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3 Oncology Working Party

4 Guideline on the evaluation of anticancer medicinal  
5 products in man  
6

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10 This guideline replaces guideline / NfG Reference.

11

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## 72 **Executive summary**

73 The purpose of this guideline is to provide guidance on all stages of clinical drug development for the  
74 treatment of malignancies, including drug resistance modifiers or normal tissue protective compounds.  
75 Supportive measures such as anti-emetics and haematopoietic growth factors, however, are covered  
76 by separate guidelines.

77  
78 Alongside conventional aims such as defining the proper dose(s) and schedule(s), the importance of  
79 identifying a target population with optimised benefit risk is emphasised in Section 6: Exploratory  
80 Studies. Guidance is also provided on combination studies. Combinations of drugs with minimal activity  
81 as monotherapy, but synergistic effects when combined, as well as combinations of conventional  
82 cytotoxics, are also discussed.

83  
84 Convincingly demonstrated favourable effects on overall survival (OS) are from both a clinical and  
85 methodological perspective the most persuasive outcome of a clinical trial. Prolonged progression-free  
86 or disease-free survival (PFS/DFS), however, are in most cases as such considered relevant measures  
87 of patients benefit, but the magnitude of the treatment effect should be sufficiently large to outbalance  
88 toxicity and tolerability problems. In order to capture possible negative effects on the activity of next-  
89 line therapies and also treatment related fatalities, informative data on overall survival compatible with  
90 a trend towards favourable outcome are normally expected at time of submission. This has  
91 consequences with respect to interim analyses and cross-over, which thus should be undertaken only  
92 when survival data will provide the information needed for a proper evaluation of benefit/risk.

93  
94 An assessment of benefit/risk should encompass all relevant data on efficacy and safety, also taking  
95 into account uncertainties as well as external data of relevance in relation to the experimental  
96 compound and the disease to be treated. Therefore no precise definition of "trend towards favourable  
97 effects on survival" or "reasonably excluding negative effects on OS" is given in this document. If a  
98 major increase in toxicity is foreseeable (see section 8), it is recommended that confirmatory studies  
99 are undertaken with the aim to show an OS benefit. It is also acknowledged that improved safety  
100 without loss in efficacy may constitute tangible aims and the design of non-inferiority studies are  
101 discussed in 8.7.3.

102  
103 In section 10, definitions and abbreviations used in this guideline are summarised. Appendix 1 provides  
104 methodological guidance on the use of PFS as endpoint in confirmatory studies. A planned appendix 2  
105 will focus on the use of patient report outcome (PRO) measures and health-related quality of life  
106 (HRQoL) from a regulatory perspective. A revised paediatric guideline is also foreseen.

## 107 **1. Introduction**

108 The guideline on anticancer medicinal products adopted in 1996, and revised in 2001 and 2003,  
109 focused on conventional cytotoxic compounds. In 2005, a major revision was undertaken, aiming at  
110 covering non-cytotoxic compounds, to expand on the sections on exploratory trials and to provide  
111 more guidance with respect to methodological issues. Later, there followed an appendix on  
112 methodological issues related to use of PFS and in early 2010 an appendix on haematological  
113 malignancies followed. In this appendix disease specific guidance was introduced and the section on  
114 confirmatory studies based on aims of therapy and relative toxicity was restructured. These latter  
115 elements have now been incorporated in the revised main guideline. In this revision, the chapter on  
116 exploratory trials for cytotoxic compound has been shortened as it was considered too detailed and too  
117 prescriptive. The section on condition specific guidance has been expanded and now includes Non-  
118 Small Cell lung Cancer, Prostate Cancer, Chronic Myeloid Leukaemia, Myelodysplastic Syndrome and  
119 Haematopoietic Stem Cell Transplantation.

## 120 **2. Scope**

121 Whilst the thrust of a regulatory guideline should be on confirmatory studies, the aim of this guideline  
122 is also to underline the importance of exploratory studies in order to properly define the most  
123 appropriate target population in addition to the usual aims: to define dose, schedule, tumour type and  
124 line of therapy. The role of biomarkers to achieve these objectives is also further emphasised in this  
125 revised guideline.

126 There are numerous possible ways to classify anti-cancer drugs such as direct anti-tumoural vs.  
127 indirect anti-tumoural, or based on pharmacology or molecular target (*e.g.* hormones, immune

128 modulators, nuclear-targeting, signal-transduction targeting, etc.). As this document is meant to  
129 provide guidance on clinical drug development, the aim has been to classify compounds according to  
130 reasonable designs of exploratory studies, i.e. cytotoxic compounds where toxicity and ORR are  
131 considered suitable markers of activity in drug development vs. non-cytotoxic compounds where ORR  
132 and/or toxicity may not serve this purpose.

133 A very large number of anti-cancer compounds have been and currently are under development. Only  
134 a minority, however, have completed the clinical development and obtained a marketing authorisation,  
135 due to insufficient evidence of efficacy or evidence of a detrimental safety profile. Until non-clinical  
136 models with good predictive properties have been defined, this situation is likely to remain essentially  
137 unchanged and the absence of such models is considered to constitute the greatest hurdle for efficient  
138 drug development within the foreseeable future.

139 Since chemoprotective agents and drug resistance modifiers are used as part of anticancer regimens,  
140 some guidance on these agents will also be provided in appropriate sections of this guideline. Anti-  
141 emetics and haematopoietic growth factors, however, are covered in separate documents.

142 Additional recommendations of relevance for childhood malignancies and paediatric drug development  
143 are provided as a separate "*Addendum on paediatric oncology*".

### 144 **3. Legal basis**

145 This document should be read in conjunction with Directive 2001/83/EC, as amended. Applicants  
146 should also refer to other relevant European and ICH guidelines on the conduct of clinical trials,  
147 including those on:

- 148 ➤ Nonclinical evaluation for anticancer pharmaceuticals EMEA/CHMP/ICH/646107/2008 (ICH S9)
- 149 ➤ Reflection paper on methodological issues associated with pharmacogenomic biomarkers in relation  
150 to clinical development and patient selection EMA/CHMP446337/2011
- 151 ➤ Clinical Investigation of the Pharmacokinetics of Therapeutic Proteins CHMP/EWP/89249/2004
- 152 ➤ Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Impaired Hepatic  
153 Function - CPMP/EWP/2339/02
- 154 ➤ Investigation of drug interactions - CPMP/EWP/560/95
- 155 ➤ Points to Consider on Adjustment for Baseline Covariates - CPMP/EWP/2863/99
- 156 ➤ Points to Consider on Multiplicity Issues in Clinical Trials - CPMP/EWP/908/99
- 157 ➤ Guideline on the choice of the choice of non-inferiority margin - CPMP/EWP/2158/99
- 158 ➤ Guidance on Statistical Principles for Clinical Trials - CPMP/ICH/363/96
- 159 ➤ Guideline on clinical trials in small populations- CPMP/EWP/83561/2005
- 160 ➤ Choice of Control Group in Clinical Trials -CHMP/ICH/364/96 (ICH E10)
- 161 ➤ Guideline on clinical evaluation of diagnostic agents - CPMP/EWP/1119/98
- 162 ➤ Note for guidance on clinical safety data management: definitions and standards for expedited  
163 reporting - CPMP/ICH/377/95 (ICH E2A)
- 164 ➤ Note for guidance on clinical safety data management: data elements for transmission of individual  
165 case safety reports - CPMP/ICH/287/95 (ICH E2B)
- 166 ➤ Points to consider on application with 1. Meta-analyses 2. One pivotal study - CPMP/EWP/2330/99

### 167 **4. Pharmacokinetics**

168 In general, the same recommendations are valid for anticancer products as for other medicinal  
169 products and reference is made to the clinical pharmacology guidelines available including the conduct  
170 of food interaction studies prior to phase III. In the past, mass-balance studies have not been  
171 performed to the same extent for anticancer drugs as for other medicinal products. Due to the  
172 importance of the information gained in these studies for the understanding of the clinical  
173 pharmacology of the investigational drug, including the drug-drug interactions assessment, mass-  
174 balance studies are strongly recommended. (Investigation of drug interactions, CPMP/EWP/560/95)  
175

176 Studies to be undertaken in patients with impaired organ function should mainly be selected based on  
177 prior information on the mode of elimination of the drug and formation/elimination of potential  
178 pharmacologically active metabolites. If a study in hepatic impairment is needed, as a first step a  
179 study in patients with liver metastases is warranted. Whether studies in more advanced liver disease  
180 are needed should be decided on a case by case basis.

181  
182 It is recommended to evaluate the influence of intrinsic factors through population PK analyses of  
183 sparse phase III plasma concentration data. This evaluation could include factors such as age, weight,  
184 renal function, S-bilirubin, genotype etc. (Evaluation of the Pharmacokinetics of Medicinal Products in  
185 Patients with Impaired Hepatic Function, CPMP/EWP/2339/02)

186  
187 It is recommended to collect sparse samples in pivotal trials. This information aids in understanding  
188 the exposure-response relationships for the drug, and may allow for a rational selection of treatment  
189 strategies in patients who are risk for excessive toxicity or ineffective therapy.

190  
191 Exploratory studies, including PK, in patients with malignant ascites or other third space conditions are  
192 encouraged.

## 193 **5. Biomarkers**

194 In order to optimise benefit – risk, it is essential to identify the proper target population for therapy.  
195 This might be possible to accomplish through the judicious use of biomarkers in all phases of clinical  
196 drug development. A biomarker should be capable of measuring and evaluating a normal biological  
197 process, a pathological process or the pharmacological response to a therapeutic intervention,  
198 depending upon its purpose.

199  
200 Irrespective of pharmacological class, it is assumed that entrance into clinical development of new  
201 molecule today is guided by translational research. This means that in most cases there are  
202 hypotheses to be tested and candidate biomarkers available. The utility of biomarkers is broad e.g.  
203 prospective stratification of clinical trial subjects according to biomarker status, determination of the  
204 biologically effective dose, early proof of mechanism or concept, assessment of toxicity and an  
205 indication of the natural course of a disease. However, although efforts to identify targets and explain  
206 variability in PK and PD are essential, the need to confirm the findings should not be overlooked in the  
207 planning of the drug development programme (technical and clinical validation).

208  
209 It is acknowledged that biomarkers tested in early clinical trials often were exploratory in nature, but it  
210 is essential that technical/quantitative reliability is assured. While serum biomarkers or other sources  
211 of biological samples might be informative, tumour samples are expected to constitute an integral part  
212 of the biomarker exercise if not properly justified based on pharmacological properties. Normal tissues  
213 samples may also be used in early clinical studies, if non-clinical studies indicate that there is a  
214 correlation between the changes observed in normal tissues and changes in tumour tissue. The role of  
215 functional imaging in early drug development is not regarded as well established, but its use is  
216 encouraged.

217  
218 The development of companion diagnostic methods should be considered early in clinical development,  
219 maximising the clinical application of the technology. Commercially available diagnostic assays should  
220 comply with the requirements laid down in IVD Directive (98/79/EC).

221  
222 For the use in confirmatory studies and e.g. as measures of efficacy, biomarkers must be carefully and  
223 rigorously validated following systematic evaluation in well designed prospective clinical trials  
224 (Reflection paper on methodological issues associated with pharmacogenomic biomarkers in relation to  
225 clinical development and patient selection EMA/CHMP446337/2011). In order to assist in interpretation  
226 of results across studies and limit sources of variability when developing biomarkers, the use of  
227 available guidelines is encouraged, e.g. reporting recommendations for tumour marker prognostic  
228 studies (REMARK).

## 229 **6. Exploratory studies**

230 Exploratory studies are essential in rational drug development. The distinction between Phase I/II  
231 exploratory and Phase III confirmatory trials has been adhered to in this Guideline. However, this does  
232 not mean that exploratory aims should not form an important part of Phase III trials. Similarly,  
233 hypothesis generation, testing and confirmation may form parts of Phase II trials.

## 234 **6.1. Cytotoxic compounds**

235 This refers to conventional cytotoxic agents, i.e. compounds inducing irreversible lethal cellular lesions  
236 following short-term exposure through interference with DNA replication, mitosis, etc. For these  
237 compounds, toxicity and tumour response are considered suitable indicators of activity.

238  
239 As for non-cytotoxic compounds, non-clinical and clinical studies encompassing aims to characterise  
240 prerequisites for activity/resistance and to identify markers of resistance are encouraged.

### 241 **6.1.1. Phase I, single agent dose and schedule finding trials**

242 The basic assumption governing the design of these trials is that, for dose finding purposes, toxicity is  
243 an acceptable endpoint. The main objective is thus to define dose-limiting toxicities and the dose to  
244 bring forward into further trials. While meeting this objective is generally straightforward, in spite of  
245 the fact that the inter-patient variability in PK might be large, it is often more complex to define  
246 reasonable dose schedules to study further.

247 It is accepted that the dose initially is calculated per body surface area (BSA), but the empirical  
248 support for the notion that this approach meaningfully reduces inter-patient variability in exposure is  
249 weak. Whether a flat dose or a dose calculated according to BSA or weight is used, it is recommended  
250 that the importance of BSA or weight for variability in exposure is explored through modelling-

#### 251 **Main Objectives**

252 ➤ Maximum Tolerated Dose (MTD), Dose Limiting Toxicity (DLT) and a recommended Phase II dose  
253 (RP2D) (usually one dose step below MTD) should be identified for defined schedules and modes of  
254 administration.

255 ➤ Frequent side effects and target organs for toxicity should be characterised as regards relationship  
256 to dose and schedule. Extent, duration and reversibility should be determined.

257

#### 258 **Eligibility of patients**

259 These trials should normally be undertaken in cancer patients without established therapeutic  
260 alternatives.

#### 261 **Routes of administration and schedules**

262 In most cases, intravenous administration, when feasible, is advisable for first use in man studies since  
263 it eliminates variability related to bioavailability.

264 For schedule finding, experience related to class of compounds is helpful. Non-clinical data with respect  
265 to cycle dependency and the ratio tumour / normal tissue cytotoxicity *ex vivo* may be of some interest.

#### 266 **Dose escalation**

267 In case of minimal toxicity, or occasionally in case of non-significant toxicity, within-patient dose  
268 escalation may be appropriate in order to reduce the number of patients exposed to non-active doses,  
269 but is acceptable only if non-clinical data provide no evidence of cumulative toxicity.

270 If toxicity is acceptable, the patient may be re-exposed upon recovery and preferably should receive at  
271 least 2 cycles at the same dose level.

#### 272 **Evaluation of toxicity**

273 The minimal requirements for evaluation of adverse effects include assessment of symptoms, physical  
274 examination, ECG, blood and urine laboratory analyses and radiological assessment as appropriate.  
275 Preclinical data should be used to guide the need for further examinations. If there are no signals with  
276 respect to QTc in preclinical studies or related to class of products, no dedicated QTc studies are  
277 expected, but inclusion of ECG as part of routine monitoring is recommended. Local toxicity at the site  
278 of administration should be specifically recorded. The toxicity should be graded according to a  
279 generally recognised system (e.g. WHO toxicity criteria, Common Terminology Criteria for Adverse  
280 Events, CTCAE).

281 Factors influencing toxicity (organ dysfunction, concomitant therapy) should be explored as  
282 appropriate. These factors should be further elucidated in Phase II/III.



## 283 **6.1.2. Phase II, single agent therapeutic exploratory studies**

284 Phase II trials may investigate single-agent activity in a variety of tumour types, or in a selected  
285 tumour type, or investigate activity and feasibility of combination or multimodality regimens.

286 This section is focused on trials where the primary objective is to estimate single agent antitumor  
287 activity in patients with a defined tumour type in order to identify compounds to bring forward to  
288 confirmatory trial.

### 289 **Objectives and design**

290 Phase II trials may use a variety of study designs and early studies should provide initial evidence of  
291 treatment activity and tolerability. Inclusion of a randomised control arm is ~~to be~~ encouraged,  
292 particularly if only one confirmatory pivotal trial is foreseen  
293

294 The studies are intended to:

- 295 ➤ To assess the probability of response in the target tumour type and conclude on the need for  
296 further studies (investigate earlier stages of the disease, combinations, compare with standard  
297 therapy).
- 298 ➤ To investigate pharmacogenomics, where appropriate
- 299 ➤ Further characterise dose and schedule dependency, with respect to safety and activity
- 300 ➤ Further characterise the side-effects of the medicinal product:
- 301 ➤ When applicable, further characterise the optimum route of administration

### 302 **Selection and number of patients**

303 Exact definition of the target disease, previous therapy (if any) and stage should be given, in line with  
304 internationally agreed diagnostic criteria.

305 Provided safety and activity is reasonably established and there is a scientific rationale, it might be  
306 appropriate to conduct studies also in patients for whom alternative therapies are available. This  
307 includes the neo-adjuvant setting in treatment naïve patients scheduled for surgery, provided that  
308 delay in surgery cannot be detrimental to the patient. The safety and interests of the patient must  
309 always be guaranteed and a detailed justification should be provided in the study protocol. In these  
310 cases, the use of sensitive measures of anti-tumour activity is expected.

### 311 **Dose and schedule**

312 The dose and schedule should be clearly defined. Details on the administration of the medicinal product  
313 with special precautions (hydration of patients, protection against light and temperature, etc.) should  
314 be stated as well as other agents, which are contraindicated during the study period.

- 315 ➤ Guidance should be supplied outlining dose modifications related to the severity of the observed  
316 toxicity.
- 317 ➤ Rules for dose escalation in case of low toxicity should be considered.
- 318 ➤ Consideration should be given to study high-risk patients (e.g. high risk with respect to target  
319 organ toxicity or compromised metabolic or excretory mechanisms for the experimental compound)  
320 separately.

321 Any evidence of cumulative toxicity should be recorded and estimated as a function of total dose. This  
322 should be specifically studied according to target organ or function.

### 323 **Evaluation of activity**

324 ORR should be documented according to international standards (e.g. RECIST, or WHO criteria).  
325 Modifications of these criteria may be appropriate in certain situations, but should be justified.

326 In evaluating ORR, data for all patients entered into the trial should be reported. Where ORR in the  
327 per-protocol analysis set is considered to be of primary interest, then data for all patients included into  
328 the trial should also be reported. External independent review of tumour response is encouraged,  
329 according to the objectives of the trial.  
330

331 In haematological malignancies, disease specific response criteria are unavoidable in many cases and  
332 full harmonization has not yet been accomplished for some disease entities. Therefore it is of  
333 importance to follow the progress made by international working groups on these issues. Especially if



334 less conservative disease specific response criteria are introduced in new clinical guidelines, a  
335 justification with focus on aspects of drug development is expected from the sponsor.  
336  
337 Data on duration of response, TTP/PFS and available data on OS should normally be reported.  
338 The use of tumour biomarkers and other dynamic measures of activity is encouraged.  
339 In patients with symptomatic disease at base line, the assessment of symptom control is encouraged,  
340 if a randomised phase II trial is undertaken.

## 341 **6.2. Non-cytotoxic compounds**

342 This refers to a very heterogeneous group of compounds ranging from antihormonal agents to  
343 antisense compounds, signal transduction, angiogenesis or cell cycle inhibitors, immune modulators,  
344 etc. The common element affecting the design of clinical trials is that toxicity may not be an  
345 appropriate endpoint in dose and schedule finding trials and ORR may not be an appropriate measure  
346 of anti-tumour activity.

347 For these reasons, the early stages of clinical drug development are more complex and have to be  
348 tailored according to the assumed pharmacology of the individual compound as defined in non-clinical  
349 studies. The rather strict delineation between Phase I and II trials, as for conventional cytotoxic  
350 compounds, may be less relevant as measures of anti-tumour activity, e.g. based on assessment of  
351 biomarkers might be needed early in order to define dose and schedule.

352 Otherwise, most of the elements discussed in relation to cytotoxic drugs are of relevance also here  
353 such as restrictions with respect to patient eligibility, recommendations as regards routes of  
354 administration, evaluation of toxicity and anti-tumour activity, etc. These issues will not be further  
355 discussed here.

### 356 **6.2.1. Phase I, single agent dose and schedule finding trials**

357 Based on preclinical tolerability and toxicology findings and the assumed pharmacology of the  
358 compound, early trials may sometimes be conducted in healthy volunteers. Tolerability, safety, PK and,  
359 if at all possible, PD measures of activity are appropriate objectives.

360 Non-clinical data and, when available, data from healthy volunteers should be used to design the  
361 studies to be conducted in patients, e.g. as regards eligibility criteria and starting dose. In accordance  
362 with the guidance for cytotoxic compounds, availability of established therapies should normally be  
363 regarded as an exclusion criterion. Refractoriness to conventional cytotoxic compounds, however, may  
364 confer resistance also to some clearly non-related compounds. This obviously affects the possibility to  
365 define a dose/concentration – effect relationship. All sensible and ethically acceptable measures  
366 undertaken to increase the assay sensitivity of these clinical trials, including the conduct of window of  
367 opportunity studies are encouraged. Whenever appropriate, this includes measuring the expression of  
368 the assumed target(s) for drug activity.

369 PD measures may include biochemical measures (receptor binding, enzyme inhibition, downstream  
370 events, etc. as defined in non-clinical studies), functional imaging, proteomics, immunological  
371 measures (antibody or T-cell response), etc. Population PK/PD studies are encouraged. For compounds  
372 shown to be cytostatic in non-clinical models, prolonged exposure may be needed to elicit tumour  
373 shrinkage in clinical studies. If in these cases unexpected, early tumour shrinkage is observed this  
374 constitutes a signal indicating that further studies exploring the underlying mechanisms behind early  
375 response are warranted.

376 While it is acknowledged that drug development for compounds with a single main target for activity,  
377 such as mutated BRAF, is more straight forward, it is still expected that the pharmacological rationale  
378 behind poly-targeting compounds is reflected in the exploratory studies programme, e.g. in terms  
379 of biomarkers selected in order to identify the proper target population for treatment.

380 Until now available experience indicates that tumour selectivity is not to be expected. Tolerability and  
381 toxicity thus remain important measures in dose and schedule finding studies. Even if, e.g. saturation  
382 of the target for drug activity, or a desired PD activity can be demonstrated without significant toxicity,  
383 it is still advisable to investigate higher dosages in order to better define the safety of the compound  
384 and possible irregularities in PK and PD. This may include defining MTD.

385 If not pharmacologically justified, proper analyses of biopsies from tumours (primaries and metastatic  
386 lesions), are expected to constitute a pivotal role in studies undertaken to identify the proper target

387 population for confirmatory studies. This might be crucial and has to be considered in the recruitment  
388 of investigators and patients.

389 As for conventional cytotoxic drugs, the use of tumour markers and sensitive imaging techniques, in  
390 combination with conventional methods, are recommended in order to delineate possible antitumor  
391 activity. Also in exploratory trials it is recommended that technical standardisation of, e.g. functional  
392 imaging techniques, is implemented in order to reduce inter-centre variability.

393 Eligibility criteria and the number of patients should be defined according to the objectives of the study,  
394 also taking into account variability in PK and PD at doses and schedules selected for further studies.

## 395 **6.2.2. Phase II, single agent therapeutic exploratory studies**

396 For the purpose of simplification, it is assumed that a dose/exposure range has been defined that  
397 shows pharmacological activity/target occupancy with or without dose limiting toxicity. If not otherwise  
398 justified, it is postulated that activities related to identification of the proper target population, as  
399 discussed above, continues in these studies.

### 400 ***Study designs and measures of activity***

401 ORR, despite all its shortcomings related to patient-selection, etc, is a rather convincing measure of  
402 activity as for most tumours, spontaneous regression fulfilling criteria for at least partial response is an  
403 uncommon phenomenon. For exploratory purposes, studies without a randomised reference are  
404 therefore considered interpretable and guidance provided in the section about cytotoxic compounds is  
405 relevant. Irrespective of this, inclusion of a randomised reference arm is encouraged and might be of  
406 special interest in order to explore whether, e.g. a selected biomarker is prognostic and/or predictive.

407 Time to progression (TTP) and progression-free survival (PFS), however, are in principle a function of  
408 underlying tumour growth rate and the activity of the anti-tumour compound. Also, if documented  
409 progressive disease is an inclusion criterion, underlying growth rate is hard to define in most patients  
410 and historical data will be even harder to interpret. Therefore, the interpretation of TTP/PFS data  
411 without a randomised reference is problematic.

### 412 **Exploratory trials with time-related endpoints**

413 There is probably no ideal yet feasible design of exploratory studies for compounds assumed to mainly  
414 elicit tumour growth control. In the following some design alternatives are discussed, all with pros and  
415 cons, but in principle acceptable from a regulatory perspective.

416 ➤ A randomised, dose comparative trial, e.g. comparing the lowest dose likely to be  
417 pharmacologically active with higher dose(s), if showing a difference in TTP/PFS, will obviously  
418 provide evidence of activity, but not in absolute terms.

419 ➤ Randomised withdrawal of therapy in patients with non-progressive disease after a defined  
420 period of time on experimental therapy. The acceptability of this design to patients and  
421 investigators, however, may constitute an obstacle and carry-over effects may be a reality for  
422 some compounds.

423 ➤ In previously treated patients, a within patient comparison of TTP/PFS might provide evidence  
424 of activity. Here TTP on last prior therapy is compared with TTP/PFS on the experimental  
425 therapy. It should be noted, however, that the underlying assumption of non-decreasing  
426 growth rate over time cannot always be substantiated. For exploratory purposes this  
427 constitutes no major concern. It is advisable to recruit patients with secondary as well as  
428 primary resistance on prior therapy. This ensures at least to some extent, that the study  
429 population is representative. It should also be noted that patients with early failure (primary  
430 resistance) on prior therapy may show some inversions in terms of TTP just due to fluctuations  
431 in tumour growth rate and variability related to imaging techniques.

432 For certain indications, a within patient comparison may be justified also in treatment naive  
433 patients.

434 ➤ A randomised phase II study versus a compound known to be active in the selected population  
435 (or placebo/BSC if justified) provides another alternative. If such a study is regarded as  
436 exploratory, there is no need for, e.g. well-defined non-inferiority criteria. In a comparison in  
437 terms of TTP it should be noted, that a purely growth inhibitory compound is "favoured"  
438 compared with a compound inducing tumour shrinkage, as progression is defined in relation to  
439 best tumour response. At the time of tumour progression, the tumour burden in patients failing

440 a purely growth inhibitory compound will therefore be higher than in patients where tumour  
441 shrinkage was elicited. .

442 ➤ If no more refined techniques are applicable, TTP/PFS without an internal reference has to be  
443 accepted as a measure of Phase II anti-tumour activity. A systematic literature review is  
444 advised in these cases. Fixed-time related endpoints such as percentage of patients without  
445 progression after a predefined period of therapy may be used in order to define whether the  
446 apparent anti-tumour activity is sufficiently high to justify the conduct of, e.g. Phase III  
447 confirmatory studies.

448 In principle, a statistical approach similar to that for Phase II trials with ORR as outcome measure is  
449 applicable. It is harder to set up criteria for early termination, however. The number of patients should  
450 be sufficient to obtain a reasonably precise estimate of the percentage of progression-free patients at a  
451 predefined time point. The underlying assumptions as regards progression rate without therapy are  
452 more problematic and "promising activity" is harder to define.

453 For these studies, the use of conventional criteria for ORR and tumour progression is recommended  
454 and independent review is encouraged. It is recognised, however, that, e.g. an apparent increase in  
455 tumour size due to inflammatory oedema might be a first sign of activity for certain compounds. If  
456 prior trials indicate that this is the case, it is accepted that this is accounted for in the study protocol.  
457 The use of ORR and TTP as key measures of activity should not be regarded as contradictory to the use  
458 of tumour/PD markers in parallel.

459 If a randomised design is considered appropriate, the use of generally accepted instrument to estimate  
460 HRQoL or symptom control may provide valuable information.

461 For window of opportunity studies and if sensitive measures of pharmacological activity are available,  
462 e.g. functional tumour imaging, and a target population has been identified with tumours likely to be  
463 sensitive, placebo-controlled trials with one or preferably more doses of the experimental compound  
464 might be feasible. Sensitive measures, even if not fully validated with respect to relationship to ORR,  
465 are from a regulatory perspective acceptable for exploratory purposes and allow not only for refined  
466 dose comparisons, but also early escape in case of absence of activity. It is advisable though to clearly  
467 define in the protocol criteria for progressive disease, whether a composite (e.g. biomarkers, or  
468 imaging, or symptoms) is used or not.

### 469 **6.2.2.1. Monoclonal antibodies (MoAb)**

470 Monoclonal antibodies may affect tumour cells directly, e.g. through ADCC and/or blocking of growth  
471 factor/anti-apoptotic receptor signalling, or through the targeting of growth factors for the tumour or  
472 tumour supportive structures.

473  
474 As appropriate, tumour cells or plasma should be screened for (over-)expression of the target and the  
475 relationship between target expression and activity should be investigated.

476  
477 Tumour specificity is frequently not attainable, but it is possible to screen for "unwanted" targets in  
478 vitro, facilitating the safety assessment.

479  
480 Understanding PK provides some guidance for dose-finding as clearance may be related to target  
481 saturation.

482  
483 If, e.g., a growth factor receptor is targeted and pending of the characteristics of the MoAb (Ig  
484 subclass, association with toxin, etc.) it is of relevance to try to elucidate whether blockade of the  
485 receptor or ADCC is of prime importance for antitumor activity. Studies conducted in the neo-adjuvant  
486 setting allowing for repeated microscopic examinations may provide means to investigate this.

487  
488 The experience as regards immunogenicity of MoAbs in other fields of clinical medicine should be taken  
489 into account with respect to choice of assays, markers for loss of activity and possible safety problems.

### 490 **6.2.3. Immune modulating compounds including tumour vaccines**

491 Therapeutic cancer vaccines are aimed to induce specific anti-tumour immunity toward existing  
492 malignant disease. Such immune therapy is normally aimed to induce an adaptive T cell immune  
493 response in cancer patients. The nature of the drug substances used is highly variable, including  
494 synthetic peptides, recombinant proteins, virus-like particles, immune-modulating antibodies, gene  
495 therapy, and cell-based products. As it is difficult to break tolerance towards tumour antigens which

496 are normally derived from self-antigens, cancer vaccines are often combined with pharmacologically  
497 active adjuvants such as cytokines or toll-like receptor agonists. One other approach to break immune  
498 tolerance is to block T cell inhibitory signals. The resulting T-cell activation and proliferation leads to  
499 wanted and unwanted immune stimulatory effects: the desired anti-tumour effect as well as the  
500 appearance of immune related toxicities like colitis and endocrine insufficiency.

501 Non-clinical in vitro and in vivo proof-of-concept studies should be presented to justify the planned  
502 doses and schedule in early clinical studies. The dose level and the schedule in the non-clinical  
503 toxicology studies should be based on a dose that showed biological activity in proof-of-concept studies.  
504 It is acknowledged that for products relying on human-specific antigens which need to be presented on  
505 human MHC molecules, predictive animal models are often not available. Nevertheless, animal models  
506 using homologous antigens or animals being human MHC transgenic might be considered for non-  
507 clinical pharmacology and toxicology studies, if available.

509 The aim of early clinical trials is to determine the safety and the dose and schedule that induced a  
510 desired immune response. Monitoring the immune response, i.e. the induction of antigen-specific T  
511 cells or the presence of a humoral response is essential to determine appropriate dose and schedule.  
512 To achieve this goal multiple monitoring assays may be necessary and these should be carefully  
513 explored. The analytical methods should be described in detail in the clinical trial protocol.

515 Tumour biopsy data taken before and after treatment is expected to play a pivotal role in assessing the  
516 extent and type of immune activation in the target tissue and could serve as an early marker for  
517 possible anti-tumour activity.

519 The induction of tumour response in patients with high tumour burden might be a too high hurdle to  
520 overcome and may favour the inclusion of patients with minimal or low tumour burden. Examples are  
521 therapy of patients with NSCLC after complete tumour resection where cancer immunotherapy can be  
522 assessed in the adjuvant setting. Another example is patients suffering from non-resectable NSCLC  
523 who have responded to chemotherapy. The design of clinical studies using clearly experimental  
524 therapies in patients with limited and measurable disease, not heavily pretreated with cytotoxic  
525 regimens has to be carefully justified. As for other non-cytotoxic or cytotoxic agents evidence of anti-  
526 tumour activity is essential prior to the initiation of confirmatory studies.

527 Oncology patients are usually taken off treatment upon disease progression. Induction of an effective  
528 immune response and clinical response may need more time to develop (delayed effect) compared to  
529 classical cytotoxic compounds. Patients may thus experience disease progression prior to the onset of  
530 biological activities or clinical effects. Discontinuation of active cancer immunotherapy in case of slow  
531 progression may not be appropriate. In these situations a detailed definition of "slow progressive  
532 disease" is expected in the study protocol. In exploratory studies, revised criteria defining progression  
533 is accepted if properly justified, while in confirmatory studies OS should be prioritized.

535 Possible toxicities like induction of autoimmune reactivity (cellular and humoral) and induction of  
536 tolerance should be carefully monitored during the clinical development.

### 537 **6.3. Combination therapy studies**

538 Conventional cytotoxic compounds have for long been used in combination in order to increase the  
539 anti-tumour activity at acceptable levels of toxicity. This may be accomplished by combining  
540 compounds with at least partly non-overlapping toxicity and, perhaps, partly non-overlapping  
541 prerequisites for activity/resistance. Regulatory agencies, as well as learned societies, have accepted  
542 this approach, but it is acknowledged that it is frequently unknown whether combined use results in a  
543 better long-term outcome than consecutive use.

#### 544 **6.3.1. Combining conventional cytotoxic compounds**

545 In the selection of patients with available alternative therapies, the documented activity of the  
546 individual components of the combination regimen should be taken into account.

547 The exploratory phase encompasses the determination of MTD and RP2D for the combination and a  
548 preliminary assessment of anti-tumour activity in terms of ORR and PFS/TTP. While the degree of anti-  
549 tumour activity for a new combination relies on assumptions, it is often possible to predict toxicity,  
550 based on the toxicities of the individual components. If relevant PK interactions can be excluded, and  
551 pending on the dose-response/toxicity profiles, dose-finding studies may be initiated at about 1/2 of  
552 the recommended mono-therapy dose for each compound. It might also be appropriate to start at the

553 full recommended mono-therapy dose for one of the compounds and reduced dose (<50%) for the  
554 other compound. As the sequence of administration may be of importance with respect to potential PK  
555 interactions and anti-tumour activity, this has to be accounted for in the design of the studies. More  
556 patients on each dose level are normally needed compared with single agent dose finding studies.

557 There is no uniform way to balance dose intensity between components of a combination regimen to  
558 optimise benefit – risk. It is thus accepted that, e.g. priority in terms of dose intensity is given to the  
559 compound with the highest monotherapy activity.

560 If one of the components is regarded as an acceptable treatment regimen in monotherapy, a  
561 randomised phase II study comparing the monotherapy regimen with the combination is informative.  
562 For confirmatory studies a comparison with the best available, evidence-based reference regimen is  
563 expected.

### 564 **6.3.2. Combinations involving a non-cytotoxic drug.**

565 If there are no strong biological/pharmacological arguments to the contrary, the selected  
566 chemotherapy regimen to be combined with the non-cytotoxic should normally be “best available”. If  
567 the dose intensity/systemic exposure of the chemotherapy regimen is unaltered it can be assumed that  
568 all patients will receive appropriate therapy. Therefore there is no need to restrict the eligibility of  
569 patients from this perspective.

570 Whenever previous non-clinical and clinical experience has suggested that PD markers, etc. might be  
571 informative with regard to anti-tumour activity, they should be part of the experimental plan. This may  
572 include investigations whether the expression of the target for the non-cytotoxic compound is affected  
573 by treatment with cytotoxic agents and if appropriate *vice versa*.

574 Given the current status with respect to predictability of add-on activity in non-clinical models,  
575 randomised phase II studies comparing the experimental regimen with the chemotherapy-alone  
576 regimen are considered essential. For these studies, it is recommended that conventional anti-tumour  
577 activity data (ORR and TTP) are supplemented with tumour markers and sensitive measures of, e.g.  
578 tumour metabolic activity as appropriate.

579 When add-on activity of the non-cytotoxic compound to a chemotherapy regimen has been  
580 demonstrated, the need for further randomised phase II studies when new indications are studied may  
581 be dispensable. This, however, should be justified as the importance of target expression and inhibition  
582 thereof might differ between malignancies.

583 If the expression of the target for the non-cytotoxic compound may be differently affected by different  
584 chemotherapy regimens, it is advisable to study target expression during treatment with a new  
585 chemotherapy regimen prior to the conduct of add-on studies.

586 Research aiming at understanding the mechanisms and prerequisites for the add-on effects is  
587 encouraged, as it may allow for an improved characterisation of target populations in future studies.

588 It is conceivable that for some non-cytotoxic compounds, combinations are needed not only to  
589 optimise anti-tumour activity, but actually are required in order to obtain activity. For such compounds,  
590 e.g. target saturation in monotherapy and, importantly, non-clinical toxicity for the combination may  
591 be used to define suitable starting doses and schedules. Otherwise dose/schedule exploratory and  
592 therapeutic exploratory studies may proceed essentially as for a monotherapy regimen.

593  
594 If supported by strong biological and/or pharmacological non-clinical and early proof-of-principle  
595 clinical data, two new compounds may be combined in a co-development program.

596  
597 Uni-enhancement refers to scenarios when one combination partner *B*, which has no or minimal anti-  
598 tumour activity per se, but enhances the anti-tumour activity of the other partner *A* (e.g. through  
599 prevention of resistance development). The contribution of *B* needs to be established by data from  
600 appropriate non-clinical models. In phase II the comparison to a reference treatment is encouraged,  
601 while Phase II monotherapy data for *B* may be considered dispensable. An appropriate phase II design  
602 would be a randomised three-arm study *AB vs. A vs. reference treatment*.

603  
604 Co-enhancement is considered when both combination partners demonstrate (modest) anti-tumour  
605 activity per se and the anti-tumour activity of the combination is considerably increased. In phase II,  
606 the new combination should be compared to both combination partners as single agents at efficacious  
607 doses and preferably a reference treatment: *AB vs A vs B vs reference treatment*. Depending on the  
608 phase II results one or both monotherapy arms may be dispensable in phase III.

609



610 Synthetic lethality refers to a scenario when both combination partners have no or minimal anti-  
611 tumour activity per se but exhibit potent activity as a combination. If the contribution of both partners  
612 is established by data from appropriate models and if dose escalations studies investigating an  
613 extensive range of doses have excluded that inappropriately low doses led to the assumption of  
614 minimal anti-tumour activity in monotherapy, monotherapy treatment arms may be dispensable for  
615 phase 2 studies.

## 616 **7. Phase III, confirmatory trials**

617 Confirmatory trials should be designed with the aim to establish the benefit - risk profile of the  
618 experimental medicinal product, including supportive measures, in a well-characterised target  
619 population of relevance for clinical practice.

620 In the general part of this section (8.2 – 8.4), the aim of therapy, curative versus long term disease  
621 control vs. palliation and not the underlying disease has been used to structure the discussion. This is  
622 of relevance also for medicinal products developed for the treatment of conditions where there are no  
623 meaningfully active treatment options.

624 For some malignancies where treatment is administered without curative intent, there are alternative,  
625 in clinical practise still well established regimens, showing major differences in anti-tumour activity.  
626 This reflects that selection of therapy in the clinic is guided by efficacy and safety. It is therefore of  
627 relevance in the planning phase to take into account the expected tolerability/toxicity profile of the  
628 experimental regimen compared with the selected reference regimen. It is fully acknowledged that  
629 safety data may be rather limited prior to the conduct of the first confirmatory trial, but main toxicities  
630 should normally have been identified and this should be sufficient for a rough estimate of the expected  
631 relative toxicity of the experimental regimen compared with alternative reference regimens.

632 Three categories are used in this document: Reduced or similar toxicity, increased toxicity and major  
633 increase in toxicity. No precise definition is given here due to heterogeneity of the conditions. "Major  
634 increase in toxicity", however, in most cases refers to a fear that the experimental regimen might be  
635 associated with an increase in treatment related deaths, irreversible adverse events with an impact on  
636 QoL, or severe impairment to patient condition. Other issues to take into account include risk for  
637 secondary tumours. This categorisation is mainly meant for guidance in the planning of confirmatory  
638 studies and in order to provide advice on regulatory expectations with respect to study outcome  
639 measures in order to enable a proper benefit – risk assessment.

### 643 **7.1. Design**

#### 644 **7.1.1. Patient population**

645 With respect to diagnosis, criteria for initiation of treatment, eligibility, response criteria and choice of  
646 reference therapy, a justification based on scientific evidence and/or generally acknowledged and  
647 updated treatment guidelines are expected. While this is true in general, it is also expected that the  
648 exploratory studies through the judicious use of biomarkers provide guidance with respect to selection  
649 of patients in order to optimise benefit – risk, whether in need for confirmation or not in the planned  
650 phase III trials.

651 There is a general wish to reduce heterogeneity of study populations in order to increase the ability of  
652 the study to detect differences between study arms. This has to be balanced against the availability of  
653 patients for inclusion and the wish to enrol a clinically representative selection of patients. Therefore  
654 investigators should normally be encouraged to include patient's representative of those likely to be  
655 treated with the experimental compound in clinical practice. Restrictions as regards, e.g. performance  
656 status should be reflected in the SPC. With respect to studies with a non-inferiority efficacy objective,  
657 please refer to 8.7.3.

658 Patients are expected to be characterised by relevant tumour parameters, e.g. stage, grade, target  
659 expression, other biological markers of importance for prognosis and/or tumour sensitivity, prior  
660 therapy (responsive/ resistant/refractory as appropriate), as well as performance status, co-morbidity,  
661 organ dysfunction, etc. Stratification based on important and well established prognostic covariates  
662 should be considered. In case adjusted analyses are to be undertaken for covariates other than those  
663 used for stratification, these factors should be pre-specified in the protocol or the statistical analysis  
664 plan (Points to Consider on Adjustment for Baseline Covariates CPMP/EWP/2863/99).

667 If exploratory studies provide a basis for including/excluding certain patients based on tumour  
668 phenotype/genotype, this will be reflected in the labelling. As a corollary, if patients with tumours not  
669 expressing the target for activity are eligible, a restricted labelling may still be appropriate if it has not  
670 been demonstrated, e.g. by subgroup analyses, that target expression is irrelevant for anti-tumour  
671 activity.

672  
673 As some of the conditions are rare, it is understood that the sponsor might wish to define the target  
674 population using alternative criteria to those commonly employed. For example, in studies  
675 investigating the activity of a compound targeting a specific, molecularly well-defined structure  
676 assumed to be pivotal for the condition(s), it might be possible to enrol patients with formally different  
677 histological diagnosis, but expressing this target. The driving role of the target in different histological  
678 diagnoses must be demonstrated. This should also be addressed in exploratory studies, but it is  
679 accepted that formal testing with adequate statistical power of such a hypothesis cannot always be  
680 done. Possible consequences with respect to selection of proper reference therapy(ies) must be  
681 considered and the study should be designed so that it is possible, based on all available evidence,  
682 including non-clinical and pharmacological data, to conclude on the benefit – risk in the different  
683 subgroups of patients for which a claim is to be made, taking into account multiplicity issues (Points to  
684 Consider on Multiplicity Issues in Clinical Trials CPMP/EWP/908/99). Prior to the initiation of  
685 confirmatory studies using non-conventional criteria for eligibility, EU scientific advice should be sought.  
686

687 Some possible target indications comprise very small groups of patients, so small that “exceptional  
688 circumstances” might apply. Unless the target for activity is expressed only in these rare conditions,  
689 sponsors are in general advised to initiate confirmatory studies in these small patient groups when  
690 benefit – risk is established in indications allowing a more comprehensive evaluation, especially with  
691 respect to safety.

## 692 **7.1.2. Reference therapy**

693 The choice of reference regimen should be justified and normally this regimen should be selected from  
694 best available, evidence-based therapeutic options. In this context, “best available, evidence-based”  
695 should be read as a widely used, but not necessarily licensed regimen with a favourable benefit-risk  
696 convincingly documented through randomised trials and considered at least as good from a benefit/risk  
697 perspective as alternative, treatment options. It is acknowledged that there are different, region-  
698 preferred standards. For superiority studies (test vs. ref.) this should normally not constitute a problem  
699 as long as the reference is evidence-based. For add-on studies (ref. + test vs. ref.), it might be  
700 possible to use a few, region-preferred references. Here a convincing clinical/pharmacological  
701 justification is needed, and EU scientific advice is recommended.  
702

703 If the aim is to demonstrate non-inferiority, the selected reference regimen must enable a proper  
704 definition of the non-inferiority margin. In most cases, this would require randomized well-controlled  
705 studies have showed the superiority of the selected reference versus control. This is of particular  
706 relevance if the reference regimen is non-licensed. Please also refer to 8.6.3.  
707

708 Amongst best available references, regimens with similar cycle lengths should be prioritised as it  
709 facilitates the identical scheduling of tumour assessments. If the objective is not to improve tolerability  
710 and toxicity, a regimen with similar expected toxicity to the experimental regimen is also preferred  
711

712 In some cases there is no well documented reference regimen, even though patients in clinical practice  
713 are treated with certain regimens. Even though BSC is acceptable in these cases, an active comparator,  
714 documented e.g. in terms of response rate, is often preferable. If a single reference regimen cannot be  
715 defined, investigator’s best choice is an option. In these cases reference regimens with low toxicity are  
716 favoured and superiority in terms of patient relevant endpoints should be demonstrated.  
717

718 The absence of evidence-based therapies often refers to patients who have failed several lines of  
719 therapy. In this situation, it might be easier to obtain the data needed for marketing authorisation  
720 based on a properly conducted randomised study in less advanced patients, supported by “salvage”  
721 single arm studies, compared with conducting a last line, randomised BSC/investigator’s best choice  
722 comparative study.



723 **7.1.2.1. Single agent and combination therapies**

724 Whether the experimental agent is used as a single agent or in combination, the experimental regimen  
725 should be compared with the “best available” comparator again referring to benefit/risk, not only to  
726 efficacy.

727  
728 If the experimental agent (A) is added to an established regimen (B), superiority of AB vs. B should be  
729 demonstrated and benefit-risk should be shown to be favourable. A discussion is expected based on  
730 available data as regards dose intensity of B and benefit risk. Traditionally, this type of studies does  
731 not include an A alone third arm, but this should be justified based on available exploratory study data.  
732

733 In case of substitution studies, i.e. studies where a component (C) of an established regimen (BC) is  
734 replaced with an experimental agent (A) and if non-inferiority (BC vs. BA) is the aim, the contribution  
735 of C to the activity of BC has to be well defined (Guideline on the choice of the choice of non-inferiority  
736 margin CPMP/EWP/2158/99).

737  
738 Uncommonly, an entirely new combination AB is tested against a reference regimen. In these cases,  
739 solid non-clinical and clinical phase I/II data should support the need for all components in the  
740 experimental regimen.

741 **7.1.3. Cross-over**

742 In order to enable a qualified benefit – risk assessment, cross-over at time of progression should be  
743 undertaken only when precise estimates of OS data have been established (see Appendix 1).

744 **7.1.4. Randomisation and blinding**

745 Randomisation and stratification should adhere to the general principles laid down in current guidelines  
746 (Guidance on Statistical Principles for Clinical Trials CPMP/ICH/363/96). In many cases, a double-blind  
747 design is no option due to obvious differences in toxicity between study regimens or due to safety  
748 concerns. If the study has to be conducted as an open label study, this has implications with respect to  
749 choice of study endpoints and conduct of sensitivity analyses and other measures to be undertaken to  
750 limit potential bias related to the open-label nature of the trial.

751 **7.1.5. Endpoints**

752 Confirmatory trials should demonstrate that the investigational product provides clinical benefit. There  
753 should thus be sufficient evidence available demonstrating that the chosen primary endpoint can  
754 provide a valid and reliable measure of clinical benefit in the patient population described by the  
755 inclusion criteria. In the following, superiority trials are the focus of the discussion.  
756

757 Acceptable primary endpoints include cure rate, OS and PFS/DFS. Convincingly demonstrated  
758 favourable effects on survival are, from both a clinical and methodological perspective, the most  
759 persuasive outcome of a clinical trial. Prolonged PFS/DFS as such, however, is considered to be of  
760 benefit to the patient. The choice of primary endpoint should be guided by the relative toxicity of the  
761 experimental therapy, but e.g. expected survival after progression, available next-line therapies and  
762 the prevalence of the condition must also be taken into account. Irrespective of chosen primary  
763 endpoint, it is emphasised that it is the magnitude of the treatment effect on all relevant outcome  
764 measures that forms the basis in the benefit – risk assessment.  
765

766 If PFS/DFS is the selected primary endpoint, OS should be reported as a secondary and *vice versa*.

767  
768 When OS is reported as secondary endpoint, the estimated treatment effect on OS should be  
769 sufficiently precise, to ensure that there are no relevant negative effects on this endpoint, in most  
770 cases by showing trends towards superiority. In situations where there is a large effect on PFS, a long  
771 expected survival after progression, and/or a clearly favourable safety profile, precise estimates of OS  
772 may not be needed for approval.  
773

774 When OS is reported as primary endpoint, consistency is expected as regards effects on PFS. If  
775 foreseen not to be the case, e.g. in case of certain immune modulating therapies, this should be made  
776 clear already in the study protocol.

777 For some conditions, events of progression will be observed at a slow rate making frequent  
778 assessments of events of progression a burden to the patients. Event rate at a pre-specified and  
779 justified fixed point in time might be used as primary measure in these cases. When event rate at a  
780 single point in time is selected for the primary analysis, it is in most cases recommended that all  
781 patients should have been on study for that period of time. PFS, in a time to event analysis, and as  
782 assessed by the investigator should be reported as a secondary endpoint when a fixed time-point  
783 assessment is used as primary outcome measure.

784  
785 For further methodological guidance as regards PFS, please refer to appendix 1.

786  
787 It should be noticed that it is expected that the tumour's drug resistance profile is affected by therapy.  
788 This might be of relevance for the activity of next-line therapies. This is most obvious if  
789 maintenance/prolonged therapy is compared with no treatment or placebo such as in areas where a  
790 fixed number of cycles is the standard, for example, first-line ovarian cancer, NSCLC and some  
791 haematological conditions. The consequences of progression **on** maintenance therapy, signifying  
792 resistance to at least the maintenance regimen, might thus differ from progression **off** therapy. In  
793 principle, this applies to all comparisons between different regimens, i.e. the degree of cross resistance  
794 as regards next-line therapy might differ between experimental and control regimens.

795  
796 From a regulatory perspective, this concern has mainly been emphasised in settings where a new  
797 concept is introduced such as maintenance therapy or an increased number of "induction" cycles. If at  
798 all possible, these studies should therefore be designed with the aim to document patient benefit in  
799 terms of survival. If non-feasible, endpoints such as PFS on next-line therapy (PFS 2) should be  
800 determined. This should be done within the study so that agreed next line therapy is used after  
801 progression in the control and maintenance arms and so that PFS 1 and 2 in the maintenance arm can  
802 be compared with PFS 1 and 2 the control arm. In order to capture possible negative effects on next-  
803 line therapy and to outbalance tolerability and toxicity concerns related to maintenance therapy, it is  
804 expected that PFS2 in the experimental arm is sufficiently superior to PFS2 in the control arm. As the  
805 regulatory experience is limited and as methodological issues are foreseeable, EU scientific advice  
806 should be considered.

807  
808 Alternative primary endpoints, such as TTP or time to treatment failure (TTF) might uncommonly be  
809 appropriate. This has to be fully justified.

810  
811 In patients with tumour-related symptoms at base line, symptom control, if related to anti-tumour  
812 effects, is a valid measure of therapeutic activity and may serve as primary endpoint in late line  
813 therapy studies, provided that sources of possible bias can be minimised. In certain cases, time to  
814 symptomatic tumour progression may also be an adequate primary measure of patient benefit.

815  
816 There are also examples where tumour response-related activities, e.g. limb-saving surgery may be  
817 reasonable primary measures of patient benefit. Analyses of location- or cause-specific events,  
818 however, should in general be avoided as the focus may be drawn away from the main objective,  
819 namely the overall success of the treatment strategy in question.

820  
821 Biomarkers convincingly demonstrated to reflect tumour burden can be used, in combination with  
822 other measures of tumour burden, to define tumour response and progression, an example being  
823 multiple myeloma and the M-component. For new classes of compounds, however, it has to be  
824 demonstrated that the marker is a valid measure of tumour burden and that no bias in the assessment  
825 is introduced, e.g. through differential suppression of the tumour marker.

826  
827 The first line of therapy administered after tumour progression on study drugs should be documented  
828 and when feasible further therapy. The putative effects of treatments after progression on study drugs  
829 on later events should be discussed in the study report.

#### 830 **7.1.5.1. Secondary endpoints and exploratory analyses**

831 Irrespective of the choice of primary endpoint OS or PFS, ORR and rate of tumour stabilisation for, e.g.  
832 3 or 6 months should be reported. Especially in the palliative setting, HRQoL/PRO using generally  
833 accepted instruments might provide valuable information (Appendix 2)

## 834 **7.2. Treatment administered with curative intent**

835 The ultimate aim of developing new therapies, e.g., in patients with high grade lymphoma, germ cell  
836 tumours or in the adjuvant setting, is to improve cure rate and survival or to relevantly decrease  
837 toxicity without loss of efficacy. Nevertheless, in some cases and due to the complexity of administered  
838 therapies, e.g. in AML, the impact of a relevantly active experimental compound on these endpoints  
839 may be hard to demonstrate.

840 It is foreseen that the experimental compound rarely will be used as single agent therapy, but will be  
841 used as add-on to an established, perhaps modified regimen, or as substitution for a compound being  
842 part of the established regimen. In this context, maintenance therapy may be regarded as add-on  
843 therapy if maintenance therapy is considered non-established.

844 In the treatment of acute leukemia, lack of achievement of CR, relapse and death without relapse are  
845 counted as events in an EFS analysis. Those patients who did not reach CR during the pre-specified  
846 induction phase will be considered as having an event at time 0.

847 In case EFS is found to be a justified primary endpoint, it is of importance that study data are analysed  
848 only when sufficiently mature, i.e. when it is foreseen that the EFS plateau is stable or when additional  
849 disease recurrence is rare.

850 In patients with high grade lymphoma or solid tumours, PFS may be used as outcome measure. Not  
851 achieving at least PR after a defined period/number of cycles may be regarded as treatment failure in  
852 some protocols and only those achieving at least PR continue on therapy. In the primary analysis it is  
853 recommended that patients not reaching PR are followed off or on next-line therapy until an event of  
854 progression or death is reached.

855 When improved cure rate is the objective of therapy, it is advised that disease-free survival at a pre-  
856 specified time point is used as outcome measure (see above with respect to timing).

### 857 **7.2.1. Reduced or similar toxicity expected**

858 In most cases, a substitution design is foreseen. From a regulatory perspective, a non-inferiority  
859 design is acceptable and in most cases EFS or PFS, as appropriate, are acceptable primary endpoints.

860 In cases where induction is followed by consolidation and/or maintenance therapy, confounding effects  
861 of therapies administered after the end of experimental therapy may make endpoints other than PFS  
862 or EFS more appropriate. This means that CR (and CR + PR, if specifically justified) after end of  
863 experimental therapy could be an acceptable primary endpoint when further therapy is scheduled. In  
864 these cases, the possible influence of the experimental compound on the activity of consolidation  
865 therapy should always be addressed and outcomes with respect to CR should be supported by EFS or  
866 PFS data.

867 It is recommended that CR is defined according to established clinical criteria, but supportive evidence  
868 in terms of Minimal Residual Disease (MRD) as defined by molecular criteria should be sought when  
869 applicable. MRD data, however, should only be used after proven intra- and inter-laboratory validation.

### 870 **7.2.2. Increased toxicity expected**

871 Substitution or add-on designs may apply. In most cases, superiority in terms of EFS, PFS, or OS as  
872 appropriate, should be demonstrated and the benefit in terms of prolonged time to event should be  
873 sufficiently large to balance increased toxicity.

874 A major increase in CR after induction therapy associated with trends in PFS or EFS, and survival,  
875 however, might be sufficient if scheduled treatments administered after the end of the experimental  
876 therapy are likely to confound overall outcome. This is of special relevance if the target population is  
877 small.

### 878 **7.2.3. Major increase in toxicity expected**

879 The aim should be to demonstrate increased cure rate or improved OS. In some cases, such as in  
880 small study populations, a major increase in EFS or PFS, as appropriate and supportive data  
881 compatible with a favourable trend on survival might be sufficient.

882 **7.3. Treatment administered with the intent to achieve long-term disease**  
883 **control**

884 Typical conditions include early lines of therapy in advanced breast cancer, colorectal cancer, low-  
885 grade lymphomas and the chronic leukaemias for which established reference therapies are available  
886 and next-line treatment options are likely to be meaningfully efficacious.

887 **7.3.1. Reduced or similar toxicity expected**

888 Substitution or single agent studies are foreseen. From a regulatory perspective, a non-inferiority  
889 design is acceptable and PFS is considered an appropriate primary endpoint. In case of relevantly  
890 reduced toxicity, mature survival data may be submitted post licensure if justified by study data.

891 **7.3.2. Increased toxicity expected**

892 The aim should be to demonstrate superiority at least in terms of PFS.

893 Survival data should be made available at the time of submission. It is acknowledged that mature  
894 survival data cannot be expected in all cases, though a justification explaining why this is the case  
895 should be provided. Post approval follow-up with respect to survival is expected in these cases. If  
896 absence of an increase in treatment-related mortality is not established with reasonable certainty,  
897 mature survival data should be available for the assessment of benefit – risk prior to licensure.

898 It is acknowledged that alternative endpoints may be more appropriate in certain situations, e.g. when  
899 maintenance therapy is investigated in areas where this has not established (Endpoints, 8.1.5). The  
900 aim may also be to enable a long treatment-free interval after intense induction therapy.

901 **7.3.3. Major increase in toxicity expected**

902 The principal objective should be to demonstrate improved survival.

903 In individual cases this might be non-achievable due to expected good prognosis with respect to  
904 survival and availability of several active next-line regimens, including experimental therapies, at the  
905 time of disease progression and a small target population. If PFS is the selected primary endpoint for  
906 the study, this requires a thorough justification. A careful discussion at the planning stage is also  
907 needed for the assessment of possibly therapy-related fatalities. Even though only a major benefit in  
908 terms of PFS prolongation would be acceptable, whenever possible the number of patients included  
909 should be sufficient to obtain an estimate on overall survival where a trend in a favourable direction is  
910 expected.

911 **7.4. Palliative therapy**

912 In the context of this appendix, this mainly refers to last line settings where the prognosis for survival  
913 is poor and where it might be problematic to identify sufficiently documented reference therapies. In  
914 other cases, patients are considered not suitable for intensive, potentially curative therapy as defined  
915 by clear and as far as possible unambiguous criteria.

916 In cases where there is no established reference therapy, investigator's best choice or BSC are  
917 acceptable.

918 In a study conducted with BSC as reference therapy, the objective should be to demonstrate prolonged  
919 OS and/or globally improved symptom control or quality of life (QoL). The latter requires that all  
920 efforts are undertaken to reduce possible bias (Appendix 2) and that the treatment is well tolerated. If  
921 the reference regimen is known to be active, but not established, superiority in terms of PFS might be  
922 acceptable. In these cases, the following will be taken into account in the benefit – risk assessment:  
923 the evidence showing activity of the reference therapy, the magnitude of the PFS benefit over the  
924 reference regimen, the tolerability/toxicity profiles and the prevalence of the condition.

925 It is acknowledged that patients may be considered suitable only for palliative therapy at baseline due  
926 to, e.g. poor performance status, but may respond so well that further therapy can be administered  
927 with curative intent, including, e.g. reduced intensity HSCT. How to handle these patients should be  
928 defined in the analysis plan.

929 **7.5. Special considerations**

930 **7.5.1. Haematopoietic stem cell transplantation, methodological**  
931 **considerations**

932 If allogeneic haematopoietic stem cell transplantation (HSCT) is a foreseeable treatment option, it is of  
933 importance to define how transplantation should be handled in the analysis plan. It is fully  
934 acknowledged that criteria for HSCT (e.g. patient eligibility, HLA matching, conditioning regimen, graft  
935 versus host disease prevention, etc) vary between institutions and regions. Nevertheless, these criteria  
936 should be defined as far as possible in the protocol and reasons for performing or not performing HSCT  
937 should be captured by the CRF.

938 Even though transplant related mortality is an issue and long-term benefit need prolonged follow-up, it  
939 is normally expected that patients undergoing HSCT are followed for OS and EFS as randomised.  
940 Patients may be censored at time of conditioning for HSCT as a sensitivity analysis.

941 As treatment administered prior to transplantation might affect outcome of HSCT, proportion of  
942 patients undergoing HSCT is not considered to be a suitable primary outcome measure even if all  
943 patients responding sufficiently well to treatment are scheduled for transplantation.

944 Autologous stem cell transplantation constitutes less of a concern from an assessment perspective and  
945 may be viewed as intensified consolidation therapy where the consequences on short-term mortality  
946 and possible long-term benefit are less pronounced than after HSCT. Nevertheless, heterogeneity in  
947 the conduct of autologous transplantation should be avoided as far as possible, but censoring should  
948 normally not be undertaken.

949 With respect to drug development specifically in relation to HSCT, please refer to 9.5.

950 **7.5.2. (Neo)adjuvant therapy**

951 In the adjuvant setting, the ultimate aim is to increase cure rate. While effects on DFS are considered  
952 relevant to the individual patient, it is of importance to consider in the planning of the study whether it  
953 is at all possible to demonstrate a favourable effect on cure rate, i.e. in analyses conducted when  
954 recurrence rates have reached an apparent plateau.

955  
956 As the use of adjuvant therapy may limit therapeutic options at time of recurrence OS data should be  
957 reported. For established areas of adjuvant therapy, e.g. breast and colorectal cancer, and if benefit-  
958 risk is considered favourable for the experimental regimen based on DFS and available safety and  
959 survival data, mature survival data may be reported post-licensing. In some cases and due to toxicity  
960 concerns, favourable effects on OS have to be demonstrated.

961  
962 The objectives of neoadjuvant therapy may include improved overall outcome and organ preservation  
963 (e.g. more conservative surgery). If organ preservation is the main objective, at least non-inferior  
964 DFS/PFS should be documented. As for adjuvant therapy, a defined number of cycles is frequently  
965 administered. Pending on the objectives of the study it is accepted that treatment is withdrawn if  
966 tumour shrinkage is not observed after a defined treatment period.

967  
968 When pathological CR at time of surgery is reported as secondary endpoint, patients withdrawn should  
969 be considered as non-responders. Major increase in pathological CR over established therapy in high  
970 risk patient such as those with inflammatory breast cancer, might be indicative of patient benefit if not  
971 associated with major increase in toxicity.

972 **7.5.3. Drug resistance modifiers, chemoprotective agents and radio/chemo**  
973 **sensitisers**

974 In principle, the design of confirmatory studies for experimental drug resistance modifying agents and  
975 radio/chemo sensitizers (A) is straight forward; AB should be demonstrated to be more active than an  
976 established regimen (B) in terms of anti-tumour activity and the benefit – risk for the combination  
977 should be shown to be favourable. If there are PK interactions, or dynamic interactions not related to  
978 anti-tumour activity, dose adjustments of B in the combination arm might be needed in order to make  
979 the comparison AB vs. B at similar overall toxicity. If the full effects of the PK interaction is captured by  
980 changes in the plasma levels of B (e.g. no changes in distribution), however, dose adjustments of B in  
981 order to compare AB vs. B at similar exposure of B is preferred.

---



982 For a chemoprotective agent, it has to be shown that normal tissues are more protected from toxicity  
983 than tumour tissue. For most cytotoxic compounds, it is, however, easier to detect dose-related  
984 differences in toxicity than in efficacy. This means that in many cases very large studies are needed  
985 with tight confidence intervals around measures of anti-tumour activity in order to prove that normal  
986 tissue protection is achieved without loss of anti-tumour activity. Co-primary endpoints are thus  
987 needed, testing the hypotheses of improved safety and non-inferior anti-tumour activity. In some  
988 cases, it might actually be easier to convincingly demonstrate differential tissue protection by  
989 increasing the dose of the cytotoxic compound in the experimental arm aiming to show enhanced anti-  
990 tumour activity without increased toxicity.

991  
992 However, if it can be shown conclusively that there is no PK interaction and that the chemoprotective  
993 compound cannot interact with the tumour, e.g. by absence of target in tumour cells, it might be  
994 acceptable only to show reduced toxicity without formal non-inferiority testing of tumour protection.

#### 995 **7.5.4. Tumour Prevention**

996 Regulatory experience is limited, but conceptually the situation is rather similar to the adjuvant setting.  
997 Thus individuals at risk should be defined so that the observed risk reduction in tumour incidence  
998 outweighs the side effects of therapy. As tumour prevention may select for tumours with altered  
999 biological behaviour, comparative data on tumour pheno/genotype are expected and data on OS may  
1000 be needed. In the planning of these studies, regulatory scientific advice is recommended.

### 1001 **7.6. Methodological considerations**

1002 Frequently, only one single study is foreseen for a specific indication. Licensing based on one pivotal  
1003 study, however, requires demonstration of efficacy at levels beyond standard criteria for statistical  
1004 significance (CPMP/EWP/2330/99). This is of special relevance in non-inferiority trials, in trials with PFS  
1005 as primary endpoint and in a comparison with BSC/investigator's best choice. It is acknowledged that  
1006 supportive evidence from confirmatory studies conducted in other indications should be taken into  
1007 account in the assessment. The supportive value of these studies might vary and a discussion is  
1008 expected as regards the relevance of these findings in relation to the application for the new indication.

#### 1009 **7.6.1. Interim analyses**

1010 Interim analyses are frequently undertaken in Phase III trials, but early stopping whether for futility or  
1011 superiority is a sensitive issue. Early stopping for superiority requires an assumption of proportional  
1012 hazard, i.e. that the treatment effect in patients with rapidly progressing tumours is similar to that in  
1013 less aggressive tumours in the absence of data demonstrating that the magnitude of effect is  
1014 maintained.

1015 If a clear majority of the total number of expected events in the long term has been observed and a  
1016 difference has been documented, this is normally accepted as an indicator that the study is reasonably  
1017 mature and that the study results will remain stable over prolonged follow-up. The interpretation of  
1018 interim analyses conducted on a less mature data set is problematic.

1019 In cases where the treatment effect has been underestimated in the planning of the study, this may  
1020 create a dilemma if statistically convincing effects in terms of overall survival have been demonstrated  
1021 before a representative and mature dataset is available. Other monitoring committee decisions might  
1022 be investigated in this instance such as restricting the continuation of the trial to the under-  
1023 represented subsets to which the observed effect cannot be extrapolated. Analyses according to  
1024 stratification factors of major importance for prognosis might provide insights.

1025 In general, interim analyses based on PFS data are not encouraged (Appendix 1).

#### 1026 **7.6.2. Time to event analyses and assessment of response and progression**

1027 For studies with PFS/DFS as primary endpoint, symmetry with respect to imaging and study visits is  
1028 pivotal and adherence to protocol-defined schedules is essential and deviations should be reported  
1029 (Appendix 1).

1030  
1031 As discussed above (Exploratory trials with time-related endpoints), a comparison in terms of PFS  
1032 between a predominantly tumour shrinking compound and a predominantly growth inhibiting  
1033 compound may "favour" the latter compound with respect to tumour burden at time of progression.

1034 Until now, there is no regulatory experience with respect to comparisons with clearly discordant  
1035 outcomes in terms of ORR and PFS and there are no established ways to adjust for this. If exploratory  
1036 studies indicate that this might become the case, alternative endpoints such as OS should be  
1037 considered.

1038  
1039 Differences in mode of action between the experimental and reference therapy might generate  
1040 problems in relation to measurements of tumour burden and anti-tumour activity, one example being  
1041 early tumour swelling as discussed previously. Whenever such problems are foreseen, which may  
1042 require deviation from standard approaches (RECIST, WHO), it is recommended that agreement is  
1043 reached with regulatory agencies prior to the initiation of pivotal trials. Similarly, if tumour assessment  
1044 techniques cannot be used that allow for independent adjudication, it is advisable to discuss available  
1045 alternatives with regulatory agencies.

1046  
1047 Pseudo-response should always be considered a possibility when tumour related oedema is an issue  
1048 such as in high grade gliomas. Updated response and progression criteria taking this into account  
1049 should be applied when available. If such criteria has not yet been established, scientific advice is  
1050 recommended in order to discuss alternative ways forward.

### 1051 **7.6.3. Non-inferiority studies**

1052 Guidance of design, conduct and analysis of non-inferiority studies is given in other regulatory  
1053 guidance documents (Choice of a Non-Inferiority Margin CPMP/EWP/2158/99), but some topics deserve  
1054 particular attention in the oncology setting. For a PFS endpoint, which can be considered a composite  
1055 endpoint, the discussion of a non-inferiority margin should consider the effect of the reference  
1056 treatment overall but inference should also include a discussion on each type of progression (local,  
1057 distant, clinical, radiological etc.) including description of the effect of the reference regimen on each  
1058 component. If differences in the profiles of progressive disease in each treatment arm might be  
1059 expected, this should be accounted for in the planning stage with a suitably conservative margin and  
1060 appropriate sample size to obtain the required number of events for reliable inference.

1061 Given the importance of study sensitivity (i.e. the ability of a trial to detect differences) for the  
1062 assessment of non-inferiority trials, where similar activity is assumed for test and reference, it is of  
1063 importance to plan in advance for a subgroup analysis excluding patients with poor prognostic factors  
1064 at baseline such as poor PS, co-morbidities, etc. as in these patients it might be harder to detect a  
1065 difference in activity between treatment regimens, if there were one. Similarly a per protocol analysis  
1066 set should be defined so that protocol violations, compliance problems, etc. do not reduce the  
1067 possibility to detect a difference. These analyses are expected to be undertaken with the aim to show  
1068 consistency.

### 1069 **7.6.4. Analyses based on a grouping of patients on an outcome of 1070 treatment**

1071 Comparisons of time-to-event variables (like OS, or PFS) by grouping patients on a post-randomisation  
1072 outcome of treatment are problematic. Since outcomes like tumour response, dose intensity, toxicity,  
1073 or compliance represent an interaction between therapy, patient and tumour the contribution of  
1074 therapy cannot be disentangled. Nevertheless, certain unexpected outcomes such as clearly improved  
1075 survival despite dose-reduction due to toxicity, or absence of prolonged survival in responding patients  
1076 might be informative. A search for unexpected findings constitutes a rationale for conducting these  
1077 exploratory analyses.

1078  
1079 Response duration comparing groups of patient on different therapies may be regarded as informative.  
1080 Data should be reported with confidence intervals for the individual study arms, but significance testing  
1081 comparing duration of response between study arms should not be undertaken as the comparison  
1082 refers to groups that are not fully randomised. "Time in response" where patients without response are  
1083 assigned a duration of zero enables a statistical comparison between study groups.

### 1084 **7.6.5. Studies in small study populations, very rare tumours**

1085 For some truly rare tumours or very narrow indications, whether due to tumour phenotype or  
1086 restrictions related to target expression, it is simply not possible to recruit a sufficiently large number  
1087 of patients to conduct reasonably powered, randomised studies in order to detect clearly relevant  
1088 differences in anti-tumour activity. In some cases a small, randomised, reference controlled study is



1089 the best option, in other cases a within-patient TTP/PFS analysis (or the combination) might be a  
1090 better alternative. In the latter case, TTP on last prior therapy is compared with time to progression or  
1091 death on the experimental therapy. This would require that the clinical appropriateness of the last  
1092 administered therapy prior to study therapy and progression on prior therapy is independently  
1093 adjudicated and that the study protocol clearly defines the proper conditions for the analysis.  
1094 Superiority should be demonstrated.

1095 Problems related to studies in small populations are further discussed in the Guideline on clinical trials  
1096 in small populations (CPMP/EWP/83561/2005). In these small target populations all evidence with  
1097 respect to efficacy and safety must be taken into account. This encompasses clinical response rate,  
1098 duration of response as well as outcome measures such as HSCT rate, use of minimal residual disease  
1099 (MRD) to define response rate and recurrence of disease, as appropriate. Mature time to event  
1100 endpoints such as PFS and OS should be reported even though it is acknowledged that formal  
1101 statistical significance cannot always be expected, even if the experimental compound is relevantly  
1102 more efficacious.

1103  
1104 As there is no general solution to the problem of how to document benefit – risk in these cases,  
1105 scientific advice is recommended.

## 1106 **7.7. Special populations**

### 1107 **7.7.1. Elderly and frail patients**

1108 In many indications elderly patients represent the majority of the patient population. In these cases it  
1109 is expected that the study data base makes a benefit – risk assessment possible in the elderly.

1110 Some compounds may be specifically suitable for the treatment of elderly, e.g. due to PK properties  
1111 such as low sensitivity to impaired organ function. In these cases, dedicated studies in the elderly are  
1112 encouraged. It is acknowledged that it may be hard to identify appropriate reference therapies in some  
1113 of these cases and that other outcome measures than PFS/OS might become more relevant. In these  
1114 cases it is advisable to seek regulatory agreement on the development program.

1115 Frail patients, whether elderly or not, with clearly impaired performance status (PS) constitute a  
1116 vulnerable group of patients rarely included in conventional confirmatory studies. Clinical studies in this  
1117 group of patients are encouraged from a regulatory perspective.

### 1118 **7.7.2. Children**

1119 See *Addendum* (CPMP/EWP/569/02 under revision).

### 1120 **7.7.3. Gender**

1121 For some tumours and/or therapies, a difference in antitumor activity related to gender has been  
1122 reported. Where a priori it is likely that there may be a treatment by gender interaction, this should be  
1123 taken into account in the design of the study. Otherwise it is expected that the proportion of females  
1124 and males reflects the prevalence of the disease and that the sponsor provides exploratory subgroup  
1125 analyses (efficacy and safety) by gender.

### 1126 **7.7.4. Patients with impaired organ function**

1127 Please refer to Section 5, Pharmacokinetics.

## 1128 **7.8. Safety**

1129 In addition to standard reporting of adverse events, it is expected that effects of preventive measures,  
1130 such as anti-emetics or use of growth factors are delineated. Acute, sub-acute, chronic and late  
1131 toxicities should be described. Safety in special populations, as detailed above, should be summarised  
1132 from the full studies programme.

1133  
1134 For common events, safety in relation to treatment cycle, first, second, third etc., is of value. Similarly,  
1135 timing and duration, including grade, of some events such as diarrhoea, mucositis, or cytopenias  
1136 should be reported.

1137 Monitoring of frequency and type (viral, bacterial, fungal) of possible, probable or proven infections  
1138 should be undertaken in patients undergoing more intensive cytotoxic/immunosuppressive therapy. For  
1139 compounds known or suspected to cause long term immunodeficiency, monitoring for opportunistic  
1140 infections for up to one year after the end of therapy should be considered.

1141  
1142 Cumulative toxicity should always be investigated.

1143  
1144 If cure is the objective, long term follow up for toxicity is highly relevant. Late toxicity includes  
1145 secondary malignancies and certain organ toxicities (e.g. CNS, cardiovascular). The number of patients  
1146 suffering from late toxicities may increase over time and is therefore an objective for post licensure  
1147 pharmacovigilance activities.

1148  
1149 As radiation therapy is a standard treatment option in malignant tumours, it is foreseeable that  
1150 patients will be receiving radiation therapy, e.g. for symptom palliation, concomitantly with or in a time  
1151 frame close to administration of the medicinal agent. Safety information on concomitant or sequential  
1152 use of the medicinal agent with radiotherapy should be collected throughout the entire study  
1153 programme, including data on "radiation recall".

1154  
1155 In haematological malignancies, bone marrow failure is often a presenting symptom and is frequently  
1156 aggravated by treatment. In contrast to the approach in solid tumours, dose reduction for this reason  
1157 is often not indicated, in particular if the aim is curative.

1158  
1159 If the aims of the study include demonstration of improved safety, the protocol should specify how this  
1160 should be accomplished. It is not acceptable to focus on one toxic effect only. The outcome measure(s)  
1161 should provide unbiased information on overall toxicity and tolerability, perhaps in addition to a specific  
1162 item such as neuropathy where a clinically relevant improvement is expected. As there is limited  
1163 experience with this type of studies, EU regulatory advice should be considered.

1164  
1165 Where appropriate, pharmacogenomics may be used to identify patients at increased risk for severe  
1166 toxicities.

## 1167 **8. Condition specific guidance**

### 1168 **8.1. Non-small cell lung carcinoma**

1169 NSCLC is a leading cause of cancer morbidity and mortality. Most patients diagnosed with NSCLC  
1170 present with advanced disease and many of the patients who do present early will go on to develop  
1171 metastatic lung disease. Common disease related symptoms include pulmonary effects (cough,  
1172 dyspnoea) and general symptoms of pain, anorexia and high degrees of psychological distress.

1173  
1174 Recent developments in the knowledge of NSCLC biology have uncovered targets for therapeutic  
1175 agents, creating new opportunities but also adding complexity to the interplay between potential  
1176 biomarkers and drug candidates and consequently, to the assessment of their value in the  
1177 management of this disease

1178 These factors warrant a specific guidance for the assessment of medicinal agents directed at the  
1179 management of NSCLC in the context of the present guideline. Namely, criteria, definitions, and other  
1180 reflections are provided for the use of biomarkers, the systematization of therapeutic phases in the  
1181 course of the disease, and the endpoints applicable to the assessment of clinical benefit.

#### 1182 **Classification of NSCLC**

1183 NSCLC must be classified using pathological and molecular features. The importance of consistent,  
1184 accurate and reproducible histological subtyping cannot be understated.

1185  
1186  
1187 Pathological evaluation using internationally agreed criteria should determine the histological  
1188 classification (WHO Classification) and the extent of the disease (UICC TNM Classification).

1189 Immunohistochemical analysis may improve pathological diagnosis, particularly for small biopsies.

1190 Pathological evaluation should also determine the molecular features of the tumour and this must  
1191 include EGFR status, presence of k-ras mutation, level of expression of ERCC1, RRM1 and thymidylate  
1192 synthase and the presence of ALK translocations.

#### 1193 **Stratification according to disease and patients characteristics**

1194

1195 Exploratory trials should clearly test hypotheses of activity in accordance with known or presumed  
1196 biological roles of their intended molecular targets. For this purpose, trial subjects must be constituted  
1197 by patients with disease that is well characterized according to relevant biomarkers. Subsequently, the  
1198 same applies to confirmatory trials which must restrict inclusion to categories of patients with clinical  
1199 and molecular characteristics that increase the likeliness of response and hence clinical benefit.

1200  
1201 It is particularly important to perform specific trials, or at least to stratify patients based on baseline  
1202 characteristics such as tumour histology and expression of predictive molecular biomarkers. Such  
1203 markers help delineate distinct disease entities, enriching the patient population to those with the  
1204 target of interest and defining subsets of patients most likely to benefit from therapy. However, the  
1205 success of such an approach depends heavily on having an accurate diagnosis.

1206  
1207 At least a third of lung cancer patients are 70 years or older, older patients should be actively recruited  
1208 into clinical trials. Other variables such as smoking status and geographical origin should also be  
1209 considered in the recruitment of patients.

### 1210 **Treatment definitions**

1211 Adjuvant or neoadjuvant therapy may improve survival in certain groups of patients by decreasing the  
1212 risk of metastatic disease. For adjuvant therapy, patients should generally be relatively young without  
1213 significant co-morbidities who have undergone complete resection by lobectomy. The tolerability of any  
1214 adjuvant therapy must be considered. Neoadjuvant therapy may reduce tumour volume, control  
1215 micrometastasis and if adequate tumour samples are obtained may provide valuable information  
1216 regarding tumour response and tumour biology.

1217  
1218 The concept of maintenance therapy should be considered for well tolerated medicinal products and a  
1219 maintenance approach may represent an effective way of delivering second line therapy. Maintenance  
1220 therapy is the prolongation of treatment at the end of a defined number of initial treatment cycles  
1221 following tumour control (tumour response or stable disease). Continuation or true maintenance  
1222 therapy refers to the continuous administration of at least one of the agents given in first line therapy  
1223 (either at the same intensity or at a lower intensity). Switch maintenance or early second line therapy  
1224 refers to the immediate administration of a different agent not included as part of the first line regimen  
1225 following completion of therapy.

### 1226 **Efficacy endpoints**

1227  
1228 For exploratory studies, ORR is an acceptable endpoint for early evaluation of new medicinal products  
1229 in NSCLC, though modest response rates may in fact underestimate patient reported benefits. In light  
1230 of this, endpoints which capture clinical benefit and record palliative control (pain control, weight loss,  
1231 performance status) may be included in the study design. Prognostic and predictive molecular markers  
1232 and mechanisms of resistance should be actively investigated.

1233  
1234 Improving survival remains the principal objective for patients with NSCLC and in many cases OS  
1235 should be selected as the primary endpoint for confirmatory studies. If, however, the experimental  
1236 regimen is likely to be well tolerated, PFS benefit might enable a proper benefit – risk assessment,  
1237 especially if supported by data on HRQoL/PRO (Appendix 2).

1238  
1239 For maintenance studies, if conducted versus placebo/BSC, the recommended endpoint is OS (8.1.5).

## 1240 **8.2. Prostate cancer**

1241  
1242 The proper design of prostate cancer studies is a challenge since there are several complicating issues.

1243 Firstly there is a large variability in the biology of prostate cancer. Almost every man will ultimately  
1244 develop prostate cancer, the majority being slowly progressive, but some are aggressive with fatal  
1245 outcome. There is thus a risk related to the detection of indolent tumours and a challenge to identify  
1246 clinical significant prostate cancer of importance to treat. Treatments with curative intent include  
1247 surgery and/or radiotherapy but active surveillance is an alternative and reduces the risk for  
1248 overtreatment and side effects related to radical therapy.

1249 Secondly there are to date no method to properly quantify the tumour burden, making it difficult to  
1250 interpret therapy outcome. Imaging techniques such as computed tomography (CT), magnetic  
1251 resonance imaging (MRI), radionuclide imaging and positron emitting tomography (PET) with different  
1252 tracers are less suitable to estimate bone disease and soft tissue metastases are uncommon clinical  
1253 presentation of prostate cancer.

1254 Prostate specific antigen (PSA) is not cancer specific but changes in PSA levels during different  
1255 therapies are used as a biomarker. Individuals' PSA values are not comparable to each other but  
1256 changes and nadir are prognostic.

1257 Prostate cancer is diagnosed on histopathology of core biopsies, but the likelihood to detect a cancer is  
1258 dependent on number of biopsies, the prostate volume and the cancer location (anterior cancer and  
1259 cancer located near the urethra is difficult to biopsy using transrectal technique).

#### 1260 **Cancer prevention studies**

1261 The recommended primary outcome measure in prostate cancer prevention trials is disease free  
1262 survival or the rate of diagnosed prostate cancer at a predefined point in time.

1263  
1264 Baseline risk factors of likely prognostic importance include age, ethnicity, family history of prostate  
1265 cancer, serum PSA, normal/abnormal digital rectal examination or transrectal ultrasonography.

1266  
1267 It is crucial to have identical diagnostic procedure between active and placebo groups in order to avoid  
1268 sampling bias and long observation periods are needed as both the induction period and the latency  
1269 period to detect a prostate cancer are long. Even small differences in management between the  
1270 treatment groups may harbour confounding factors of importance. It is also crucial to assess the  
1271 clinical relevance of the diagnosed cancer, i.e. the diagnosed cancer should be clinically significant.

1272 Stage, Gleason score and PSA level are regarded as the most appropriate prognostic factors of  
1273 outcome of new diagnosed prostate cancers.

#### 1274 **Minimally invasive treatment**

1275 Since available treatment options with curative potential are associated with side effects that interfere  
1276 with health related quality of life, a concept of minimal invasive treatment has been introduced. The  
1277 aim is to delay or avoid the need for, e.g. surgery using techniques and/or medicinal compounds that  
1278 offer low risk of side effects.

1279 As a first step, anti-tumour activity has to be proven. This may be achieved in trials using subjects  
1280 planned for radical surgery where one lobe containing cancer is treated with the minimally invasive  
1281 concept before radical surgery.

1282 For confirmatory trials, an acceptable primary end point is time to need for radical therapy, or  
1283 proportion of patients in need for such therapy at a predefined point in time. Until now, however, there  
1284 is no consensus as regards criteria defining need for radical therapy. Clinical guidelines developed by  
1285 European Urology Association (EAU), National Cancer Comprehensive Network (NCCN) and National  
1286 Institute for health and clinical excellence (NICE) suggest several options. This unfortunate situation is  
1287 acknowledged; nevertheless clear criteria defining need for radical therapy should be in place in study  
1288 protocols, especially if the study cannot be conducted under double-blind conditions. Independent  
1289 adjudication is recommended.

1290 PROs and genitourinary function preservation should be reported as secondary endpoints.

1291  
1292 Prognostic factors of relevance in the planning of the study include: age/life expectancy, disease stage,  
1293 Gleason score and PSA.

#### 1294 1295 **Neoadjuvant and Adjuvant therapy**

1296 As more treatment options become available in the metastatic setting, more trials are expected also in  
1297 the (neo)adjuvant treatment.

1298 Adjuvant treatment using hormones has been proven effective in patients receiving radiotherapy or  
1299 surgery in terms of improved progression free survival; however adjuvant androgen deprivation has  
1300 improved overall survival only for patients receiving radiotherapy. Neoadjuvant hormonal treatment  
1301 prior to radiotherapy improves progression free survival but prior to surgery hormonal treatment only  
1302 reduces the number of positive surgical margins without any favourable outcome on progression free  
1303 survival.

1304 The definition of progression-free survival is usually based on PSA, and differs between radiotherapy  
1305 and surgery groups. After successful surgery the PSA levels is immediately <0.2 ng/ml and a  
1306 commonly used definition of relapsed disease is any measurable PSA levels above 0.2 ng/ml confirmed  
1307 by two consecutive measures. But after successful radiotherapy a decrease in PSA is observed over  
1308 several months not always reaching levels <0.2 ng/ml.

1309

1310 There have also been cases of demonstrated “PSA bounce” in patients proven relapse-free with long-  
1311 term follow-up. This type of PSA kinetics after radiotherapy has urged for a consensus and a definition  
1312 of relapse after radiotherapy is an increase from nadir of 2.0 ng/ml (RTOG-ASTRO criteria Phoenix).  
1313

1314 It is acknowledged, however, that there is an ongoing debate on how to best define relapse.  
1315 Irrespective of this, criteria defining progression should be clearly stated in the protocol. PSA  
1316 measurement and any other clinical assessment should be done at the same pre-specified time-point  
1317 in experimental and control groups. The rate of locally and systemic failure should be reported  
1318 separately.  
1319

### 1320 **Therapy for locally advanced disease**

1321 No consensus regarding the definition of locally advanced disease has been reached, but the term  
1322 often refers to either a bulky tumour with growth outside the prostate capsule (T-stage 3-4) based on  
1323 per rectal assessment, or a tumour that express several high-risk factors indicating a more advanced  
1324 tumour stage. Common is the absence of distant metastases; however this is a function of which  
1325 diagnostics is performed.

1326 The protocol should define methods to be used to exclude distant metastases. Digital rectal  
1327 examination is still considered the most appropriate method to assess local progression. If studies  
1328 cannot be conducted under proper double blind conditions, examination by two independent urologists  
1329 is recommended. Response criteria are otherwise similar to those for metastatic disease presented  
1330 below.

1331 Distant metastases-free survival, PFS including local progression, genitourinary function and validated  
1332 PRO questionnaires constitute relevant outcome measures.

### 1333 **Therapy for metastatic disease**

#### 1334 Hormone naive

1335 During more than 60 years the treatment of choice in metastatic prostate cancer has been androgen  
1336 depletion therapy. More than 90% of the cancers are androgen dependent, but eventually the disease  
1337 becomes castration refractory. Currently androgen depletion is often introduced in the adjuvant setting  
1338 or at PSA relapse without detectable metastases. The first sign of castration refractory state is often  
1339 detected as PSA increase despite S-testosterone at castration levels.

1340 Several definitions have been discussed, but a consensus has been reached during the work of The  
1341 Prostate Cancer Clinical Trials Working Group (PCWG2). The PCWG2 proposes that subjects should be  
1342 categorised according to rising PSA state (non-castrate or castrate) and the occurrence of clinical  
1343 detectable metastases (non-castrate or castrate) throughout the natural prostate cancer history.

1344 It is foreseen that active medicinal agents in late castration refractory state of prostate cancer will  
1345 challenge the use of androgen depletion therapy in order to avoid the symptoms associated with  
1346 castration treatment.

1347 The use of anti-androgens provides an additional treatment option in the hormone naive status. The  
1348 anti-androgens treatment has both a direct effect and a withdrawal effect. This has to be taken into  
1349 account when designing clinical trials and it is often stated that anti-testosterone treatment should  
1350 have been removed at least 4-6 weeks before inclusion to avoid PSA decrease from withdrawal effect.

1351 For medicinal products aiming at achieving medical castration, it is sufficient to convincingly  
1352 demonstrate this while for non-hormonal products to be used as add-on or instead of, it is expected  
1353 that favourable effects on PFS (see below) or OS are demonstrated.

#### 1354 Castration refractory

1355 In the castration refractory state of the disease, there is still some hormonal treatment available  
1356 including CYP-17 inhibitors, anti-androgens, oestrogens and corticosteroids before the disease is  
1357 classified as androgen refractory. Androgen depletion should continue during the disease course as  
1358 androgen sensitive clones are assumed to prevail.

1359 It is important to emphasise that androgen-independent prostate cancer is a heterogeneous group of  
1360 disease and today known prognostic factors include: Gleason score, PSA levels and kinetic, tumour  
1361 stage at diagnose (including bone only, nodal visceral spread), primary treatment, time to relapse,  
1362 duration of androgen depletion therapy, time to castration refractory disease, time with clinical  
1363 detectable metastatic disease, use of cytotoxic and the response. Additionally, general performance  
1364 status, age and co-morbidity are important prognostic factors. From this perspective, it is advisable to  
1365 consider whether it is more informative to conduct separate studies in high and low risk patients.



1366 The evaluation of response is performed according to RECIST criteria when soft-tissue metastases are  
 1367 detectable. However, prostate cancer is characterised by osteoblastic bone metastases not suitable to  
 1368 assessment according to RECIST. Therefore the relevance of new bone lesions as a marker for  
 1369 progressive disease is emphasized. However, subclinical lytic bone lesion successfully treated may  
 1370 firstly responds with an osteoblastic reaction before restitution. Specifically for bone scan it is also of  
 1371 importance to consider uptake caused by trauma and other benign conditions such as osteoporotic  
 1372 fractures. Medicinal compounds acting as inhibitors of osteoblast activity may confound the assessment  
 1373 of disease activity by bone scans.

1374 Progression in bone metastases is often accompanied by PSA increase. PSA increase may thus be  
 1375 taken into account in the definition of progressive disease based on imaging, although PSA increase  
 1376 alone cannot serve as primary end point in confirmatory studies. PSA can even decrease in progressive  
 1377 late castration refractory state due to a dedifferentiation of the cancer cells making them unable to  
 1378 produce PSA.

1379 Currently a large number of new medicinal products are under late clinical development or have  
 1380 recently been marketed. Guidance is therefore not provided as regards suitable reference therapies in  
 1381 patients with castration resistant tumours.

1382 Time to symptomatic progression, PFS and OS are considered appropriate outcome measures and the  
 1383 overall guidance provided in the general section apply.

### 1384 **8.3. Chronic Myeloid Leukaemia**

1385 CML is uniquely well characterised among human malignancies with respect to underlying molecular  
 1386 cause, course of disease, response to BCR-ABL tyrosine kinase inhibitors (TKI) and molecular events  
 1387 causing drug resistance. Due to the continuous scientific advance in this field it is of major importance  
 1388 to follow the progress with respect to standardisation of laboratory techniques used in the assessment  
 1389 of the disease. Generally acknowledged clinical diagnostic and treatment guidelines should also be  
 1390 followed and CHMP regulatory advice is recommended particularly when new diagnostic techniques or  
 1391 treatments emerge.

1392 The diagnosis and stage of the disease should be well documented in any clinical study. Diagnosis of  
 1393 CML should be based on investigation of full blood count (FBC), bone marrow, cytogenetics and real  
 1394 time quantitative reverse transcriptase (RQ-PCR) for BCR-ABL transcripts.

1395 When assessing the response to treatment there are three aspects that should be evaluated:

- 1396 1. Haematological response
- 1397 2. Cytogenetic response
- 1398 3. Molecular response

1399 The degree and timing of haematologic, cytogenetic and molecular responses provide very important  
 1400 prognostic information as time-dependent variables. Additionally, other prognostic scores such as age,  
 1401 spleen size and FBC should also be considered when defining high risk groups. The Sokal and Hasford  
 1402 scores are considered validated predictors of response in newly diagnosed patients.

1403 Current international practice guidelines classify response to first line standard treatment (imatinib)  
 1404 into three categories and this approach including future updates should in general, be followed. An  
 1405 example as described by the ESMO is shown in Table 1. Other international practice guidelines such as  
 1406 those provided by the US National Comprehensive Cancer Network may also be acceptable. For newer  
 1407 drugs whose response may be faster, landmarks and standards of success and failure may need to be  
 1408 reassessed.

1409 **Table 1** **Definition of response to imatinib**

	Optimal	Suboptimal	Failure
1410 3 months	CHR	<CHR	No HR
1411 6 months	≥PCgR	<PCgR	No CgR
1412 12 months	CCgR	<CCgR	<PCgR
1413 18 months	≥MMoIR	<MMoIR	<CCgR
1414 Any time	No response loss Mutations <sup>a</sup>	Loss of MMoIR Loss of CCgR	Loss of CHR Mutations <sup>b</sup>

1419 CHR, complete haematological response (WBC <math>10 \times 10^9/l</math>, differential with no immature granulocytes and <math>< 5\%</math> basophils, platelet <math>< 450 \times 10^9/l</math>,  
1420 spleen non palpable);  
1421 PCgR, partial cytogenetic response (Ph+ metaphases 1%–35%); CCgR, complete cytogenetic response (Ph+ metaphases absent);  
1422 MMolR, major molecular response (BCR-ABL:ABL <math>< 0.10\%</math> by International Scale, on RT-Q-PCR).  
1423 <sup>a</sup>BCR-ABL KD mutations still sensitive to imatinib.  
1424 <sup>b</sup>BCR-ABL KD mutations still insensitive to imatinib.  
1425 [Chronic Myeloid Leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow up; *Annals of*  
1426 *Oncology* 21 (supplement 5); v 165-167, 2010]

1427 Monitoring the therapeutic response and level of residual disease is essential and the following guide is  
1428 recommended. However, if responses with a new therapeutic agent are more rapid testing at more  
1429 frequent intervals may be required.

1430 1. During the first 3 months clinical, biochemistry and haematological monitoring should be  
1431 assessed every 2 weeks.

1432 2. From the third month on:

- 1433 • cytogenetics (chromosome banding analysis of marrow cell metaphases) should be  
1434 performed at least every 6 months until a complete cytogenetic response has been  
1435 confirmed
- 1436 • RT-Q-PCR (BCR-ABL:ABL % on blood cells) should be performed every 3 months until  
1437 a major molecular response is confirmed.

1438 3. Once a complete cytogenetic response and major molecular response have been confirmed:

- 1439 • Cytogenetics every 12 months
- 1440 • RT-Q-PCR every 6 months

1441 Screening for BCR-ABL KD mutations will be expected in cases of failure or suboptimal response.

1442 Measuring drug concentration in blood may be required in some cases, such as failure, suboptimal  
1443 response, dose-limiting toxicity and adverse events.

1444 More frequent monitoring may be advisable in certain cases, for example when studies are conducted  
1445 on a high risk population.

1446 It is recommended that monitoring will take place in specialised central laboratories.

1447 Whenever possible, it is expected that the mechanisms contributing to the lack or suboptimal response  
1448 will be explored and may include the following:

- 1449 • Mutations in the BCR-ABL kinase domain
- 1450 • Clonal evolution, defined as the presence within CML cells of additional translocations that are  
1451 thought to drive disease progression
- 1452 • Pharmacokinetic variability (poor compliance, drug interactions, variability in metabolic  
1453 enzymes etc)
- 1454 • Amplification of the BCR-ABL fusion gene
- 1455 • Overexpression of drug transporter genes and tyrosine kinases such as the SFKS
- 1456 • Toxicity leading to dose interruptions or reductions

1457 **Chronic Phase (CP)**

1458 More than 90% of patients are diagnosed in CP.

1459 As there are currently several medicinal products approved for the treatment of CML in CP a  
1460 comparative trial should be undertaken against a licensed reference product.

1461 If the aim is to show superiority versus a licensed comparator the recommended primary endpoint is  
1462 major molecular response at 18 months. Appropriate secondary endpoints include complete  
1463 cytogenetic response at 12 months, PFS and overall survival. Long term follow up of at least 8+ years  
1464 is expected.

1465 In the case of non-inferiority trials, a longer follow up will be required in order to evaluate the primary  
1466 endpoint and major cytogenetic response after at least 2 years is recommended .



1467 In patients failing a licensed TKI, studies may be undertaken in all patients fulfilling established criteria  
1468 for non-response or secondary failure; alternatively patients may be enrolled also taking into account  
1469 mutation patterns if properly justified.

1470 When studies are conducted in special groups such as patients intolerant to prior TKI therapy, resistant  
1471 to prior treatments (primary or secondary resistance), high risk patients or with new secondary  
1472 mutations baseline characteristics should well defined before enrolment. Symptoms and signs defining  
1473 intolerance to the prior TKI should be documented in detail (including grading) prior to inclusion in the  
1474 study. As class related adverse reactions are common, it is of importance that “cross-intolerance” is  
1475 excluded as objectively as possible due to the subjective nature of “intolerance” in many cases.

1476 It is acknowledged that mutation analysis remains an essential assessment for patients in second line  
1477 treatment and beyond. Enrolled patients should be well characterised with respect to secondary  
1478 mutations and an important aim is to confirm activity in relation to relevant mutations. If justified by  
1479 data, patients with certain mutations associated with low activity for the experimental compound may  
1480 be excluded, but this will be reflected in the labelling.

1481 If patients with increased risk of efficacy failure to TKIs are identifiable at baseline, it is foreseen that  
1482 add-on studies with a non-TKI that is active in patients with CML may be undertaken. Superiority  
1483 should be demonstrated comparing the combination regimen with a single TKI. In studies exploring the  
1484 combination of two TKI the potential of additive toxicity should be fully addressed.

1485 In cases where the target population may be small, for example patients who have no other available  
1486 treatments, EU regulatory advice is recommended prior to the initiation of phase II/III trials.

#### 1487 **Advanced disease (Accelerated Phase, Blast Crisis)**

1488 It is foreseen that the vast majority of these patients have been treated with a TKI.

1489 For those patients that are on accelerated phase (AP) but had prior treatment for chronic phase a trial  
1490 versus another TKI may be conducted if possible. In the case presentation at diagnosis is accelerated  
1491 phase without prior chronic phase a trial versus a first line TKI will be expected. In general, as  
1492 treatment on AP depends on type of prior therapy the comparator used will be defined by prior patient  
1493 treatment history.

1494  
1495 Patients on blast crisis receive conventional chemotherapy with or without allogeneic SCT. Due to the  
1496 rarity of blast crisis and the foreseen complexity of the therapeutic situation, EU regulatory advice  
1497 should be considered.

### 1498 **8.4. Myelodysplastic Syndromes**

1499 Myelodysplastic Syndromes (MDS) are a heterogeneous group of malignant clonal disorders which  
1500 share two main features, i.e., progressive cytopenia and risk for transformation to AML. Until recently,  
1501 supportive care, low dose Ara-C, intensive chemotherapy or HSCT were the only available treatment  
1502 options. HSCT is potentially curative, but poses high mortality risk in the predominantly elderly MDS  
1503 population. Supportive care options include blood transfusions, antibiotics, erythropoietin (EPO) and  
1504 granulocyte colony-stimulating factor (G-CSF).

#### 1505 **Diagnosis and Classification of MDS**

1506 Many patients with MDS are asymptomatic at the time of diagnosis, but eventually develop  
1507 symptomatic anaemia, thrombocytopenia and neutropenia alone or in combination. The clinical course  
1508 is highly variable and several classification systems have been developed, including FAB, WHO and the  
1509 International Prognostic Scoring System (IPSS).

1510 IPSS is based on the percentage of bone marrow blasts, cytogenetics and number and degree of  
1511 peripheral cytopenias at diagnosis, enabling identification of four risks groups: low, intermediate-1,  
1512 intermediate-2, and high risk. Recently, new clinical and laboratory variables were identified that might  
1513 add prognostic information to the IPSS (red blood cell transfusion dependency, high levels of LDH).  
1514 Sponsors are therefore advised to follow closely the expected refinement of prognostic scores to be  
1515 used in the design of clinical trials when sufficiently validated.

1516 The WHO classification of myeloid neoplasms encompasses disorders that show both dysplastic and  
1517 proliferative features at the time of diagnosis. The following disorders belong to this category: chronic  
1518 myelomonocytic leukaemia (CMML), atypical chronic myeloid leukaemia, juvenile myelomonocytic  
1519 leukaemia, and myelodysplastic /myeloproliferative disease, unclassifiable (MDS/MPD, U).

#### 1520 **Inclusion Criteria in Exploratory and Confirmatory Trials**

1521 Since evolution of bone marrow failure and survival depend on patients' baseline characteristics, any  
1522 efficacy or safety conclusion may apply only to patients sharing similar prognostic features. It is,  
1523 however, also acknowledged that pharmacological activity may vary in relation to, e.g. cytogenetic  
1524 characteristics. There is thus a need for rather extensive exploratory studies in order to identify the  
1525 proper target population for confirmatory studies.

1526 Even though it is unwise in general to include patients with highly variable prognosis if left untreated,  
1527 this might become necessary if exploratory studies indicate similar activity irrespective of prognostic  
1528 score, e.g. due to common expression of a certain drug target. Stratification using a well established  
1529 prognostic score such as IPSS is recommended in such cases.

### 1530 **Treatments Aiming at Symptom Improvement**

1531 Alleviation of symptoms related to cytopenia is an acceptable aim of treatment in patients with MDS.  
1532 In most cases this means reduction of anaemia-related symptoms. Due to prevalent co-morbidities in  
1533 this elderly population, symptom scales, even if properly validated, may be too insensitive to capture  
1534 also relevant differences between treatment groups especially as transfusion of red blood cells must be  
1535 individualised due to e.g. concomitant cardiovascular disorders. Loss of need for transfusion for a  
1536 defined period of time (in combination with improved haemoglobin levels) is therefore considered an  
1537 acceptable outcome measure.

1538 These trials, however, must investigate the impact of treatments (test and reference) on safety and on  
1539 more global outcome variables, including disease evolution. OS and disease evolution must therefore  
1540 be prospectively assessed to exclude detrimental effects of the test drug that would outweigh  
1541 documented benefits.

1542 Placebo on top of best supportive care based on currently available treatment options is an acceptable  
1543 comparator if no specific active drug is available to treat the targeted symptoms. It is acknowledged  
1544 that EPO is not licensed within the EU for the treatment of anaemia in patients with MDS, but  
1545 subgroups of patients are identifiable with an increased likelihood of meaningful response. For these  
1546 patients EPO may serve as comparator. Alternatively, patients non-responsive to EPO may be enrolled.

### 1547 **Treatments aiming at reducing risk for disease progression**

1548 Since progression to more severe stages of MDS and to AML is common and signals poor prognosis,  
1549 any treatment that could delay or avoid progression is expected to have a positive impact on clinical  
1550 outcome. Concerning the respective merits of disease progression-related endpoints and OS, all  
1551 recommendations expressed in the main text of this guideline apply. Haematological or cytogenetic  
1552 responses cannot be accepted a priori to assess efficacy, and response rate is more suitable for  
1553 exploratory trials (detecting activity and dose-effect relationships) than for efficacy purposes (and  
1554 detection of a clinical benefit).

1555 Confirmatory studies are expected to be randomised and well controlled using a licensed or evidence  
1556 based medicinal product as reference. In principle, PFS is an acceptable primary endpoint, but survival  
1557 data are needed in order to exclude with reasonable certainty detrimental effects on survival. In high  
1558 risk MDS, however, survival is the preferred measure of patient benefit. In the case HSCT is a realistic  
1559 treatment option in responding patients, please refer to the section "Treatment administered with  
1560 curative intent". The definition of progression must be based on a combination of standardised clinical  
1561 and biological data and centralised blinded review is needed in order to establish progression.

1562 MDS is a condition that irrespective long-term prognosis severely can compromised patients QoL. With  
1563 respect to the possible role of PRO/QoL outcome measure, please refer to appendix (X to be released  
1564 for comments next year). The influence of treatments aiming at symptom improvement as part of  
1565 background SOC on parameters relevant for the evaluation of safety and efficacy of the experimental  
1566 drug, should be carefully addressed.

## 1567 **8.5. Haematopoietic Stem Cell Transplantation**

1568 Drug development in relation to HSCT can be conducted as part of conditioning treatment for HSCT  
1569 and also for the mobilisation of peripheral blood (PB) stem cells that will be utilised in a peripheral  
1570 blood stem cell transplant (PBSCT). Immune therapy in relation to HSCT, however, is not covered.

### 1571 *a) Conditioning treatment*

1573 The outcome measures will need to focus on two aspects, engraftment (short term outcome)  
1574 and a long term outcome which depends on the indication and type of transplant. In addition

1575 long term follow up will be required and its duration will depend on the clinical setting.  
1576  
1577 If autologous HSCT is established in a certain condition such as in multiple myeloma, a  
1578 randomised comparison with an established conditioning regimen is expected. The guidance as  
1579 regards long term endpoints provided in the general guideline document apply. If not  
1580 established, a comparison with standard of care with survival as outcome measure is expected.  
1581  
1582 In allogeneic HSCT, standardisation as far as possible as regards immune suppressive therapy  
1583 and post transplant infection prophylaxis are warranted.  
1584  
1585 In both cases it is advisable to restrict inclusion so that variability in prognosis is reduced, not  
1586 least if the primary aim is to show improved tolerability and safety and non-inferiority in terms  
1587 of efficacy.  
1588  
1589 *b) PBSC mobilisation*

1590 This section reflects use of medicinal products for the mobilisation of autologous PBSC. The  
1591 target population in terms of the condition to be treated, prior therapy etc. should be reflected  
1592 in the eligibility criteria. Extrapolation to other patient populations will in general not be  
1593 acceptable.  
1594  
1595 Endpoints should include short term and long term outcome. A target number of CD34 cells  
1596 that translates into a successful engraftment together with long term data on the engraftment  
1597 will be required for approval. Possible effects on the underlying condition should also be  
1598 addressed.  
1599  
1600 Details on engraftment (time to engraft, outcome of engraft etc) will be expected. The  
1601 potential for tumour stem cell mobilisation and graft contamination should be addressed.  
1602  
1603 Specific short and long term safety data in relation to the HSCT should be submitted. Data on early  
1604 complications such as mucositis, infections, sinusoidal obstruction syndrome (also known as hepatic  
1605 veno-occlusive disease) and transplant-related lung injury will be required. Delayed complications  
1606 including fertility toxicity, secondary malignancies and impaired growth and development in children  
1607 will also need to be collected.  
1608  
1609 In the case of allogeneic HSCT particular attention should be given to data on acute and chronic graft  
1610 versus host disease (GVHD) including details on specific prophylaxis and treatment measures and  
1611 donor type (related or unrelated HLA matched transplant).

## 1612 9. Definitions and Abbreviations

1613 **Chemoprotectant:** A compound which counteracts the activity of anti-tumour compounds on normal  
1614 tissue without (or clearly less) affecting the anti-tumour activity.  
1615

1616 **Chemosensitizer (or drug resistance modifier):** A compound without own anti-tumour activity  
1617 which increases the activity through pharmacodynamic interaction with anti-tumour compound(s).  
1618

1619 **Cytostatic:** Anticancer compound shown to inhibit cell division without direct effects on tumour cell  
1620 viability in non-clinical studies.  
1621

1622 **Cytotoxic:** Anticancer compounds inducing irreversible lethal lesions through interference with DNA  
1623 replication, mitosis, etc. following short term exposure in non-clinical studies.  
1624

1625 **Data maturity:** A clinical study is considered mature if the distribution of events over time (early –  
1626 late) makes it feasible to estimate the treatment effect in the full study population. This refers to the  
1627 assumption that there is a biological difference between e.g. tumours progressing early and late and  
1628 that the treatment effect might differ. The number of late events should therefore be large enough for  
1629 study data to be stable. In practice, if a treatment difference has been established and a clear majority  
1630 of events expected over long term have occurred, the study may in most cases be regarded as  
1631 “mature”.  
1632

1633 **Non-cytotoxic:** Anticancer compounds not belonging to the class of cytotoxic compounds.

1634 **Primary (innate) resistance:** Progression without prior objective response or growth inhibition.  
1635  
1636 **Refractory:** Progression on therapy or within a short period of time after last cycle of therapy.  
1637  
1638 **Resistance:** Progression within a defined timeframe after end of therapy.  
1639  
1640 **Randomised phase II trial:** Randomised exploratory study designed to provide data of importance  
1641 for the design of Phase III confirmatory studies, e.g. with respect an estimate of the possible  
1642 magnitude of the effect using a clinically relevant measure of activity and/or biomarkers.  
1643  
1644 **Secondary resistance:** Progression after documented objective response or period of growth  
1645 inhibition.  
1646  
1647 **Window of opportunity:** Under certain well-defined conditions it is acceptable to conduct a clinical  
1648 study with an experimental compound in settings (line of therapy, stage, etc.) where available data for  
1649 this compound normally would be regarded as too limited. The conditions for conducting such a study  
1650 must be set rigorously so that the interest of the patient is guaranteed. Circumstances to take into  
1651 account include benefit-risk of available therapies, available safety/activity data for the experimental  
1652 compound, tumour-related symptoms (in most cases absent), expected evolution of the disease if left  
1653 untreated or treated with available therapies, ease of frequent monitoring of tumour evolution  
1654 (including use of biomarkers), planned intervention post chemotherapy, etc.  
1655  
1656 **ADCC:** Antibody dependent cellular cytotoxicity  
1657  
1658 **ANC:** Absolute neutrophil count  
1659  
1660 **BSA:** Body surface area  
1661  
1662 **BSC:** Best supportive care – include antibiotics, nutritional support, correction of metabolic disorders,  
1663 optimal symptom control and pain management (including radiotherapy), etc. but does not include  
1664 tumour specific therapy  
1665  
1666 **CR:** Complete response  
1667  
1668 **CRF:** Case report form  
1669  
1670 **DFS:** Disease-free survival (time from randomisation to recurrence or death from any cause)  
1671  
1672 **DLT:** Dose limiting toxicities  
1673  
1674 **EFS:** Event-free survival in this guideline refers to lack of achievement of CR, relapse and death  
1675 without relapse are counted as events in an EFS analysis. Those patients who did not reach CR during  
1676 the pre-specified induction phase will be considered as having an event at time 0.  
1677  
1678 **HRQoL:** Health related quality of life  
1679  
1680 **MoAb:** Monoclonal antibody  
1681  
1682 **MTD:** Maximum tolerated dose, often defined by dose-limiting toxicity occurring in at least 2 of 6  
1683 patients so that further dose-escalation is not undertaken.  
1684  
1685 **ORR:** Objective response rate (the proportion of patients in whom a CR or PR was observed)  
1686  
1687 **OS:** Overall survival (time from randomisation to death from any cause)  
1688  
1689 **RP2D:** Recommended phase 2 dose  
1690  
1691 **PD:** Pharmacodynamics  
1692  
1693 **PK:** Pharmacokinetics  
1694  
1695 **PR:** Partial response

1696 **PRO:** Patient reported outcome

1697

1698 **PFS:** Progression-free survival (time from randomisation to objective tumour progression or death  
1699 from any cause)

1700

1701 **TTF:** Time to treatment failure (time from randomisation to discontinuation of therapy for any reason  
1702 including death, progression, toxicity or add-on of new anti-cancer therapy)

1703

1704 **TTP:** Time to tumour progression (time from randomisation to observed tumour progression, censoring  
1705 for death without progression)

1706

## 1707 **Appendix**