EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Submission of comments on 'Draft Guideline on evaluation of anticancer medicinal products in man' (EMA/CHMP/205/95 Rev.5)

Comments from:

Name of organisation or individual
Xavier Paoletti (Gustave Roussy), Thomas Jaki (Lancaster University), Ralf-Dieter Hilgers (RTWH Aachen) and Franz König (Medical University of Vienna)* on behalf of the **IDEAS** (This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 63356, see http://www.ideas-itn.eu/) and **IDeAl** (IDEAL is a research project funded by the European Union's 7th Framework Programme for research, technological development and demonstration under grant agreement no. 602552, http://www.ideal.rwthaachen.de/). * correspondence to franz.koenig@meduniwien.ac.at Disclaimer: The views and opinions expressed are those of the authors and should not be attributed to any organisation with which the authors are employed or affiliated.

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30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	The EMA has to be congratulated for its EMA initiative on data transparency which gives the opportunity to access patient level data. Therefore the Agency may consider expand the section on how historical (external) data could be used in a pre-specified way in drug development programs when designing and executing both exploratory and pivotal clinical trials in oncology (see Eichler et al., 2016). Proposed changes: e.g. expand section 7.6.7 and discuss also clinical trial design which incorporate both historical and concurrent controls. It might be worth discussing the differences of incorporating external information in exploratory and pivotal trials.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Line 95, L 839		Comment: The agency should explain more precisely in which way the term ”cross-over“ is used in the context of this guideline, i.e., a switching from the treatment in the control group to the experimental treatment in case a pre-specified event is reached. (Usually the term cross-over would be associated with cross-over trials). Proposed change (if any): Expand explanation (line 95, line 839) and consider an alternative term “treatment switch”. Discuss more specifically how this cross-over impacts the final analysis of OS and reporting of treatment effects.	
L137:		Comment: The aim of this guideline is to underline the importance of exploratory studies to identify the most appropriate population, but very few designs are proposed as the related sections mainly focus on endpoint and comparator’s choice Proposed change (if any): To add a specific paragraph in each section where biomarker assessment is encourage	
L144, L378, …		Comment: Not all abbreviations used are introduced the first time when they are used, e.g. ORR (line 144) or TTP (line 378).	

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		Proposed change: E.g., “Objective Response Rate (ORR)” (line 144). In this respect it would be good to include all abbreviations used (SmPC, NSCLC, …) in the appendix (from line 1494).	
L242		Comment: The notion of convincing evidence of biomarker selectivity established in exploratory trials may be ambiguous as only randomized trials enable to define the predictive value of a biomarker. Proposed change (if any): At least a randomized trial on the whole population should be requested (possibility in an other indication) before a subgroup of patients is excluded from researches.	
L314		Comment Section 6.1.1., p9: While intra patient dose escalation is certainly desirable, it is unclear how low toxicity (or non-significant toxicity) is established prior to a phase I study. Related it is unclear why 2 cycles of the same dose would be desirable specifically in the light that often only cycle 1 toxicities are considered in the dose-escalation decision	
L342-344		Comment Section 6.1.2 p10 l342-344: clearly advocates the use of response as the primary endpoint in these studies when it is well known that alternative measures such as tumor size	

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		directly are more powerful. See also p11 l372-374.	
L399		Comment: The guideline underlines that the delineation between phase I and phase II is not always relevant. However, no guidance is provided on the so-called expansion cohorts that are commonly designed with huge number of patients and few clear decisions rules and controlled errors. Proposed change (if any): Recall that any design before going to confirmatory studies should adequately quantify and control for risks of errors	
L407		Comment Section 6.2.1 p12: Surly non-clinical data are equally important when designing a phase I trial for a cytotoxic agent.	
L466-467		Comment: Unclear why individual PK variability means that 75% is an acceptable level. Moreover what does “no dose-reduction” mean in the light of these agents being given continuously.	
L478onwards		Comment: many of the non-toxic agents act by slowing/stopping tumor growth (rather than shrink). All the proposed endpoints (ORR, PFS TTP), however, rely on no increase in tumor size and hence are not sensitve for these	

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		agents. Direct modelling of tumor size will be more appropriate.	
L506		Comment: Within patient comparisons, in absence of control arm (so-called PFS ratio or tumour growth modulation index) is encouraged. However, very few experiences has been gained, which increases the risk of erroneous conclusions. In particular the hypothesis that the subsequent line of treatment should be shorter than the previous line of treatment in absence of clear treatment effect is poorly documented. Correlation between 2 consecutive lines of treatment is rarely provided. Previous reports indicate that it depends strongly on the tumor type and histology. The greater variability induced by taking the ratio makes its interpretation difficult. Last, the risk of selection bias is important as only patients with progressive disease during period 1 can be analysed in period 2. (see Buyse et al JCO 2010) Proposed change (if any): This endpoint should not be encouraged outside of randomized trials (real cross-over) and without a documented estimate of the correlation between 2 consecutive lines of treatment	
L535 - 621		Comment: The word pseudo-progression is often used in situations of delayed response with immune checkpoint blockers. The issue of misleading imaging due to oedema	

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		might be seen as error on response (obtained due to the impact of corticoid on oedema for instance) Proposed change (if any): Give a definition	
L601		Comment: for immune compounds where there is no clear dose effect at the explored doses, it is suggested that schedule can be an important factor. However, no schedule finding is requested. Proposed change (if any): a schedule-finding experiment could be considered.	
L747		Comment: it is also expected that the exploratory studies through the judicious use of biomarkers provide guidance with respect to selection of patients in order to optimise benefit – risk. While population enrichment appears highly advisable when there has been a clear demonstration of the value of a biomarker to predict response to treatment, one should always separate exploratory from confirmatory trials; the use of a biomarker to select population should be limited to the case where the biomarker has been confirmed as a predictive maker. The current wording seems to suggest that exploratory studies may provide good rational to select population. Proposed change: Enrichment of the population in phase III should be restricted to the cases where the biomarker has	

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		been demonstrated to be predictive of the response to treatment.	
L841onwards		Comment: Within the IDeAl project it could be shown, that randomization does not protect against bias in general. According to the ICH E9 guideline, the potential impact of bias on the study results should be investigated. Consequently the selection of the randomization procedure which best protect against bias in the particular study setting, should be based on scientific arguments by conduct of a scientific comparative evaluation study. The IDeAl project has developed the software and framework for this evaluations study. Proposed Changes: In blue text in section 7.1.4. ("Randomisation and blinding": Randomisation and stratification should adhere to the general principles laid down in current guidelines (CPMP/ICH/363/96). **The selection of a particular randomization procedure should be based on scientific arguments, taking into account the clinical trial setting as well as the resulting impact of bias on the study results.** In many cases, a double-blind design is no option due to obvious differences in toxicity between study regimens or due to safety concerns. If the study has to be conducted open label, this has implications with respect to choice of t**he randomization procedure,** study endpoints, independent review, conduct of	

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		sensitivity analyses and other measures to be undertaken to limit potential bias related to the open- label nature of the trial.	
L903		Comment: Collecting time to initiation of next line therapy and reasons for selecting the next line therapy is encouraged for all studies. This endpoint is highly dependent upon investigators' choice and patient status. Therefore, in absence of blinded trial, the interpretation of such endpoints is delicate. While it is an alternative when progression is difficult to access (for example in Ovarian cancer trials), it is expected to bring more confusion in the interpretation of the results. Proposed change: this endpoint should be restricted to settings where progression is difficult to access or time to second progression is not applicable.	
L861 onwards, L114 onwards Line 861		Comment: In section 7.1.5 ("Endpoints") it would be worth discussing clinical trial designs where PFS and OS are both used as multiple primary endpoints, where the trial is considered as successful if at least one yields statistical significance. As the number of events needed for PFS analysis is usually reached earlier than the number of events needed for OS, this is sometimes addressed by including an interim analyses for OS at the time of the (final) PFS analysis. The Agency could elaborate on its view on how to distribute the alpha between endpoints (and interim analysis if applicable).	

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		Line 861 and line 242: In this respect it could be worth discussing clinical trial design allowing testing both the overall population and a subgroup of interest (defined by a biomarker). See e.g., Ondra et al. 2016, Brannath et al. Graf et.al, 2015.	
L1038 – 1049, L1174-1185, L1132 - 1152:		The EMA should consider more advanced analysis methods for time-to-event data, e.g., multi-state or competing risk analysis (such as the Fine and Gray model) or at least discuss their potential role as sensitivity analyses.	
L1098onwards L1130onwards		Comment: We acknowledge that planning, conducting and finally interpreting a clinical trial with an interim analysis with survival data has some logistical and methodological challenges (see Magirr et al, 2016). However, as group sequential designs are routinely applied in survival trials and as also a recent review on scientific advices given by SAWP/CHMP on adaptive designs showed that about half adaptive design proposals were in oncology (Elsäßer et al. 2014), the paragraphs concerned should acknowledge the current practise and be more encouraging with respect to interim analysis. In adaptive enrichment and adaptive seamless designs (see Bauer et al. 2016) it might be more efficient to base adaptations, e.g., such as which population or treatment shall be carried over to next stage, rather on PFS than on (pre-mature) survival data.	

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		In this regards (line1125-1127) it should be explicitly stated that only pre-specified adaptive designs allowing enrichment will control the type I error rate, but doing it post-hoc not. But the current version of the text might be interpreted as the latter one. Furthermore there is an inconsistency in disregarding PFS for decision making at interim, because in other sections of the guidance document it is acknowledged that PFS may be an acceptable primary endpoint on its own. Another aspect to be taken into account is that some survival studies may run for many years. Then it is of particular importance to monitor the data and prospectively forsee interim analysis with the option to adapt the design rather than doing it in a post-hoc way. Proposed change: Re-phrase partly the paragraphs concerned and replace sentence “In general, interim analysis based on PFS data other than for futility are not encouraged” by “In general, stopping the trial for efficacy solely on PFS is not encouraged. However, using information on PFS to stop the trial for futility or changing the trial design at interim (e.g., selection of population in adaptive enrichment designs or treatment selection in adaptive seamless designs) may be informed better by PFS interim data than using pre-mature OS interim data.”	