EUnetHTA JA3 WP4 – Pharmaceutical technologies – PTJA01
External Comments to the project plan
July 2017

Organisation	Page	Line	Comments	Author's reply
university of Liege	8	4	I would not use Azacitidine as comparator since patients offered azcitidine are generally less fit than those given classical chemotherapy	We are generally aware that the population in which azacitidine is used in practice is most likely older and less fit than the population in which Midostaurin is likely to be used. However, since azazitidine is indicated for those ineligible for SCT in this indication, this is now listed in the PICO. Overall, we do not expect that formal indirect comparison of midostaurin and azacitidine is possible due to reasons mentioned in the comment. Perhaps just a short discussion and reasons for not performing this comparison in the assessment is expected.
university of Liege	7	24	the dose of daunorubicin in induction is relevant since the MRC trial has demonstrated that FLT3-ITD patients do better with 90 mg/m2 daunorubicine than with 60 mg/m2 daunorubicine (https://doi.org/10.1182/blood-2016-04-712091)	Daunorubicine 90mg/m2 used in induction has been added to the list of comparators.
University of Groningen	7		population: it should be stated: fit for intensive chemotherapy: so: Adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation-positive and fit for intensive chemotherapy	Fitness for intensive chemotherapy will discussed in the assessment and this comment will be considered during the assessment phase. We agree in principle on this comment. However, in this stage the population is now defined as in the currently expected indication without this restriction.
University of Groningen	7		intervention: it should be stated: cytarabine combined with any anthracline according to local protocols and in doses as is standard according to local protocols	The aspect of local differences in treatment protocols and variations in induction and consolidation are reflected in table 3 (intervention) in a note.

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University of Groningen	8		comparison: in my opinion the comparison should be as stated with the first bullet; but NOT azacitidine, since these patients are not fit for intensive chemotherapy.	See previous comment on azacitidine.
University of Groningen	8		outcomes: I would suggest to use outcome definitions as defined by ELN 2017 recommendations.	The outcomes have been now defined mainly based on what is available. We will consider reflecting this comment in the actual assessment report.
University of Groningen	9		project approach and method: Please also consider: Especially the effect of the allelic burden of Flt3-ITD should be analysed.	We have requested subgroup analyses and allelic burden of FLT3 is one of the key interests. This aspect will be covered in the assessment.
University of Groningen			General remark: I would suggest also to consider a critical appraisal of the statistical plan of the report: balanced groups? Sensing equally distributed amongst the comparators?	We will try to arise any concerns related to study design and conduct in the assessment.
University of Groningen			General remark: Also a statement on how to deal with Midostaurin post allo transplant should be made, especially since this question is not addressed in the Ratify study, though other TKI seem to have some effects in this context.	We will try to reflect this point in the assessment phase.