**4**
Ipilimumab (NN)	advanced & mMelanoma (1st line)	Not curative	OS	2a	≤1 year	2.1	0.72 (0.59–0.87)	HR > 0.65-0.70 OR OS < 1.5-2.4 m	2	+28 ≥grade 3 AE : Grade (-1)	-	-1	**1**	**3**
Nivolumab (CheckMate66)	inoperable/ metastatic melanoma (1st line)	Not curative	OS (PFS)	2b[7]	≤6 months	+30.8% (2.9)	PFS: 0.43 (0.34-0.56)	HR ≤ 0.65 AND PFS ≥ 1.5m	3	-5.4% ≥grade 3 AE	2d:-1[8]	-1[9]	**2**	**4**
Trametinib (METRIC)	advanced/ mMelanoma (BRAF V600 mutation)	Not curative	PFS (OS)	2b	≤1 year	PFS:3.3 OS: +14%	PFS: 0.45 (0.33-0.63)	HR ≤ 0.65 AND PFS ≥ 1.5m	3	+8%≥grade 3 AE;	2d:-1	-1[8]	**2**	**4**
Vemurafenib (BRIM-3)	melanoma (BRAF V600 mutation) (1st line)	Not curative	OS	2a	≤1 year	3.9	0.70 (0.57-0.87)	HR > 0.65-0.70 OR OS 1.5-2.4m	2-3	≥grade 3 AE **+18% cSCC** (-1) +5% discontinuation	-	-1	**2**	**4**

Abbrevations: AE=adverse events; HR = hazard ratio, m = months, MG = median gain, PE = primary endpoint, SAE= Serious adverse events, SE= secondary endpoint, QoL = quality of life

1 Median OS data from Updated analysis; form 2a was used, since OS data available
2 only PFS data, OS not available
3 only PFS data, OS not available
4 form 2a was used, since OS data available
5 form 2a was used, since OS data available
6 reduction of OS
7 Form 2b was used although OS was the primary endpoint, but at the time of analysis it had not been reached
8 Adjustment d) Downgrade 1 level if the drug ONLY leads to improved PFS, QoL assessment does not demonstrate improvement
9 only PFS data, OS not available

In addition we discussed the ESMO-MCBS in a meeting of the Piperska-group for “rational prescribing” , a group of health authority personnel, advisers and academics from across Europe

involved with developing models to optimise the managed entry of new medicines [3, 4] and collected comments based on experiences with applying the proposed scores.

Lastly, we compared our scoring with drug-assessments of several countries (IQWiG, NICE, HAS, SMC, pCODR, etc.) [5] (table 2) and found a good correlation between oncology medicines scored with 1-2 on the ESMO-MCBS scale with oncology medicines not recommended for funding due to a lack of efficacy or poor cost-effectiveness.

Table 2: Comparison of Scoring with HTA (and conditional agreements)

Active substance	Indication	Pre-reimbursement assessments & Managed entry agreement	HSO/ ESMO
Aflibercept	mCRC (2nd line)	Germany (IQWIG): MI France (HAS): ASMR 5 England (NICE): NR Canada (pCODR): NR Belgium (RIZIV/INAMI): MEA Italy (AIFA): MEA Norway (NOKC): NL Poland (AOTMiT): PL Scotland (SMC): R	1 (0)/1
Regorafenib	mCRC	Germany (IQWIG): MI France (HAS): ASMR 5 Canada (pCODR): NR Belgium (RIZIV/INAMI): MEA Poland (AOTMiT): NL	1 (0)/1
Nab-Paclitaxel	m adenocarcinoma of the pancreas (1st line)	France (HAS): ASMR 4 England (NICE): NR Canada (pCODR): CE-Ratio Belgium (RIZIV/INAMI): MEA Italy (AIFA): MEA Poland (AOTMiT): NL Scotland (SMC): R	1/3
Afatinib	locally advanced/ mNSCLC (1st line)	Germany (IQWIG): CO France (HAS): ASMR 5 England (NICE): R Canada (pCODR): CE-Ratio Italy (AIFA): MEA Poland (AOTMiT): PL Scotland (SMC): R	3/4
Crizotinib	NSCLC (ALK positiv) (>1 Therapie)	Germany (IQWIG): CO France (HAS): ASMR 3 England (NICE): NR Canada (pCODR): CE-Ratio Belgium (RIZIV/INAMI): MEA Italy (AIFA): MEA Poland (AOTMiT): NL Scotland (SMC): R	3/4
Erlotinib	NSCLC (1st line)	France (HAS): ASMR 4 England (NICE): R Belgium (RIZIV/INAMI): MEA Italy (AIFA): MEA WHO: NE Poland (AOTMiT): PL Scotland (SMC): R	3(4)/4
Gefitinib	locally advanced/ m NSCLC (EGRF) (1st line)	France (HAS): ASMR 4 England (NICE): R Italy (AIFA): MEA WHO: NE Poland (AOTMiT): PL Scotland (SMC): R	2/4
Ipilimumab	advanced & mMelanoma (1st line)	Germany (IQWIG): NO France (HAS): ASMR 5 England (NICE): R Canada (pCODR): CE-Ratio Belgium (RIZIV/INAMI): MEA Italy (AIFA): MEA Poland (AOTMiT): PL Scotland (SMC): R	1/3
Nivolumab	inoperable/ metastatic melanoma (1st line)	Germany (IQWIG): CO Belgium (RIZIV/INAMI): MEA Norway (NOKC): PL Poland (AOTMiT): MEA Scotland (SMC): NR	2/4
Trametinib	advanced/ mMelanoma (BRAF V600 mutation)	Germany (IQWIG): NO Canada (pCODR): CE-Ratio	2/4
Vemurafenib	melanoma (BRAF V600 mutation) (1st line)	France (HAS): ASMR3 England (NICE): R Canada (pCODR): CE-Ratio Belgium (RIZIV/INAMI): MEA Italy (AIFA): MEA Poland (AOTMiT): MEA, CE-Ratio Scotland (SMC): R	2/4

NB. France: Improvement of Medical Benefit (ASMR) classification 1-5, 1= Major innovation, 2= Important improvement, 3= Significant improvement, 4= Minor improvement, 5=no improvement ; Germany: Added-benefit classification: MA =major, CO= considerable, MI=minor, NQ=not quantifiable, NO=no added-benefit; England, Canada: NR = not recommended, R = recommended; Canada, Poland: CE-ratio = not cost-effective, only with lower price; Belgium, Italy, Poland: MEA= Managed Entry Agreements; Norway, Poland: PL= positive list, NL = negative list; WHO: NE= not essential medicine

We identified several limitations to the current ESMO-MCBS. Some of them have been pointed out and discussed already by others [2, 6, 7]. As a result, we propose adaptations due to perceived limitations which include:

1. The use of the lower limit of the CI (confidence interval) rather than the point estimate is not only introducing an optimistic perspective but is also systematically favouring drugs with a large CI and therefore a low certainty in results. We find the systematic bias not acceptable and not in concordance with standards for robust data in medical statistics and clinical epidemiology.
2. The focus on primary endpoints even if they are surrogate endpoints is assigning PFS (progression-free-survival) an equal weight compared to the patient-relevant endpoints of OS (overall survival) and QoL (quality of life). This is not in accordance with HTA (health technology assessment) standards of using PRO (patient-relevant outcomes) as opposed to surrogate outcomes, which are most often not validated for their actual clinical relevance. This is especially important in solid tumours with concerns with translating surrogate markers into overall survival/ length of survival.
3. The upgrading due to increased QoL, but only rarely the downgrading of cancer drugs due to worsened QoL or (S)AE ≥ 3 (serious adverse events) and/or increased discontinuation of therapy introduces again a bias towards an optimistic perspective concentrating on efficacy and ignoring risks and adverse events.
4. Lastly, no rationale or weighted arguments are provided for the threshold-values.

As seen in Table 1, our scores deviate from ESMO due to using the point estimate instead of using the lower limit of the CI. In addition, degrading because of (S)AE or if only data on PFS is available, rather than only upgrading because of an improvement in QoL, was done. Our re-calculated deviation is on average 1-2 scores lower than the ESMO scoring. We tried to extract as many data as possible in the table to show that even using the rationale of ESMO-MCBS, some of the (optimistic) ESMO-scores are not based on their own rules (alone) and some oncology medicines are upgraded without transparent reason.

We therefore propose an adapted use of the ESMO-MCBS. This includes:

- use of only OS data - if primary or secondary endpoint data is available;
- use of only OS and QoL data in the non-curative (end of life) setting;
- downgrade -1, if only data on surrogate endpoints is available;
- use point estimates;
- down-/upgrade due to toxicity(S)AE incl. reduction of OS or changes in QoL;
- increase transparency with extracting SAE and therapy discontinuation data and reasons for up-/ downgrading.

A structured and systematic approach that can discriminate between oncology medicines of higher value than others is most welcomed for assisting in the rational and appropriate use of limited public resources to deliver effective and affordable care. This is becoming more essential with increased prevalence rates world-wide.

References:

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