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Original Research

Efficacy of molecularly targeted agents given in the randomised trial SHIVA01 according to the ESMO Scale for Clinical Actionability of molecular Targets

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Abstract ***Background:*** A randomised trial SHIVA01 compared the efficacy of matched molecularly targeted therapy outside their indications based on a prespecified treatment algorithm *versus* conventional chemotherapy in patients with metastatic solid tumours who had failed standard of care. No statistical difference was reported between the two groups in terms of progression-free survival (PFS), challenging treatment algorithm. The European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of molecular Targets (ESCAT) recently defined criteria to prioritise molecular alterations (MAs) to select anticancer drugs.

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Actionable molecular alterations;
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SHIVA01

We aimed to retrospectively evaluate the efficacy of matched molecularly targeted agents (MTAs) given in SHIVA01 according to ESCAT tiers.

Patients and methods: MAs used in SHIVA01 were retrospectively classified into ESCAT tiers, and PFS and overall survival (OS) were compared using log-rank tests.

Results: One hundred fifty-three patients were treated with matched MTAs in SHIVA01. MAs used to allocate MTAs were classified into tiers II, IIIA, IIIB and IVA according to the ESCAT. Median PFS was 2.0 months in tier II, 3.1 in tier IIIA, 1.7 in tier IIIB and 3.2 in tier IVA ($p = 0.13$). Median OS in tier IIIB was worse than that in tiers II, IIIA and IVA (6.3 months *versus* 11.7, 11.2 and 12.1, $p = 0.002$).

Conclusions: Most MAs used to allocate therapy in SHIVA01 were shown to improve outcomes in other tumour types (tier IIIA). Worst outcome was observed in patients treated based on another type of alteration than the one reported to improve outcomes (tier IIIB), highlighting the crucial impact of the type of the alterations beyond the gene and the signalling pathway.

1. Introduction

Molecularly targeted agents (MTAs) given based on specific molecular alterations (MAs) were shown to be highly effective in several cancer types, such as vemurafenib in patients with V600E *BRAF*-mutated melanoma or gefitinib in patients with *EGFR*-mutated non-small cell lung cancer (NSCLC) [1,2]. Several actionable MAs were identified across tumour types, raising the question of comprehensive molecular profiling clinical utility to guide therapy. Precision medicine trials have been designed to assess the value of molecular profiling to allocate therapy in a histology-independent way [3–5].

SHIVA01 (NCT01771458) was the first randomised trial comparing matched MTA *versus* conventional therapy in patients with any kind of metastatic solid tumour refractory to standard of care [3]. SHIVA01 was negative for its primary end-point with no statistical difference in progression-free survival (PFS) between the experimental and the control groups, suggesting that SHIVA01 treatment algorithm was not able to improve patient outcomes. Improving treatment algorithms used in precision medicine trials represents a major challenge [6].

Several scales of actionability have been developed aiming at grading the levels of evidence associated with MAs [7–11], the latest one being the ESMO Scale of Actionability of molecular Targets (ESCAT) [12]. We aimed to retrospectively classify the MAs used to allocate MTAs in SHIVA01 according to the ESCAT and to evaluate MTA efficacies accordingly.

2. Patients and methods

SHIVA01 was a proof-of-concept open-label randomised controlled phase II trial conducted in France [3]. MTAs used in the experimental group were drugs given outside their indications. Patients treated with MTAs after randomisation or at crossover in SHIVA01 were included in the study.

All MAs used to allocate MTAs in SHIVA01 were classified according to the ESCAT by assessing the level of evidence in the literature (Supplementary Fig. S1). To this end, for each MA, we first searched for clinical trials performed with the MTA in the same tumour type that would support ESCAT levels of evidence tiers I or II. If no data supported tiers I or II, we then searched for clinical trials performed with the same MTA and based on the same MA but in other tumour types that would support tier III. If no data supported ESCAT tier III, we searched for preclinical and *in silico* data that would support tier IV. MAs were classified as tier V if no clinically meaningful benefit was reported.

PFS and overall survival (OS) according to the ESCAT levels of actionability were compared using log-rank tests (GraphPad Prism 7).

3. Results

3.1. Patient population

One hundred one of the 153 included patients (66%) were female (Table 1). The median age was 57 years [range: 14–86]. MAs used to allocate therapy involved the PI3K/AKT/mTOR pathway in 77 patients (50%), the hormone receptor pathway in 56 patients (37%) and the tyrosine kinase receptor (TKR)/RAF/MEK pathway in 20 patients (13%). Most frequent cancer types were breast (17%), ovarian (16%) and colorectal (12%) cancers.

3.2. Classification of molecular alterations according to the ESMO Scale of Actionability of molecular Targets

Extensive justification of the classification of MAs according to the ESCAT is available in the Supplementary Material and Table S1.

Table 1
Characteristics of patients treated with matched molecularly targeted therapy in SHIVA01.

	N (%)
	Total = 153
Gender	
Male	52 (34)
Female	101 (66)
Tumour location	
PI3K/AKT/mTOR pathway	**77 (50)**
Colorectal	14 (9)
Breast	12 (8)
Ovarian	10 (7)
Lung	8 (5)
HNSCC	6 (4)
Endometrial	5 (3)
Cervical	5 (3)
Pancreatic	3 (2)
Sarcoma	2 (1)
Cholangiocarcinoma	2 (1)
Oesogastric	2 (1)
Anal	1 (1)
Melanoma	1 (1)
Adenoid cystic	1 (1)
Hepatocarcinoma	1 (1)
ACUP	1 (1)
Germline	1 (1)
Urothelial	1 (1)
Parotid	1 (1)
TKR/RAF/MEK pathway	**20 (13)**
Lung	3 (2)
Colorectal	3 (2)
Sarcoma	2 (1)
HNSCC	2 (1)
ACC	2 (1)
Neuroendocrine	2 (1)
Ovarian	1 (1)
Hepatocarcinoma	1 (1)
Melanoma	1 (1)
Oesogastric	1 (1)
Cervical	1 (1)
Urothelial	1 (1)
Hormone receptor pathway	**56 (37)**
Breast	14 (9)
Ovarian	14 (9)
Lung	4 (3)
Sarcoma	4 (3)
Cervical	3 (2)
HNSCC	2 (1)
ACUP	2 (1)
Urothelial	2 (1)
Cavum	2 (1)
Oesogastric	1 (1)
Colorectal	1 (1)
Kidney	1 (1)
Endometrial	1 (1)
Hepatocarcinoma	1 (1)
Myxopapillary ependymoma	1 (1)
Pancreatic	1 (1)
Parotid	1 (1)
Uveal melanoma	1 (1)

ACC = adenoid cystic carcinoma; ACUP = adenocarcinoma of unknown primary; AKT = serine-threonine protein kinase; HCC = hepatocellular carcinoma; HNSCC = head and neck squamous cell carcinoma; MEK = mitogen-activated protein kinase kinase; mTOR = mammalian target of rapamycin; PI3K = Phosphoinositide 3-kinase; RAF = Rapidly Accelerated Fibrosarcoma; TKR = tyrosine kinase receptor.

3.3. PI3K/AKT/mTOR pathway

Among 77 patients treated with everolimus, 28 patients (36%) had a *PIK3CA*-activating hotspot mutation, 43 patients (56%) a *PTEN* inactivation, five patients (6%) an *AKT* mutation/amplification and one patient (1%) an *STK11*-inactivating mutation associated with a loss of heterozygosity (Table 2).

PIK3CA mutations, *PTEN* inactivations, and *AKT1* mutations were shown to predict the efficacy of everolimus in patients with HER2-positive (ERRB2 amplified gene) breast cancer patients [13]. These alterations were therefore classified as tier IIA according to the ESCAT for breast cancer and as tier IIIA for the other cancer types. *AKT* amplifications were classified as tier IIIB based on data reported with *AKT* mutations. *STK11* inactivations were classified as tier IVA because only preclinical data supported the use of everolimus for this MA [14].

3.4. TKR/RAF/MEK pathway

ERBB2 amplifications were identified in two patients with NSCLC and urothelial cancer in SHIVA01. Given the OS benefit obtained with the combination of lapatinib and trastuzumab in patients with *ERBB2*-amplified breast cancer [15], and the lack of clinical evidence supporting the use of this combination in patients with *ERBB2*-amplified NSCLC and urothelial cancer, *ERBB2* amplifications were classified as tier IIIA in these cancer types. *ERBB2* mutations were classified as tier IIIB for the two patients with neuroendocrine and colorectal cancers treated with this combination, based on the *ERBB2* amplifications data.

KIT mutations are present in most patients with gastrointestinal stromal tumor (GIST), explaining the high efficacy of imatinib in this patient population [16]. *KIT* exon 11 mutations were shown to predict the efficacy of imatinib in GIST [17] and were therefore classified as tier IIIA in NSCLC. *KIT* mutations were classified as tier IIB for melanoma, given the efficacy reported with imatinib in patients with melanoma with KIT mutations/amplifications in a single-arm phase II trial [18]. *KIT* exon 18 mutations in ovarian cancer and *KIT* exon 15 mutations in hepatocellular cancer were classified as tier IIIB, assuming the same functional impact of these mutations as for *KIT* exon 11 mutations.

EGFR amplifications in oesophageal cancers were classified as tier IIA, given the OS improvement in *EGFR*-amplified tumours in a retrospective analysis of a randomised trial with gefitinib [19]. Based on these results and given the lack of clinical evidence in head and neck squamous cell carcinoma (HNSCC) and squamous cervical cancer, *EGFR* amplifications were classified as tier IIIA for these cancer types.

BRAF V600E mutation is classified as tier IA for patients with melanoma treated with vemurafenib [20].

Table 2
Classification of molecular alterations used in SHIVA01 to allocate molecularly targeted agents according to the ESCAT.

Gene	Molecular alteration	Molecularly targeted agent	Tumour type (N)	ESCAT tier
PI3K/AKT/mTOR pathway				
PIK3CA	*PIK3CA* hotspot mutations	Everolimus	Breast (8)	IIA
			Colorectal (5)	IIIA
			Endometrial (3)	
			Cervical (2)	
			Ovarian (2)	
			Oesogastric (1)	
			Pancreatic (1)	
			Cholangiocarcinoma (1)	
			HNSCC (1)	
			ACC (1)	
			Anal (1)	
			Lung (1)	
			Cervical (1)	
PTEN	*PTEN* inactivation		Breast (4)	IIA
			Colorectal (9)	IIIA
			Ovarian (7)	
			Lung (5)	
			HNSCC (4)	
			Pancreatic (2)	
			Sarcoma (2)	
			ACUP (1)	
			Cervical (1)	
			Parotid (1)	
			HCC (1)	
			Oesogastric (1)	
			Melanoma (1)	
			Germline (1)	
			Endometrial (1)	
			Cholangiocarcinoma (1)	
			Urothelial (1)	
AKT	*AKT1* amplification		HNSCC (1)	IIIB
			Lung (1)	
	AKT2 amplification		Ovarian (1)	
	AKT1 E17K mutation		Endometrial (1)	IIIA
			Cervical (1)	
STK11	D194L mutation + LOH		Lung (1)	IVA
TKR/RAF/MEK pathway				
ERBB2	Amplification	Lapatinib and trastuzumab	Lung (1)	IIIA
			Urothelial (1)	
	S792F mutation		Colorectal (1)	IIIB
	T862A mutation		Neuroendocrine Anal (1)	
KIT	D572G mutation (Exon 11)	Imatinib	Lung (1)	IIIA
	P838S mutation (Exon 18)		Melanoma (1)	IIB
	V852I mutation (Exon 18)		Ovarian (1)	IIIB
	M722V mutation (Exon 15)		HCC (1)	
EGFR	EGFR amplification	Erlotinib	HNSCC (1)	IIIA
			Cervical (1)	
BRAF	V600E mutation	Vemurafenib	Colorectal (1)	IIIA
PDGFRA/B	*PDGFRA* amplification	Sorafenib	ACC (2)	IVA
			Sarcoma (1)	
	PDGFRB amplification		Colorectal (1)	
	PDGFRA activation (intragenic deletion)		Sarcoma (1)	
	PDGFRA L655Y mutation		HNSCC (1)	
FLT3	M665T mutation	Sorafenib	Lung (1)	IVA
RET	Amplification	Imatinib	Oesogastric (1)	IVA
LCK	Amplification	Dasatinib	Neuroendocrine (1)	IVA
HR pathway				
ER-PR		Tamoxifen	Ovarian (11)	IIB
Cervical (3)	IIIA			
Sarcoma (2)				
Lung (2)				
HNSCC (2)				
Urothelial (1)				
Cavum (1)				

(*continued on next page*)

Table 2 (*continued*)

Gene	Molecular alteration	Molecularly targeted agent	Tumour type (N)	ESCAT tier
Colorectal (1) Oesogastric (1) AR Ovarian (3) Sarcoma (2) Lung (2) ACUP (2) HCC (1) Endometrial (1) Ependymoma (1) Cavum (1) Urothelial (1) Kidney (1) Pancreatic (1) Parotid (1) Uveal melanoma (1)	IIIA	Abiraterone	Breast (14)	IIB

ACC = adenoid cystic carcinoma; ACUP = adenocarcinoma of unknown primary; AKT=serine-threonine protein kinase; AR = androgen receptor; ER = oestrogen receptor; ESCAT = ESMO Scale for Clinical Actionability of molecular Targets; HCC = hepatocellular carcinoma; HNSCC = head and neck squamous cell carcinoma; HR = hormone receptor; LOH = loss of heterozygosity; MEK=mitogen-activated protein kinase kinase; mTOR=mammalian target of rapamycin; PI3K=Phosphoinositide 3-kinase; PR = progesterone receptor; RAF=Rapidly Accelerated Fibrosarcoma; TKR = tyrosine kinase receptor.
PTEN inactivation = homozygous deletion of *PTEN*, or LOH associated with an inactivating mutation of *PTEN*, or LOH with loss of PTEN expression in immunohistochemistry, in all cases validated by immunohistochemistry.
PDGFRA activation = intragenic deletion within PDGFRA validated by overexpression of PGDFRA by immunohistochemistry.

Based on these results and given the limited efficacy of vemurafenib in patients with *BRAF* V600E–mutated colorectal cancer [21,22], *BRAF* V600E mutations were classified as tier IIIA for colorectal cancer.

The predictive value of *PDGFR*, *RET*, *LCK* and *FLT3* alterations of efficacy of *PDGFR*, *RET*, *LCK* and *FLT3* inhibitors was only evaluated in preclinical models [14,23–25]. These MAs were therefore classified as tier IVA.

3.5. Hormone receptor pathway

Hormone therapy based on the expression of oestrogen and/or progesterone receptors (ER/PR) is the standard of care in breast cancer [26]. Since antitumour activity was only reported in ER/PR-positive ovarian cancer [27], these MAs were classified as tier IIB for ovarian cancer and as tier IIIA in all other cancer types.

Androgen receptors (ARs) are expressed in prostate cancer, explaining the high efficacy of abiraterone in this patient population [28]. Antitumour activity was reported in patients with AR-positive breast cancer in a single-arm phase II trial [29]. AR expression was therefore classified as tier IIB in breast cancer and as tier IIIA in all other cancer types.

3.6. Efficacy of molecularly targeted agents given in SHIVA01 according to ESCAT levels of evidence

In total, of the 153 patients treated with matched MTAs in SHIVA01, 98 patients (64%) had a tier IIIA MA, 38 patients (25%) a tier II, seven patients (5%) a tier IIIB and 10 patients (7%) a tier IVA. No MAs were classified as tier I because of the SHIVA01 design, and none as tiers IVB and V.

Median PFS was 2 months [range: 0.5–18.2] in tier II, 3.1 months [range: 0.4–18.0] in tier IIIA, 1.7 months [range: 0.3–3.7] in tier IIIB and 3.1 months [range: 1.2–8.9] in tier IVA ($p = 0.13$) (Fig. 1a). OS was worse in tier IIIB than in tiers II, IIIA and IVA (median OS of 6.3 months [range: 2.3–11.1] *versus* 11.7 months [range: 2.5–37.4], 11.2 months [range: 2.1–29.9] and 12.1 months [4.4–20.3], $p = 0.002$) (Fig. 1b).

4. Discussion

Our study is, to our knowledge, the first study to retrospectively classify MAs used in a precision medicine trial according to the ESCAT and to reassess survival according to levels of actionability. Because ESCAT relies on published preclinical and clinical scientific data, the distribution in the different tiers will certainly evolve with time.

Most MAs used to allocate therapy in SHIVA01 were MAs shown to improve outcomes in other tumour types (ESCAT tier IIIA). Worst outcome was observed in patients who were treated based on another type of alteration (e.g. amplifications *versus* activating mutations in oncogenes) in a specific gene than the one reported to improve outcomes (ESCAT tier IIIB). The functional impact of unvalidated MAs within actionable genes may be assessed using *in vitro*/*vivo* analyses [30]. Patients with MAs in tier IVA had a longer OS than patients with MAs in tier IIIB. Although the numbers

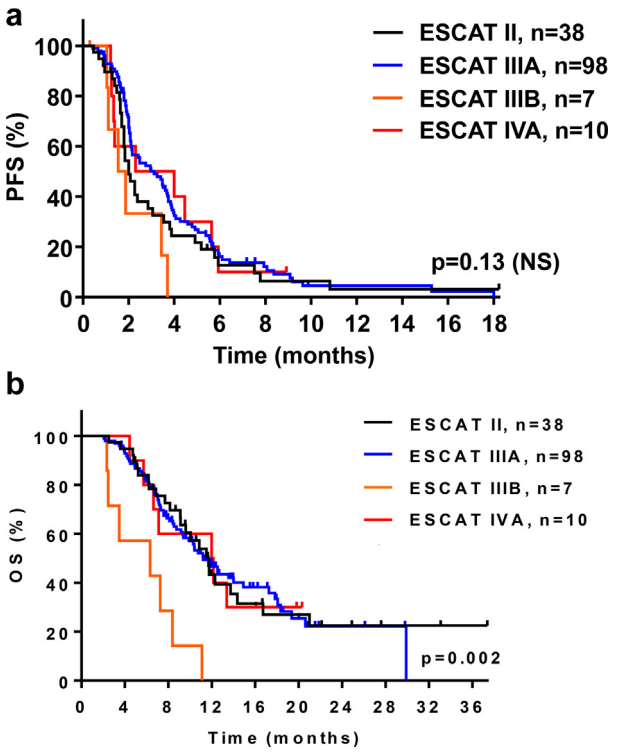

Fig. 1. Kaplan–Meier estimates of (a) progression-free survival (PFS), and (b) overall survival (OS) of patients treated with matched molecularly targeted therapy in SHIVA01 according to ESCAT Tiers.

are small, this result suggests that *in silico* functional analyses may be more informative than extrapolating potential functional impact of MAs relying on a same gene or pathway.

We encountered several limitations while classifying SHIVA01 MAs according to the ESCAT. First, we noticed that the literature interpretation was subject to inter-individual variability. In an attempt to limit this variability, the classification was validated by several experts. Second, some MTAs considered as reference treatment in some indications were not assessed in randomised trials with a molecular selection based on the MA of interest, as was the case for *KIT* mutations and imatinib efficacy in GIST [31]. Other scales of actionability have overcome this limitation by classifying in tier I Food and Drug Administration–approved drugs in a specific tumour type [7,9,10]. Third, there is no guidance in the ESCAT on how to classify MAs associated with a lack of efficacy in specific tumour types. We classified *BRAF* V600E mutations as tier IIIA for colorectal cancer based on melanoma data. However, given the limited efficacy of vemurafenib in colorectal cancer [21,22], this MA may be rather classified as tier V. Fourth, the ESCAT does not take into account the impact of coexisting MAs that may confer resistance to therapy. As an example, PI3K inhibitors were shown to be effective in patients with tumours harbouring a *PIK3CA* mutation, while coexisting *PIK3CA* and *KRAS* mutations have been reported to predict limited efficacy of PI3K inhibitors [32].

Several parameters may impact the efficacy of MTAs beyond ESCAT level of actionability such MTAs' affinity for a specific target. No recommendation exists on what should be the minimum affinity of a drug for a target to claim that an MA should be considered as a relevant target. The importance of MTA specificity is well illustrated by *PIK3CA* mutation and the use of alpelisib, an α-specific PI3K inhibitor, classified as tier IA in breast cancer based on the SOLAR-1 trial [33,34] while the same mutation in the same tumour type is classified as tier IIA for everolimus [13]. Despite the preclinical potency of sorafenib to inhibit RAF kinases [35], sorafenib did not demonstrate any efficacy in frequently *RAF*-mutated melanoma [36]. The efficacy of a drug can also be impacted by comedications or food that may influence pharmacokinetics, as well as inappropriate dose reductions [37,38].

5. Conclusions

The majority of MAs used in SHIVA01 to allocate therapy had a low level of actionability according to the ESCAT. This might in part explain the negative result of SHIVA01. Taking into account other MAs in a specific gene than the one shown to improve outcomes (tier IIIB) was associated with worst outcomes. This highlights the crucial importance of the type of alteration beyond the gene and/or the signalling pathway itself. Patients with MAs classified as tier IVA had a better outcome than those with MAs classified as tier IIIB, suggesting the value of *in vitro* and *in vivo* data for predicting MTA efficacy based on a specific MA.

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Conflict of interest statement

All authors of the manuscript declared no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.09.001.

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