snapshot on the regulatory requirements of accelerated development

Clinical development strategies to support US Accalerated / EU Conditional Approval

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Agenda

Regulatory requirements, experience and examples related to US Accelerated / EU Conditional Approval

- 1. Regulatory framework
- 2. Development strategies to support
 - 1. Phase I/II using single arm data
 - 2. Phase II Random./Control. (RCT)
 - 3. Phase III interim analysis (IA)
- 3. US / EU comparison
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- Add. aspects on combination development



Development of AA and CMA framework









US Accelerated Approval vs EU Conditional approval

New drugs and biological products	NCEs/NBEs qualifying for Centralized procedure			
Serious and life threatening illness	unmet medical need for	CMA Guideline (2016):		
Meaningful therap. benefit over existing therapies	 seriously debilitating or life-threat. diseases 	Justify that it is necessary to introduce		
based on	 <u>or</u> products used in emergency situations, 	new methods when		
 a surrogate endpoint considered reasonably likely 	• <u>or</u> orpnan drugs	 no satisfactory methods exist, or 		
to predict clinical benefit	MA granted on basis of less complete data			
 an effect on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) and reasonably likely to 	Demonstration of positive benefit-risk balance , based on scientific data, but with pending confirm.	 it is necessary to provide a major improvement over 		
predict IMM/clinical/other benefit	Likely that comprehensive data can be provided; benefit of immediate availability outweigh risk	the existing methods		
 Studies to confirm clinical benefit post-approval Adequate & well-controlled studies usually underway at time of AA 	Further clin. studies to verify benefit/risk balance \rightarrow	Feasibility of confirmatory trials to be addressed		
conducted with due diligence				
Approval is not limited in time (withdrawal possible)	Authorisation valid for one year (renewable) until pending results are provided			
Possible for initial NDA/BLA and supplemental NDA/BLA (new indication)	Possible for initial MAA of NCEs/NBEs but <u>not</u> for Type II variations for new indications			

Common principles for accelerated (AA - US) and conditional (CMA - EU) approval



Criteria to support AA or CA Early availability of new, promising therapies

HA concerns with AA/CMA:

- Approval of potentially ineffective drugs
- Lack of due diligence in conducting post-approval trials



Substantial improvement of IMP over existing treatments required to cope with uncertainty of

- Outcome from a surrogate endpoint to transfer into real clinical benefit (SoC approved based on clinical benefit)
- Comparision to historical controls in case of single arm trials / In case of RCT, limitations by Phase II-like studies



Common principles for accelerated (AA - US) and conditional (CA - EU) approval





Ph II single-arm vs Randomized trials for AA (Johnson et al. 2011, FDA)



Decline of AAs until 2010 / FDA more restrictive for AAs based on single arm, favouring RCT

Several issues using Single-arm trials for AA

- Demonstration of refractoriness for each patient for all available therapies
- Many available therapies: Impractical to accrue a sufficient number of patients who received all available treatments
- Definition of available therapy may change substantially from the start of development to AA ("available therapy" defined at the time of AA!)
- Only response rate can be assessed in single-arm trials (time-to-event endpoints require randomized trials)
- Marginal responses difficult to determine as "reasonably likely" to predict clinical benefit
- Limited safety profile (low patient numbers, no control)
- Often, no confirmatory study in progress or even no protocol provided for a planned study (extreme situation: Phase lb trial to be conducted initially if the confirmatory trial is done in a combination setting)

Advantages using Randomized trials

Less refractory populations feasible

Time-to-event endpoints (wider range of endpoints)

Combination regimens with an add-on design

More advanced safety profile from a controlled study

Continuation of the trial confirms clinical benefit and allow timely and dilligent conversion of AA to RA



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Comparison of study designs to support AA/CMA (Relevant criteria supporting US Accelerated / EU Conditional Approval)



	Ph II Single arm for AA + confirmatory Ph III for RA	<u>Ph II RCT</u> + confirmatory Ph III trial for AA	<u>Ph III with IA</u> for AA and final analysis for RA from same trial (HA preferred setting)				
Surrogate endpoints	Only ORR and DoR acceptable for AA	Time-related endpoints (PFS, O	S) can be used in addition to ORR and DoR				
Control	Only historical controls	RCT	RCT (IA analysis*)				
Safety	Assessment of safety difficult	Safety can be assessed in contr	olled fashion				
Combination development	Not appropriate for combinations	Combination feasible due to controlled design					
Clinical setting	Salvage / Limited activity of existing treatments	Better to assess superiority if e	ffective SoC available				
Confirmatory	Confirmat. Ph III usually in a dif	ferent setting (e.g. earlier line)	Same setting (within same trial)				
trial(s)	Uncertainty if Ph III setting is fu	Illy representative for AA setting					
	2nd+ line		Only this design works if no Ph III setting can be defined (e.g. AA applied in 1st line)				
	Different to Ph III IA which may ethical / methodological issues	be limited by operational /	Potentially ethical and/or bias-related issues to continue trial after IA published / AA				
Transfer to full approval	Phase III trial needed; possible transfer to RA	delay / uncertain to timely	Quick and effective transfer to RA based on continuation of same trial				



General aspects supporting AA/CMA



- Rare cancer type
- Strong efficacy outcome clearly superior over existing therapies
- Only low to moderate activty of existing tretaments / limited number of treatments / not approved
- Approval of new treatments while clinical trial of IMP is ongoing
 - Other drugs AA/CMA approved in the same clinical setting do not prevent other AA/CMA
 - New, effective drugs with full approval may prevent AA/CMA of other drugs
- Hints that the drug effect is real (predictive BM; dose-response effect shown)
- Follow-up indication: sNDA/BLA (EU: no CMA for follow-up indications possible higher hurdle?)
- Confirmatory trials ongoing



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Examples of AA/CMA based on single arm data (2010-2015) (excerpt)



Drug	Disease	Ν	ORR (95% CI)	CR	mDOR (months)	Year	NME	PMR
Brentuximab	Hodgkin	102	73 (65,83)	32	6.7 (4, 14.8)	2011	Y	
vedotin	ALCL	58	86 (77,95)	57	12.6 (5.7, NE)	-		
Crizotinib	ALK+ NSCLC	136	50 (42,59)	<1	9.6 (1.4, 9.7)	2011	Y	
	ALK+ NSCLC	119	61 (52,70)	<1	11.1 (0.9, 17.6)			
Ceritinib	ALK+ NSCLC (2L)	165	44 (36,52)	2.5	7.1 (5.6, NE)	2014	Y	
Olaparib	BRCA OC (4L)	137	34 (26,42)	2%	7.9 (5.6,9.6)	2014	Y	Y
Osimertinib	EGFR T780M	411	59 (54,64)	<1	12.4	2015	Y	
Alectinib	ALK+ NSCLC (2L)	87	38 (28,49)	NA	7.5 (4.9, NE)	2015	Y	
	ALK+ NSCLC (2L)	138	44 (36,53)	NA	11.2 (9.6, NE)	-		
Pembrolizumab	PDL1+ NSCLC (2L)	61	41 (29,54)	0	44% >6m	2015	N	
Daratumumab	Myeloma (4L)	106	29(21,39)	0	7.4	2015	Y	

Chemo + targeted therapies (prior to main IO approvals), ORR at least 30% with durable responses (DoR 6M min)

1 Examples of AA/CMA based on single arm data (2016 – 2017)



Drug	Disease	N	ORR (95% CI)	CR	mDOR (months)	Year	NME	PMR	EU data similar
Ibrutinib	Mantle Cell	111	66 (56,75)	17	17.5 (15.8, NR)	2016	Ν		*
Nivolumab	cHL	95	65 (55,75)	7%	8.7 (6.8, NE)	2016	Ν	Y	* CMA
Venclexta	CLL	106	80.2 (71.3, 87.3)	8	NR (2.9 to 19.0+)	2016	Y	Y	-
Atezolizumab	mUC	310	14.8 (11.1, 19.3)	46	NR (2.1+,13.8+)	2016	Y	Y	-
Pembrolizumab	HNSCC	174	16 (11,22)		NR (2.4+,27.7+) 82%>6m	2016	Ν	Y	-
Rucaparib	BRCA Ovarian	106	54 (44,64)	9%	9.2 (6.6, 11.6)	2016	Y	Y	-
Nivolumab	mUC	270	19.6 (15.1,24.9)	7	10.3	2017	Ν	?	*
Pembrolizumab	cHL	201	69 (62,75)	22%	11.1 (0.0+,11.1)	2017	Ν	Y	-
Avelumab	МСС	88	33 (23.3,43.8)	11%	n=29 (2.8, 23.3)	2017	Y	Y	-
Brigatinib	ALK+ NSCLC	222 (112,110)	48 (39,58) 90mg 53 (43,62)180mg		13.8	2017	Y	Y	-
Durvalumab	mUC (2L)	182	17 (11.9,23.3)	5	NR (0.9+,19.9+)	2017	Y	Y	-
Avelumab	mUC (2L)	242	13.3 (9.1,18.4) 16.1 (10.8,22.8)	9	NR (1.4+,17.4+)	2017	Ν	Y	-
Pembrolizumab	mUC (1L)	370	28.6 (24,34)	7%	NR (1.4+,17.8+)	2017	Ν	Y	_
Pembrolizumab	MSI-H, dMMR	149	39 (31.7,47.9)	11	78% >6m	2017	N	Y	*

Latest AA/CMA approvals for IO "go down to ORR of 15%" but have very durable responses (DoR 9-12M+)

<u>Regular</u> approvals based on high ORR/DoR in single arm trials in <u>rare</u> <u>diseases</u> (2002 – 2017) (Blumenthal, FDA, 2015)



Table 1 Traditional approvals based on response rate in single-arm trials (2002–2013)

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Drug Year Approval type Indication(s)		Indication(s)	Ν	ORR (95% CI)	mDOR (months)		
Tositumomab	2003	NME	Relapsed, CD-20+, follicular, Non-Hodgkin Lymphoma (NHL)	40	68	16	
Imatinib	2006	Supplement	Dermatofibrosarcoma protuberans (DFSP)	18	83	6.2	
	2006	Supplement	Myelodysplastic syndrome (MDS/MPD)	31	84	$4.6+ \rightarrow 15+$	
	2006	Supplement	Adult aggressive systemic mastocytosis (ASM)	28	61	$1 \rightarrow 30$	
	2006	Supplement	Hypereosinophilic syndrome/chronic eosinophiliic leukemia (HES/CEL)	176	74	1.5+ ightarrow 44	
Bortezomib	2006	Supplement	Relapsed mantle cell lymphoma (MCL)	155	31	9.3	
Cetuximab ^a	2006	Supplement	Recurrent squamous cell carcinoma of the head and neck (SCCHN)	103	12.6	5.8	Supported by other
Vorinostat	2006	NME	Recurrent cutaneous manifestations of cutaneous T-cell lymphoma (CTCL)	74	30	5.6	RCT trials in closely
Dasatinib ^a	2006	NME	2nd-line Ph+ acute lymphoblastic leukemia (ALL)	36	MaHR - 42	4.8	related settings!
lxabepilone ^a	2007	Supplement	Refractory metastatic breast cancer	126	12.4	6	-
Bendamustine	2008	Supplement	Indolent B-cell Non-Hodgkin Lymphoma (NHL)	100	74	9.2	More recent examples:
Romidepsin	2009	NME	2nd-line cutaneous T-cell lymphoma (CTCL)	167	34.5	13	Ibrutinib in Waldenstrom's
Vismodegib	2012	NME	Metastatic basal cell carcinoma	33	30	7.6	macroglobulinemia (2015; supplement) (n=63: ORR 62%: DoR not vet
	2012	NME	Locally advanced basal cell carcinoma	63	43	7.6	reached (2.8 – 18.8 M)
Bosutinib	2012	NME	2nd-line Ph+ chronic myelocytic leukemia (CML)	503	McyR - 53	18	Crizotinib in metastatic ROS1
Lenalidomide	2013	NME	Relapsed mantle cell lymphoma (MCL)	134	26	16.6	positive NSCLC (2016; Supplement)
Denosumab	2013	Supplement	Giant cell tumor of bone	187	25	>8	(n = 50; ORR 66%; DoR 19M)

CI, confidence interval; MaHR, major hematologic response; mDOR, median duration of response; McyR, major cytogenetic response; *N*, number of patients tested; NME, new molecular entity; ORR, overall response rate; Ph, Philadelphia chromosome.

^aCetuximab, dasatinib, and ixabepilone approvals were supplemented by concurrent approvals in closely related settings or in combination regimens based on randomized trials.



Additional aspects supporting AA/CMA based on single arm data (external and internal examples)

Endpoints

- Primary:
- ORR and DoR (follow-up critical: 6-18M)
- Durable Response Rate (DDR, e.g. at 6M/9M/12M)
 (tbc if existing treatments have a reasonable ORR but short duration)
- Secondary: Median (milestone) PFS (rate), OS (rate)
- Exploratory / Supportive: Intra-patient TTP1/PFS2; PRO

Historical control

- Thorough assessment of benefit of existing treatments (e.g. Meta analysis of literature data)
- Conduct a comparative observational study ("Pragmatic RWE RCT"), e.g. Blinatumumab, Avelumab

Extrapolation to related patient population (limited number of patients treated)

- Other treatment line (e.g. 1st L)
- Pediatric population, e.g. adolescents



DDR used by

- <u>AA: Talimogene laherparepvec</u> (IMLYGIC); Oncolytic immunoth. (injectable regionally or distantly metastatic melanoma (2015)
- Avelumab in 1st L MCC confirmatory single arm trial (2016, see next slide)



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Case study Avelumab in MCC: EMR100070-003 Part A (2L+) supported AA





* Patients may continue avelumab beyond radiologic disease progression in the absence of significant clinical deterioration and based on investigator assessment of potential benefit from continued treatment.

** Phase II single arm study in 1st L MCC agreed (with DDR as primary endpoint): Rationale:

- 1. An improvement of OS with chemo has not been demonstrated
- 2. Not ethical / loss of equipoise to do a RCT
- 3. Feasibility (important criteria for a AA/CMA)

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Recent challenges with AA based on single arm data

Rociletinib- 3rd generation EGFR T790M TKI

- Key Uncertainties:
 - dose: 500mg BID vs 625 mg BID
 - efficacy: ORR and DoR better than available therapy?
 - safety: risk of QTc prolongation leading to Torsades de pointes and cardiac death (particularly in NAT2 slow acetylators)
- April 2016: ODAC voted 12 to 1 to recommend postponing approval decision until results of RCT reported

Ponatinib – 3rd generation TKI CML/ Ph+ALL (including T315I)

- December 2012: accelerated approval CML resistant to prior TKI or PH+ALL resistant to TKI based on SAT
- October 2013: Sponsor announced temporary suspension of marketing for implementation of risk mitigation strategy and updates to PI to convey increased risk of cardiovascular AEs, including vascular and arterial occlusions
- December 2013: Sponsor announced resumption of marketing with new safety measures to address risk of serious cardiac AEs

Other EGFRT790 TKI (AA) showed better efficacy





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AA / CMA based on <u>completion of Ph II RCT</u>: *Preferred option in case of the following criteria*



RCT preferred or even required

- ORR/durability
 - is modest over existing therapies
 - uncertain as surrogate to predict benefit
- Highly toxic / poor understanding of toxicity
- Lack of understanding of the natural history of the disease
- Biomarker strategy has not been optimized (e.g. predictive vs prognostic)
- IMP used in combination
- Several effective therapies available
- HA prefer small RCT vs single arm (generally?)

Other prequisites

- High improvement of outcome expected in case of <u>TTP/PFS as endpoint</u> significantly exceeding existing treatment options to cope with
 - approval based on surrogate endpoint
 - low sample size / Ph II statistical assumptions
 - methodological issues related to PFS/TPP
- <u>Confirmatory Ph III</u> trial in another representative setting can be defined



Examples of AA(CMA) of <u>combinations</u> (2000-2017): AA(CMA); outcome from surrogate endpoint

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Efficacy improvement vs SoC: 2fold or higher (strong improvement)

Combination	Indication	Year	Design	Endpoint/Results	Comments
Pembrolizumab + pemetrexed & paclitaxel	NSCLC	2017	PhIb/II ; PhII one cohort 1:1 rando (vs Pem+Pac) n=123	ORR 29 ->55% all PR PFS 8.9 -> 13mo DoR ≥6mo: 81 -> 93%	
Olaratumab + doxorubicin	Soft tissue sarcoma	2016 (USA AA; EU CMA)	PhIb/II where PhII is RCT (vs doxo), n=133	PFSinvest 4.1 -> 6.6 mo ORR 7.5% -> 18.2% OS 14.7 ->26.5 mo	USPI lists PFS _{IBRC} 4.4 -> 8.2 mo; EU SmPC indicates key primary e.p. is PFS _{invest}
Nivolumap + Ipilimumab	Melanoma	2015	Ph II RCT (vs Ipi) 2:1 (n=109)	ORR: 11->60% PFS: 4.7M->8.9;	PhIII RCT (N+I, I, N) 1:1:1 OS & PFS
Panobinostat + Bortezomib + Dexamethason	Multiple Myeloma	2015	Ph III RCT (vs Bor/Dex) 1:1; (n=193; pre- specified subgroup only)	PFS: 5.8->10.6M ORR 41 -> 55% DoR 8.3 -> 12 mo	2 PMR: PhII different panobinostat doses, Ph3 EU not CMA
Palbociclip + Letrozole	Breast cancer	2014	Ph II RCT (vs Let) (n=165)	PFS: 10.2->20.2 mo ORR 39.4 -> 55.4%	2x HER-2 products
Trametinib + Dabrafenib (novel – novel combination as initiated before MAA of either!)	Melanoma	2014	Ph II RCT (vs Dab) 1:1:1 (2 doses of Tram) (n=162)	ORR: 54->76% DoR: 5.6M->10.5M	Approved as single products for use in combination; EU Type II var. approval on PhIII results
Pertuzumab + Trastuzumab + Docetaxel	Breast cancer (neoadjuvant)	2013	Ph II RCT (vs 3 control groups)	<mark>pCR: 21.5->39.3%</mark> (n=417)	Prior approval of combination in metastatic BC (initial BLA)
Lapatinib + Letrozole	Breast cancer	2010	RCT Ph III (vs Let) HER2+ subgr. (n=219)	PFS: 13->35.4W ORR 14.8 -> 27.9	Ph III did not include the current <u>SoC</u> (Trastuzumab); PMR Lap + Aro inh v Tras+Ai v Lap+Tras+Ai
Thalidomide + Dexamethason	Multiple Myeloma	2006	Ph III RCT vs Dexa (n=207)	ORR: 35.6->51.5%	FDA stats results; Multiplicity issues; PMR submit final CSR
Cetuximab + Irinotecan	CRC	2004	Ph II RCT (vs Cetux.!) ("Single arm")	ORR: 11->23% (n=329)	Uncontrolled in relation to Irinotecan as SoC in 2 nd L; Irinotecan resistance was "treated"
Oxaliplatin + 5FU/LV	CRC	2002	RCT Ph III (3 arm; n=821)	RR: 0->9% TTP: 4.6->6.1	AA based on IA ; OS at study completion

Phase I/II studies with combinations

<u>Combinations: Single arm (singla detection) vs RCT (full proof of concept)</u>: Consider to...

- investigate various dose combinations beyond dose escalation if the full approved/RP2D of the combination partners cannot be used (e.g. Nivolumab/Ipilimumab)
- add SoC to de-risk Phase III (if SoC is not the combination partner itself)
- add single agent arm(s) to demonstrate rationale of combination (to avoid to include in Phase III)

Generic Clinical Development of Combinations: Factorial design







- PFS gain 3.6 mts, HR=0.35 (BRCA wt and mut);
- PFS gain 6.9 mts in BRCA-mut. pts, HR=0.18

Several FDA/ODAC concerns regarding initially proposed maintenance indication

- 1. Lack of an OS benefit for maintenance therapy;
- Unreliability of the results due to loss of randomization for `gBRCAm' subgroup and small sample size (n=136);
- 3. Toxicity of therapy and risk of MDS/AML for pts undergoing maintenance therapy;
- 4. Risk of reproducibility of trial results in a larger phase III trial (i.e. potential to hinder accrual to confirmatory study)

See detailed GRASP evaluation of Olaparib EU/US approval included for ovarian indication

Small sample size and the "prospectively planned analysis of a <u>retrospectively identified</u> <u>subpopulation</u>" raise

- "uncertainties related to the validity and the reproducibility of the magnitude of effect seen in Study 19" and
- "call into question the reliability of the estimation of treatment effect."
- R/B profile of Olaparib to be considered in the context of longer intervals between CTX regimens (and particularly platinum-free intervals) which are associated with higher responses to subsequent platinum-based therapy



Examples of AA from interim analysis of a surrogate endpoint followed by regular approval of an endpoint of clinical benefit withinh the same trial (Ph III)



Drug	Indi- cation	Prim. EP	Phas e	Year AA	Year RA	АррІ. Туре	Orphan	Comments
Oxaliplatin	CRC	RR (TTP)		2002	2004	NDA	No	AA:RR (and TPP) based on in terim analysis of a randomized combination Ph 3;
								RA: OS at study completion
Sunitinib	RCC	RR (PFS)		2006	2007	sNDA	No	AA: RR (interim analysis)
								RA: within same trial, based on PFS
Imatinib	Adjuv. GIST	RFS	III	2008	2012	sNDA	Yes	AA: RFS (surrogate EP likely to predict clin. benefit)
								RA: 1) Follow-up of RFS and OS from same study
								 Completion of ongoing study of 1 vs 3y of Imatinib treatement
Nivolumab	Melano-	OS&ORR	111	2014	2016	NDA	No	AA: ORR (PFS descriptive)
	ma							RA: Completion of ongoing study based on PFS&OS

Vectibix in EGFR⁺ mCRC (2006) is only additional I can think of.



Issues related to AA / CA based on interim analysis of Ph III data (Carroll et al. 2008)



1) Interim analysis based on primary endpoint

If significant treatment effect reached, trial has met its endpoint Seek full/regular approval

2) Interim analysis based on surrogate (secondary) endpoint

- · Ethical issues to continue recruitment to control treatment
- Study integrity jeopardized following interim analysis (study design affected)

Patients (in consultation with their physicians) may wish to switch treatment regimens and, so, the data collected following the interim analysis are likely to be difficult to interpret and quite possibly downwardly biased. Release of interim data in this way might therefore serve only to make it difficult, if not impossible, to provide full data confirming a treatment benefit and thus would serve to circumvent, rather than support, a conditional approval strategy.

Problematic which may explain why very few cases are seen in practice

Possible outcome/solutions

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- 1) Stop trial at IA for early benefit (prim. + sec. EP): Full approval
- 2) Stop trial at IA for AA/CA; obtain full approval from a Ph III trial in another setting
- 3) IA for CA/AA; continue Ph III trial if trial can be reliably completed (ethically, limited bias)



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US AA vs EU CMA (2006 – 2016): Is EMA more hesitant to grant CMA compared to FDA for AA?

Two internal analysis and some external analyses (literature) (for details see back-up)

Based on same or comparabel data sets submitted...

- 1. Comparison of US AA approved drugs paperoval outcome in EU (no, CMA or full approval)
- 2. Comparison of EU CMA approved drugs paperoval outcome in US (no, AA or regular approval)
- 3. Literature, e.g. Martinalbo 2015, Hoekman 2015; CROH 2013

Limitation: Pair-wise comparison not laways feasible

- 1. More AA than CMAs overall: Later introduction and take up of CMA regulation (Mar 2006 in EU vs 1992 in US)
- 2. CMA only possible for initial application (not new indications): n=33 AA vs n=16 CMAs (Martinalbo 2015)
- 3. (1) General trend by companies to submit later in EU /

(2) CMA approval time longer than standard approval (often priority review for AA in US but Accelerated Assessment rarely used for CMA) allowing the inroduction of further data during CP (sometimes even confirmatory Ph III data) to possibly receive <u>regular</u> <u>approval (RA)</u> instead of CMA

There is no hint for a higher hurdle in EU to obtain CMA (or RA) for products which received AA in US in general, and in particular for single arm study data with a surrogate endpoint



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FDA's negative experience with confirmatory studies (Johnson et al. 2011, FDA)



- Little incentive to enroll in trials when the drug is approved and reimbursed (low diligence by industry
- Ethical implications to randomize patients to "less effective" control group
- Particularly problematic for orphan cancer diseases

Further obstacles to complete the confirmatory studies

- SoC changing (Cetuximab in CRC)
- New biomarker insights (KRAS in CRC)
- Negative study with OS as endpoint due to crossover to IMP (e.g. 41% to Cetuximab arm)
- Overall number of studies committed
 - (e.g. 10 studies with Tositumumab, 3 still ongoing today)

Status of 1992 - 2010:

- 12 out of 27 AAs not (yet) converted (confirmatory studies ongoing or under FDA review)
- 5 longest: 7.4 12.6y (Amifostine, Gemtuzumab over 10y)





ODAC 2003, 2005, 2011: Recommendations for more effective transfer of AA to RA if <u>AA was based on Ph II</u>



2003

2005

2011

2005

2011

Ph IV confirmatory studies

- Adding sites in countries where access to new cancer drug is limited
- Not necessarily be required in the exact population for which AA was granted
- **Sponsor**: preferentially be conducted by company instead of cooperative groups
- Two well-designed, randomized (confirmatory) trials required (except orphan) 2011

Single arm Ph II studies to be restricted to

- rare disease
- with a refractory population
- only in case of substantial benefit

AAs preferably based on **interim analyses of surrogate endpoint in Phase III** rather than Phase II trials (no need for recruitment to add. confirmatory Ph III trials)



Framework got

smaller

Overview of oncology products that failed to demonstrated benefit in US after approval

Since the FDA's AA regulations came into effect in 2002, within the oncology space there have been 5 drugs to date that failed to demonstrate a benefit:



AA Date	Drug	Abbreviated Indication	Outcome
3/15/1996	Amifostine	Cisplatin-Induced renal toxicity in NSCLC	Voluntarily Withdrawn by Sponsor (3/28/2006)
12/23/1999	Celecoxib	Reduction in colonic polyps familial adenomatous polyposis (FAP)	Voluntary Withdrawal by Sponsor (6/8/2012)
5/17/2000	Gemtuzumab	2nd line AML in patients >60's of age	Voluntarily Withdrawn by Sponsor (6/21/2010)
5/5/2003	Gefitinib	3rd line NSCLC	Restricted Distribution* (6/17/2005) Voluntarily Withdrawn by Sponsor (4/25/2012)
2/22/2008	Bevacizumab	1st line metastatic HER-2 neg Breast Cancer	Withdrawn by FDA (11/18/2011)

*At that time distribution was limited to patients who, in the opinion of their treating physician, were currently benefiting, or had previously benefited, from gefitinib treatment.

FDA/EMA did not remove drugs from the market solely because of the lack of due diligence to complete confirmatory trials

Agenda

Regulatory requirements, experience and examples related to US Accelerated / EU Conditional Approval

- 1. Regulatory framework
- 2. Development strategies to support
 - 1. Phase I/II using single arm data
 - 2. Phase II Random./Control. (RCT)
 - 3. Phase III interim analysis (IA)
- 3. US / EU comparison
- 4. Phase III confirmatory trials to transfer AA/CMA into regular approval
- 5. Conclusion on trends and open questions

- Comparison with full approvals
- Avelumab in MCC as case study
- Add. aspects on combination development



Conclusion on Experience (2012 – 2017)



Increasing number of AA/CMA approvals, likely due to

- 1. Public interest to approve promising oncology drugs earlier (revised regulations/guidelines)
- 2. Substantial effects by targeted therapies and immuno-oncology
- 3. Withdrawals to fail with confirmatory Ph III trials remain low
- Most AAs continue to be based on single arm trials (ORR/DoR as surrogate endpoints), although more examples with Ph II RCT or Ph III IA (PFS as surrogate endpoints) are growing
- Not only salvage but also settings where SoC are available (low/moderate activity, e.g. chemo)
 - 1. Higher ORR (e.g. Brentuximab in Hodgkin lymphoma)
 - 2. Higher DoR (e.g. Avelumab in MCC)
 - 3. Treatment of resistance to targeted therapies
 - Crizotinib in ALK pos. 1st L NSCLC
 - Sec. generation ALK inhibitors (Crizotinib, Alectinib, Ceritinib)
 - Sec. generation EGFR(T790M) inhibitors (EGFR inhibitor resistant) (Osimertib)
- Extension of appropved indications to 1st L / adolescents supported by extrapolation in very specific situations (Crizotinib, Avelumab)
 - First biomarker agnostic approval: Pembrolizumab in solid tumors with dMMR or MSI-H



Questions / open points



- Will the number of AA/CMA continue or will the hurdle getting higher?
- Will DDR allow for more single arm approvals in spite of existing treatments?
- Can we further improve historical controls to strengthen single arm trials?
- How to manage parallel AA/CMA approvals of drugs (esp. same class of drugs)?
- What is the impact of the Tecentriq failure?
- Will we get CMA for follow-up indications in EU (change legislation)?
- Will an AA/CMA of a combination based on single arm data never been possible/acceptable?

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us accelerated approval of avelumab in Mcc

Exerpt on some intersting topics

CDDF workshop, Frankfurt am Main; 12 & 13 June 2017 Jan Gross

> Merck KGaA Darmstadt, Germany

Case study Avelumab in MCC: EMR100070-003 Part A (2L+) supported AA



* Patients may continue avelumab beyond radiologic disease progression in the absence of significant clinical deterioration and based on investigator assessment of potential benefit from continued treatment. [†] Primary analysis of the study.



Observational Study 100070-Obs001 (Obs001

- External population that included treatment-naïve or previously-treated patients with metastatic MCC who were treated with chemotherapy
- A retrospective, chart review of electronic medical records obtained in community and academic centers that collected information on the outcomes of untreated (first line) and previously treated (second line) patients with metastatic MCC. No formal statistical comparisons were made between Studies 003 and Obs001.
- Primary objective for the retrospective chart review of an evaluation of ORR as determined by the treating physician according to "clinical judgment" or by an independent auditor according to RECIST 1.1.
- Database containing 686 patients with a diagnosis of MCC.
 - A total of 39 potential patients were identified by the Applicant as having metastatic MCC with evidence of receiving second line chemotherapy for metastatic disease. Based on the Applicant's chart review, 19 of the 39 patients were excluded from the dataset because 11 patients did not have evidence of metastatic disease, 4 patients were participants in a clinical trial, 3 patients did not receive second-line therapy, and 1 patient did not receive one of the selected chemotherapeutic agents as first-line therapy.
 - Of the remaining 20 patients, 6 patients were excluded from the assessment of ORR based on a history of autoimmune disease, medical conditions requiring systemic immunosuppression, and prior organ or allogeneic stem cell transplantation, i.e. those excluded from Study 003.
- For the remaining 14 patients, the ORR was 28.6% (95% CI: 8.4, 58.1), with a median duration of response of 1.7 months (95% CI: 0.5, 3.0).
- The data from this subset analysis are of interest in the attempt to establish a baseline history of the disease treated in the current clinical environment; however, the data are limited, formal comparisons to the data from Study 003 were not made, and the data are subject to selection bias.



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Case study EMR100070-003 Part B (1L) Design – Confirmatory Study (ongoing)



* Patients may continue avelumab beyond radiologic disease progression in the absence of significant clinical deterioration and based on investigator assessment of potential benefit from continued treatment.

⁺ Planned primary analysis of the study.



Efficacy results of study 003

Efficacy analyses:

All patients (N=88) had been treated or followed for at least 12 months from their first response (see Table).

Duration of response:

Among 29 responding patients, median duration of response (DOR) was not reached (range 2.8 to 23.3 + months) and 72% (21/29) of patients had ongoing responses at the data cutoff.

Subgroup analysis

86% (25/29) of responding patients maintained responses of > 6 months and 45% (13/29) maintained responses of > 12 months in duration.

Though numbers were small, treatment effect was consistent across relevant subgroups, i.e. those with visceral metastases, patients whose tumor tissue was MCV positive or negative, and PD-L1 expression status of the tumors.

FDA assessment

The durability of responses provides an advance over that observed with off-label use of chemotherapy which produces nondurable response rates (reported and observed median durations of response less than 3 months).

Primary Efficacy Analysis: Confirmed Best Overall Response According to IERC Assessment (All enrolled patients)

	Avelumab (N=88) n (%)
Confirmed Responses	29 (33.0%)
Complete Responses	10 (11.4%)
Partial Responses	19 (21.6%)
Stable Disease	9 (10.2%)
Progressive Disease	32 (36.4%)
Not evaluable*	18 (20.5%)



Avelumab in MCC (US)

BAVENCIO is indicated for the treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (MCC).

Rationale to extrapolate to 1st L MCC setting (FDA assessment)

- There are no <u>examples in oncology</u> where a drug which is not targeted to a specific resistance mutation did not result in achieving durable response rates of at least the same or greater magnitude in patients who have not been previously treated with chemotherapy
- Treatment with avelumab does not appear to negatively affect the likelihood of achieving a response to <u>subsequent</u> <u>chemotherapy</u> following disease progression (Study 003 data)
- Unmet need for patients with metastatic MCC who have <u>no FDA-approved therapy</u> and where there is a short duration
 of response to off-label use of chemotherapy
- Avelumab has a <u>relatively favorable toxicity profile</u> as compared to cytotoxic chemotherapy.
- The <u>lack of available therapies</u> for patients with metastatic MCC and the <u>more favorable toxicity profile of avelumab</u> as compared to cytotoxic chemotherapy
- Preliminary efficacy data (Part B of Study 003) from patients with metastatic MCC who have not received prior chemotherapy(n=25; at least six weeks of follow-up; 16 of these patients had at least 13 weeks of follow-up). Investigator-assessed, confirmed ORR among the 16 patients with three months of follow-up was 56% (95% CI 30, 80) which is similar to response rates to chemotherapy reported in the literature; however, the response rate in this population is expected to be as durable as in Part A. The IERC results were not yet available.
- There is an <u>ongoing clinical trial of avelumab in the frontline setting</u> (Part B of Study 003) which will characterize the durable response rate

Avelumab in MCC (US)

BAVENCIO is indicated for the treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (MCC).

Rationale to extrapolate to adolescents (12-17 years) (FDA assessment)

- <u>Disease</u>: MCC in adults and pediatric patients 12 years and older is the same disease because of the histomorphological features of MCC (cytokeratin 20; neuron-specific enolase (NSE); association with the MC polyomavirus).
- <u>Exposure</u>: Population pharmacokinetic (PK) modeling
 - included simulation of PK exposure at steady state after repeat i.v. dosing of avelumab 10 mg/kg every 2 week for patients with body weights of 30kg to 90 kg, which are equivalent to weights of adolescents demonstrating comparable PK. Also demonstrated were no differences in PK based on age.
 - simulating minimum concentration (Cmin) and the data from an in vitro target occupancy study provided by the Applicant, high target occupancy was predicted for pediatric patients 12 years and older during the entire dose interval at 10 mg/kg every 2 weeks.
- <u>Treatment of MCC</u>: Six case reports of patients with MCC, four patients in the age range 11 to 17, two of the patients had metastatic disease, one patient received <u>chemotherapy</u> and the remainder underwent surgical resection.
- 10-year-old female patient with metastatic MCC who was initially treated with 6 cycles of cisplatin and etoposide and who experienced subsequent disease progression after receiving 3 doses of <u>avelumab</u> at 10 mg/kg
- <u>Unmet need:</u> Adult and pediatric patients aged 12 and older with advanced or metastatic MCC represent a population with a serious and life threatening disease. There is no available FDA-approved therapy for the disease, and no known therapy that is either curative or is known to improve overall survival (OS). Although MCC is known to be sensitive to chemotherapy, treatment of patients with cytotoxic chemotherapy has demonstrated neither durable responses (in general, for adults, less than 6 months) nor survival advantages for patients

Avelumab in MCC (US) **Post-approval commitments**

Conduct and submit the results of a multicenter clinical trial confirming the clinical benefit of avelumab in patients with **metastatic Merkel cell carcinoma (MCC) who have not received prior systemic therapies** for metastatic MCC. The trial will enroll at least 100 patients followed for a minimum of 12 months, in order to establish the objective response rate and characterize the durability of response for first-line treatment of metastatic MCC. All patients will be followed for overall survival until at least 70% of patients have died in order to characterize effects on survival. An analysis of overall survival compared to historical control data will be provided.

Confirmatory evidence of clinical benefit will be based on a demonstration of a statistically significant and clinically meaningful durable response rate in patients with untreated metastatic MCC that are followed for at least 12 months from initiation of avelumab. The Applicant will additionally evaluate OS as compared to historical control data and incorporate assessments of other measures of the effect of avelumab on tumor-related symptoms, physical functioning and disfiguring lesions (when present). Depending on the demonstrated effect size, these data may be sufficient to support granting regular approval for this indication.

Conduct a trial in a sufficient number of **pediatric patients ages 12-18** to adequately characterize baseline risk factors, safety outcomes, and clinical responses following exposure to avelumab.

Currently available efficacy and safety data are sufficient to support approval of Bavencio (avelumab) as treatment for patients with metastatic Merkel cell carcinoma (MCC) who have progressive disease following at least one prior systemic chemotherapy regimen. Efficacy data for avelumab as a treatment for patients with metastatic MCC who have not received prior systemic chemotherapy (i.e., frontline) is limited. Metastatic MCC is a rare and life-threatening illness with no available therapy. There is biologic rationale to support extrapolation of efficacy results from the chemotherapy-refractory setting to the frontline setting to provide patients access to avelumab which is likely to offer clinical benefit. However, additional efficacy data in chemotherapy-naïve patients is required to more accurately characterize response rate and durability of responses in the frontline setting.

Other back-up slides



Surrogate endpoints

(likley to predict clinical benefit supporting AA/CMA)

ORR/DoR

- True anti-tumor effect of the drug (spontaneous responses rare); thus no control arm needed to show that the drug is active
- Has to clearly exceed ORR/DoR of other drugs (based on reliable historical controls) related to uncertainties related to the surrogate endpoint, small sample size and uncontrolled trial

TTP/PFS

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- Tumors often vary in progression (incl. pause of growth) without treatment
 + methodological/bias issues related to these endpoints,
 thus stable disease/TPP/PFS is variable and requires a controlled trial
- Or the uncertainty is outweighed with a very high outcome (e.g. Palbociclib with 10M improvement)



Confirmatory trials: Same or different clinical settings compared to intial trial supporting AA

Same population, e.g.

- Irinotecan in CRC (vs BSC)
- Dentileukin: Phase IV studies expanded to EU and Australia

Earlier line of treatament (against SoC), e.g.

- Docetaxel in BC (1st and 2nd line)
- Bevacizumab in GBM (1st line)

Controlled combination studies with SoC, e.g.

- Gemtuzumab in CML
- Capecitabine in BC
- Temozolomide (Phase Ib stopped due to toxicicity)



Comparison of current and proposed AA regulation (2012):

Relevant criteria remain, however, the scope of AA was slightly changed and extended taking (recent) developments (e.g. orphan, biomarker) and public expectations into consideration.

Previous regulation	New regulation				
Serious or life-threatening illness	Serious or life-threatening disease or condition, incl. fast-track				
Meaningful therapeutic benefit	Effect				
Over existing therapies	Taking the availability or lack of alternative treatments into consideration				
Adequate + well controlled trials	Type of trials not defined				
Surrogate endpoint (reasonably)	Surrogate endpoint reasonably likely to predict clinical benefit or				
likely to predict clinical benefit	Clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit				
No defined	Taking into account the severity, rarity or prevalence of the disease				
based on epidemiologic, therapeutic, pathophysiologic or other evidence	may include epidemiologic, phathophysiologic, therapeutic, pharmacologic , or other evidence developed using biomarkers , for example, or other scientific methods or tools				
Scope on confirmatory studies and o	consequences to fail with obligations remained basically unchanged.				



High response rates of existing treatments make an AA/CMA approach based on single arm trials difficult (if not impossible)

First anti-PD-1s agents are setting high bar for follow-on compounds (Citation from FDA assessor, Mar 2016)

The first group of PD-1 inhibitors produced "never seen" response rates in settings like melanoma, Dr. Sridhara (FDA) argued. "Once you have these products (BMS Opdivo and MSD Keytruda) already on the market, then the whole setting about how you compare to other products becomes a different design totally. I don't know that the same response rate will (support) ... accelerated approval unless you have identified a specific subgroup." "If you are depending on response rate, you have to show that the response rate is much higher than what is already approved," she noted. At some point, however, **there may be "a ceiling effect where we have seen the response rate to be so high that you may not be able" to beat it by a meaningful amount to justify accelerated approval.** The only option in those contexts might be to "**find the right biomarker and the right patient subgroup and you can get maybe a 100% response rate.**"

"Basic" ORR of 10% of existing SoCs: 30% could be a substantial improvement (supported by same/higher DoR), but what if 40 or 50% ORR from an SoC? What should you add on substantially to cope with uncertainty? 80? 90%?

Options to deal with this situation:

- Identify a (alternative/additional) predictive biomarker for a subset
- Go for AA/CMA in more refractory or resistant setting of previous (targeted) therapies
- Focus on improvement of duration of response (by comparable ORR); or estimate a higher ORR at a define minimum response duration (e.g. 6 months)
- Use Ph III trials with
 - IA for AA/CMA which can be supported by time-related endpoints or
 - if IA result is borderline for AA, finalize Ph III for analysis of clinical benefit endpoints (PRO, PFS, OS). Title of Presentation | DD.MM.YYYY

Criteria and mitigations to be considered when opening studies in 1st / early treatment lines where SoC exist

Criteria to move early into less refractory settings

- 1. <u>Level of R/B profile (mainly efficacy) of IMP to exceed SoC</u> available (incl. other drugs approved while IMP trial ongoing)
- 2. <u>Robustness of data package of IMP (PoC or Ph III or</u> approved for marketing)
 - PoC with limited data: Surrogate EP data; small safety data package; possibly uncontrolled data
 - Reminder that you replace SoC approved based on Ph III / demonstration of clinical benefit
- 3. Combination or monotherapy
 - Add-on to SoC may facilitate the move into earlier lines (SoC is given), however,

consider increased toxicity from combination and potential failure of efficacy improvement (e.g. Evofosfamide in STS)

 Replacement of SoC as part of monotherapy <u>may</u> imply a higher hurdle

Mitigations and examples:

- 1. Exclusion of patients eligible for SoC with high activity
 - ICF to indicate availability of other SoC, however, not always a solution to avoid exclusion of existing, effective therapies
 - Examples:
 - Evofosfamide in 1st line PaCa: Patients eligible for FOLFIRINOX to be excluded
 - Evofosfamide in 1st Line NSCLC: Patients for positive EGFR or ALK to be excluded in favor of SoC
- 2. <u>Staggered (overlapping) development approach from</u> more to less refractory setting

 (1) Initiate development for PoC and possibly registration in refractory settings (salvage or limited SoCs activity) advancing the development in 1st line / less refractory settings

(2) or use settings of previously failed, targeted therapies.



(A) Number CMAs 2006 – 2014; (B) Proposed Study designs in Scientific Advice intended to support CMA (Martinalbo 2015)



Figure 2. European Medicines Agency (EMA)—sponsor dialogue on early access during development. (A) EMA scientific advice (SA) and protocol assistance (PA, for orphan drugs) procedures discussing the clinical development of oncology drugs (excluding generics and biosimilars) in the period 2006–2014, including subset of requests containing specific questions related to potential conditional marketing authorisation (CMA). (B) Potential conditional approval filing strategies proposed by industry sponsors in the abovementioned SA/PA procedures (N = 101). Category 'others' includes various approaches for preliminary evidence and confirmation, e.g. combining elements of the previous strategies, subgroup analyses of studies failing on primary end point, unclear confirmation etc. DoR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RCT, randomised, controlled trial.

Cancer drugs with conditional authorisation in the EU: evidence and outcome of HTA/P&R at national level (EU4) (Martinalbo 2016)

Table 2. Cancer drugs with co	onditional authorisation in th	e EU: evidence and outcome of HTA/P&R at national level (EU4)									
Drug	Indication	Pivotal clinical trial design (N)	EU	Outcome	HTA/	P&R		Time fro	om aut	horisat	tion (m)
		Primary efficacy results (95% CI)	CMA	^a EN&W	ьDЕ	^c FR	dIT	EN&W	DE	FR	IT
Sunitinib (Sutent)	GIST 2L mono	Phase 3 RCT versus BSC (312) PFS 6.25 versus 1.46 months—HR 0.33 (0.23–0.47)	July 06 ^S	R	R	Π	R	32	n/a	2	4
	RCC 2L mono	2 × phase 2 single-arm (106, 63) ORR 25.5% (17.5%-34.9%)	July 06 ^S	R	R	III	R	37	n/a	2	4
Panitumumab (Vectibix)	CRC KRASwt 2L+ mono	Phase 3 RCT versus BSC (463) PFS 8 versus 7.3 months—HR 0.54 (0.443–0.663)	December 07 ⁸	NO	R	V	R	49	n/a	5	12
Lapatinib (Tyverb)	Breast HER2+ 2L comb. chemo	Phase 3 RCT add on to capecitabine (399) PFS 6.23 versus 4.26 months—HR 0.57 (0.43–0.77)	June 08 ^S	Susp.	R	III	R	n/a	n/a	1	11
Ofatumumab (Arzerra)	CLL 3L mono	Phase 2 single-arm (154) ORR 58% (40%–74%)	April 10 ^S	NO	R	V	R	6	n/a	6	13
Pazopanib (Votrient)	RCC 1L mono	Phase 3 RCT versus BSC (435) PFS 9.2 versus 4.2 months—HR 0.46 (0.34–0.62)	June 10 ^S	R	R	NO	R	8	n/a	8	11
Everolimus (Votubia)	SEGA paediatric 1L mono	Phase 2 single-arm (28) volume 0.93 versus 1.74 cm ³ (0.4–1.2)	September 11	n/a	R	Π	n/a	n/a	n/a	4	n/a
Vandetanib (Caprelsa)	Thyroid, MTC 1L mono	Phase 3 RCT versus BSC (331) PFS 30.5 versus 19.3 months—HR 0.46 (0.31–0.69)	February 12	n/a	3	IV	R	n/a	7	4	16
Pixantrone (Pixuvri)	DLBCL 2L mono	Phase 3 RCT versus BSC (140) CR 20 versus 5.7% (3.5–25.1); <i>P</i> = 0.021	May 12	R	5	n/a	NO	22	12	n/a	14 ^{NO}
Crizotinib (Xalkori)	NSCLC ALK+ 2L mono	Phase 1 single-arm + phase 3 RCT versus chemo (125, 318) phase 1 ORR 60%, phase 3 PFS 7.7 versus 3 months—HR 0.49 (0.37–0.64)	October 12	NO	2/5 ^f	III	R	10	6	17	29/5 ^e
Brentuximab vedotin (Adcetris)	sALCL CD30+ 2L mono	Phase 2 single-arm (58) ORR 75%, CR 33%, DoR 6.7 months	October 12	n/a	4	III	R	n/a	7	4	20/0 ^e
	Hodgkin CD30+ 3L mono	Phase 2 single-arm (102) ORR 86%, CR 59%, DoR 13.2 months	October 12	n/a	4	III	R	Exp 44	7	4	20/0 ^e
Bosutinib (Bosulif)	CML Ph+ 2L+ mono	Phase 2 single-arm (four cohorts: 502) MCyR 2L 53.4% (47.2–59.5), 3L 27% (19–36)	March 13	NO	4	V	R	7	7	11	18
Vismodegib (Erivedge)	Basal cell, met. 1L mono	Phase 2 single-arm (two cohorts: 104) ORR 30.3% (15.6-48.2), 42.9% (30.5-56.0)	July 13	n/a	3/5 ^f	IV	R	n/a	7	5	20
Cabozantinib (Cometriq)	Thyroid, MTC 1L mono	Phase 3 RCT versus BSC 2 : 1 (330) PFS 11.2 versus 4 months—HR 0.28 (0.19–0.4)	March 14	n/a	3	IV	n/a	n/a	10	8	n/a



^aEngland and Wales—NICE recommendation (impact on reimbursement): NO = not recommended; R = recommended; susp. = suspended; n/a = not appraised.

^bGermany—additional benefit rating category: 1 = considerable; 2 = significant; 3 = small; 4 = not quantifiable; 5 = not demonstrated; 6 = inferior to available therapy;

^cFrance—therapeutic value improvement: I = major, II = important, III = moderate, IV = minor, V = absent (impact on P&R). Times refer to HTA recommendations, which usually precede formal P&R

EU Conditional Marketing Authorisation vs. US Accelerated Approval **Internal assessement on the same/comparable data package**

INN	Drug	EMA start	EMA approval	FDA start	FDA approval	Delay EU- US start	Approval delay (EU)	Pivotal trial / PE (EU)	US Exp. App./Rev.
Sunitinib	Sutent	28.09.2005	19.07.2006	11.08.2005	26.01.2006	48 days (d) Med.	174 d	Ph. II (SAT) / ORR	AA/PR
Panizumumab	Vectibix	25.05.2006	03.12.2007	28.03.2006	27.09.2006	58 d	432 d	Ph. III (RCT) / PFS	AA/PR
Lapatinib	Tyverb/Tykerb	25.10.2006	10.06.2008	13.09.2006	13.03.2007	42 d	455 d	Ph. III (RCT) / TTP	PR
Ofatumumab (H)	Arzerra	25.02.2009	19.04.2010	30.01.2009	26.10.2009	26 d	175 d	Ph. II (SAT) / RR hem	AA/PR
Pazopanib	Votrient	25.03.2009	14.06.2010	18.12.2008	19.10.2009	97 d	238 d	Ph. III (RCT) / PFS	SR
Everolimus	Votubia / Afinitor Disperz	18.08.2010	02.09.2011	29.02.2012	29.08.2012	-560 d	-362 d	Ph. II (SAT) / ORR	AA/PR
Vandetanib	Caprelsa	22.09.2010	17.02.2012	07.07.2010	06.04.2011	77 d	317 d Median	h. III (RCT) / PFS	PR
Crizotinib	Xalkori	17.08.2011	23.10.2012	30.03.2011	26.08.2011	140 d	424 d	Ph. I (SAT) / ORR	AA/PR
Brentuximab vedotin	Adcetris	22.06.2011	25.10.2012	28.02.2011	19.08.2011	114 d	433 d	Ph. II (SAT) / ORR	AA/PR
Bosutinib (H)	Bosulif	17.08.2011	27.03.2013	17.11.2011	04.09.2012	-92 d	204 d	Ph. II (SAT) / MCyRR	SR
Vismodegib	Erivedge	21.12.2011	12.07.2013	08.09.2011	30.01.2012	104 d	529 d	<u>Ph. II</u> (SAT) / ORR	PR
Cabozantinib	Cometriq	17.08.2011	21.03.2014	29.05.2012	29.11.2012	80 d	477 d	Ph. III (RCT) / PFS	PR
Ceritinib	Zykadia	26.03.2014	06.05.2015	24.12.2013	29.04.2014	92 d	372 d	Ph. IB (SAT) / ORR	BT/AA /PR
Blinatumomab (H)	Blincyto	29.10.2014	23.11.2015	19.09.2014	03.12.2014	40 d	355 d	Ph. II (SAT) / CR/CR _{hem}	BT/AA/PR
Osimertinib	Tagrisso	25.06.2015	03.02.2016	05.06.2015	13.11.2015	20 d	82 d	Ph. I/II (SAT) / ORR	BT/AA /PR
Daratumumab	Darzalex	01.10.2015	20.05.2016	09.07.2015	16.11.2015	84 d	186 d	Ph. II (SAT) / ORR	BT/AA /PR
Olaratumab	Lartruvo	25.02.2016	09.11.2016	24.02.2016	19.10.2016	1 d	21 d	Ph. IB/II (RCT) / PFS	AA/PR
Ixazomib citrate	Ninlaro	20.08.2015	21.11.2016	10.07.2015	20.11.2015	41 d	367 d	Ph. III (RCT) / PFS	PR
Venetoclax	Venclyxto	04.12.2015	05.12.2016	29.10.2015	11.04.2016	36 d	238 d	Ph. II (SAT) / ORR	BT/AA/PR

EU CMA versus US AA – Regulatory & Clinical data patterns | 27.02.2017

N=19 (H) = Use of hematological endpoints in following indications: CLL (Arzerra), CML (Bosulif), and ALL (Blincyto)

Internal analysis: Cancer drug accelerated approvals US Years 2010-14

Accelerated Approval US	Outcome EU	
Adcetris (Hodgkin & NHL)*	СМА	
Xalkori (NSCLC)	СМА	
Kyprolis (Multiple myeloma)*	Unconditional	
Iclusig (CML & ALL)*	Unconditional – Accelerated Assessment	
Imbruvica (NHL)*	CMA request converted into Unconditional	
Pomalyst (Multiple myeloma)*	Unconditional	
Zykadia (NSCLC)	СМА	
Zydelig (CLL)*	Unconditional – Accelerated Assessment	
Oleparib (Ovar)	Unconditional	
Blincyto (ALL)	СМА	
Keytruda (Melanoma)	Unconditional	
Opdivo (Melanoma)	Unconditional – Accelerated Assessment	

EU approvals are usually delayed (median delay 7.3 months), therefore EU approvals granted in 2015 are included in this comparative table as well

Comparison of approval procedures of 11 CMAs with corresponding US approvals (Hoekman, 2015)



• Usually, eralier submission in US by some months

 Out of 10 CMAs, one half received AA, the other half regular approval

• Approval time takes much longer in EU compared to US (esp. in case of CMA vs RA in EU; not shown)

 More difficult to find consensus in EU multi state involvement, incl. balance and risk evaluation for CMA approval (internal meetings etc)

Time from IND to NDA/BLA/MAA: Range of 4 to 10 years



EU Conditional Marketing Authorisation *vs*. US Accelerated Approval **GRASP conclusions on main query**

- The available and analyzed data do not allow to conclude that EMA is more hesitant to grant CMA based on single arm data compared to AA in the US.
- The available data do not indicate that there is any EMA preference for "Ph II RCT".
- However, the present analysis is **neither** investigating or responding to the question, to which extent
 probability the granting of expedited approvals differs between the EU and the USA, **nor** to the issue of
 the length (intra- & inter-process) of the respective expedited approval processes ('timing patterns').
- The latter question has been investigated by several previous publications and reports too please find related information in the background section of this slide set.

GRASP data (CROH 2013): → No difference in the rates of granting CMA/AA for cancer drugs

Application characteristics	EU (EMA)	USA (EDA)	Ianan (PMDA)
	DO(LIMI)		supun (1 millin)
Number approvals NME ^a	28	27	24
NBE rate	14%	19%	12.5%
OD rate ^b	62%	52%	37.5%
Expedited review rate	7%	81%	42%
Expedited approval rate	31%	33%	na
'First-at-all-approved' rate	18°	96% ^d	4% ^e
'First-at-all-submitted' rate	18% ^f	89% ^g	8% ^h

Comparison of application characteristics and regulatory review patterns EU-USA-Japan (initial approvals, years 2006-2011).



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