

Higher Daunorubicin Exposure Benefits *FLT3* Mutated Acute Myeloid Leukaemia

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(on behalf of the UK NCRI AML Study Group).

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Whether, and for which patients with AML, the dose of daunorubicin in induction should be 90mg/m² continues to be discussed. There seems little doubt that 90mg/m² is superior to a 45mg/m² dose⁽¹⁻³⁾. In this context the reports from the E1900 trial suggest a benefit for patients less than 50 years of age who did not have adverse cytogenetics, and for patients who had mutations of *DNMT3A*, *NPM1* and *MLL-PTD*^(1,4). A more recent follow up also showed benefit for *FLT3-ITD* mutations⁽⁵⁾. The concern however is that many investigators routinely use daunorubicin at a dose of 60mg/m² thus making extrapolations from this study about which patients need 90mg/m² as opposed to 60mg/m² less reliable.

We recently reported a large trial (n=1206) comparing daunorubicin doses of 90mg/m² versus 60mg/m² in induction course 1⁽⁶⁾. After course 1, patients defined as high risk (HR), which was not based on *FLT3* status, entered the high risk arm of the trial, while the remaining patients received a second course which included 3 days of daunorubicin 50mg/m². The proportion of HR patients was the same in the 60mg and 90mg/m² arms. The trial independent Data Monitoring Committee recommended premature closure at a median follow up of 14.8 months because of an excess risk of mortality by day 60 in the 90mg/m² arm, with no suggestion, on an intent to treat analysis, of later benefit. When reported, heterogeneity tests failed to identify any subgroup where there was significant interaction other than *FLT3-ITD*, but the effect of DA90 failed to reach significance in this subgroup. We noted that this observation would require further follow-up.

We have now re-analysed the study, again by intention-to-treat, with median follow-up of 28 months. The outcomes (CIR, RFS and OS) are virtually unchanged from the initial report with no differences emerging overall. Stratified analyses again show no significant interaction with treatment of any baseline feature, with the exception of patients with a *FLT3-ITD* mutation. Here, there was significant interaction on relapse, and relapse-free and overall survival with a significant benefit for 90mg/m² in *FLT3-ITD* mutant patients (CIR 44% vs 60% HR 0.58 (0.38-0.89), p=0.01; RFS: 45% vs 33% HR 0.63 (0.43-0.94) p=0.02; OS: 54% vs 34% HR 0.65 (0.43-0.96) p=0.03). While there is some evidence of increasing benefit on RFS with greater allelic burden this is not seen when considering OS. The effect is unrelated to *NPM1c* mutations. Just over half (101/200) of the patients in this group were transplanted (50 vs 51); analyses of outcomes when censored at transplant are not significantly changed, although the point estimate is in favour of 90mg/m². The findings indicate that the benefit is due to a reduced risk of relapse in *FLT3-ITD* mutant patients treated at 90mg/m².

It is of course possible, as indicated in the detailed analysis of the E1900 trial, that there are further beneficiary patients who could be identified by more detailed molecular characterisation which has not been undertaken in our study.

Taken together, these data suggest that there is a place for escalated daunorubicin dosing for *FLT3-ITD* mutated cases. This presents a logistical challenge about the practicality of obtaining prompt *FLT3-ITD* mutation status without unduly delaying treatment. Our experience suggests that allelic ratio or *NPM1* status is not needed to inform a treatment decision. Other options, which would require prospective evaluation, are to give the higher dose on days 3 and 5 of course one, or even give the escalated dose in course 2 only. Developing therapies to improve the poor outcome for *FLT3* mutated disease is an active area of clinical research, which has been given encouragement by the recent report by Stone et al. of the *RATIFY* trial⁽⁷⁾ which added midostaurin to conventional therapy and improved overall survival from 44.2% to 51.4% at 5 years which is similar to the benefit which we show here (54% vs 34% overall at 3 years, and 53% vs 42% when censored at transplant), for the recipients of daunorubicin 90mg/m².

Authorship

AKB, RKH designed trial, AKB wrote paper, RKH performed statistical analyses; all authors contributed to data interpretation; AKB, NHR acted as chief investigator

Disclosure

AKB: CTI, employment

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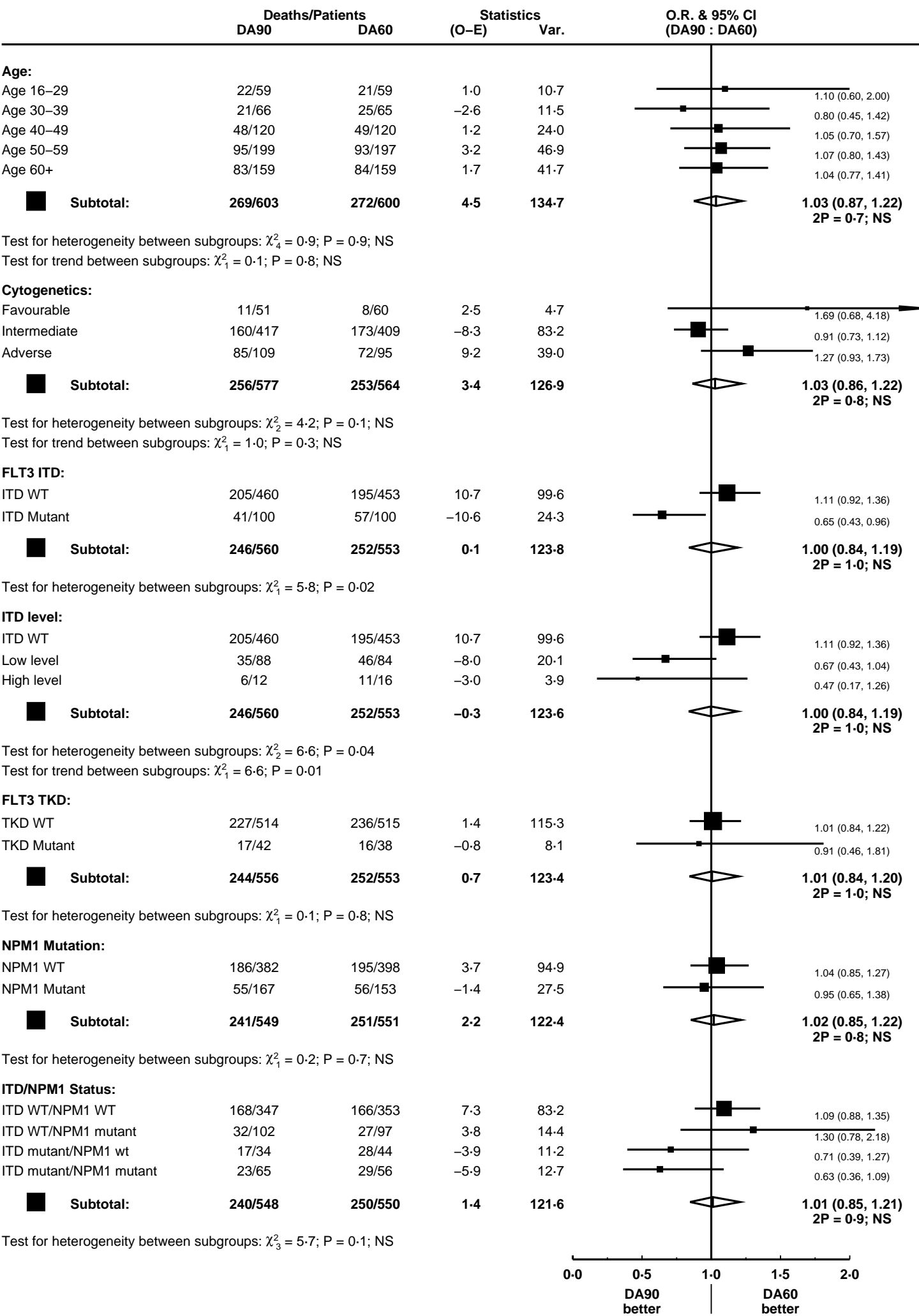
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Figure Legends:

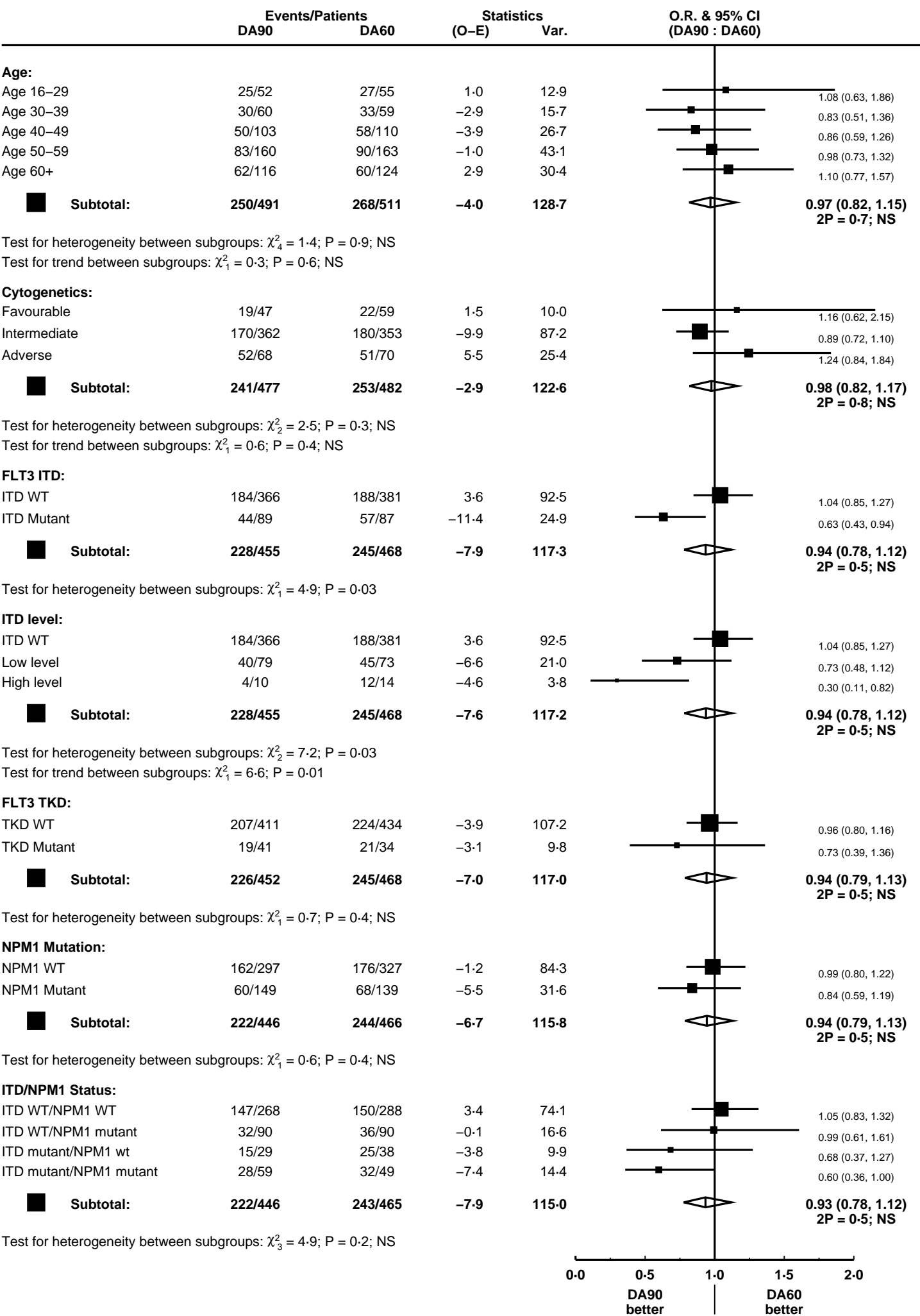
Figure 1. Stratified analyses of A) Overall Survival and B) Relapse-Free Survival

Figure 2: Survival by FLT3-ITD status, A) ITD Wild Type; B) ITD Mutant

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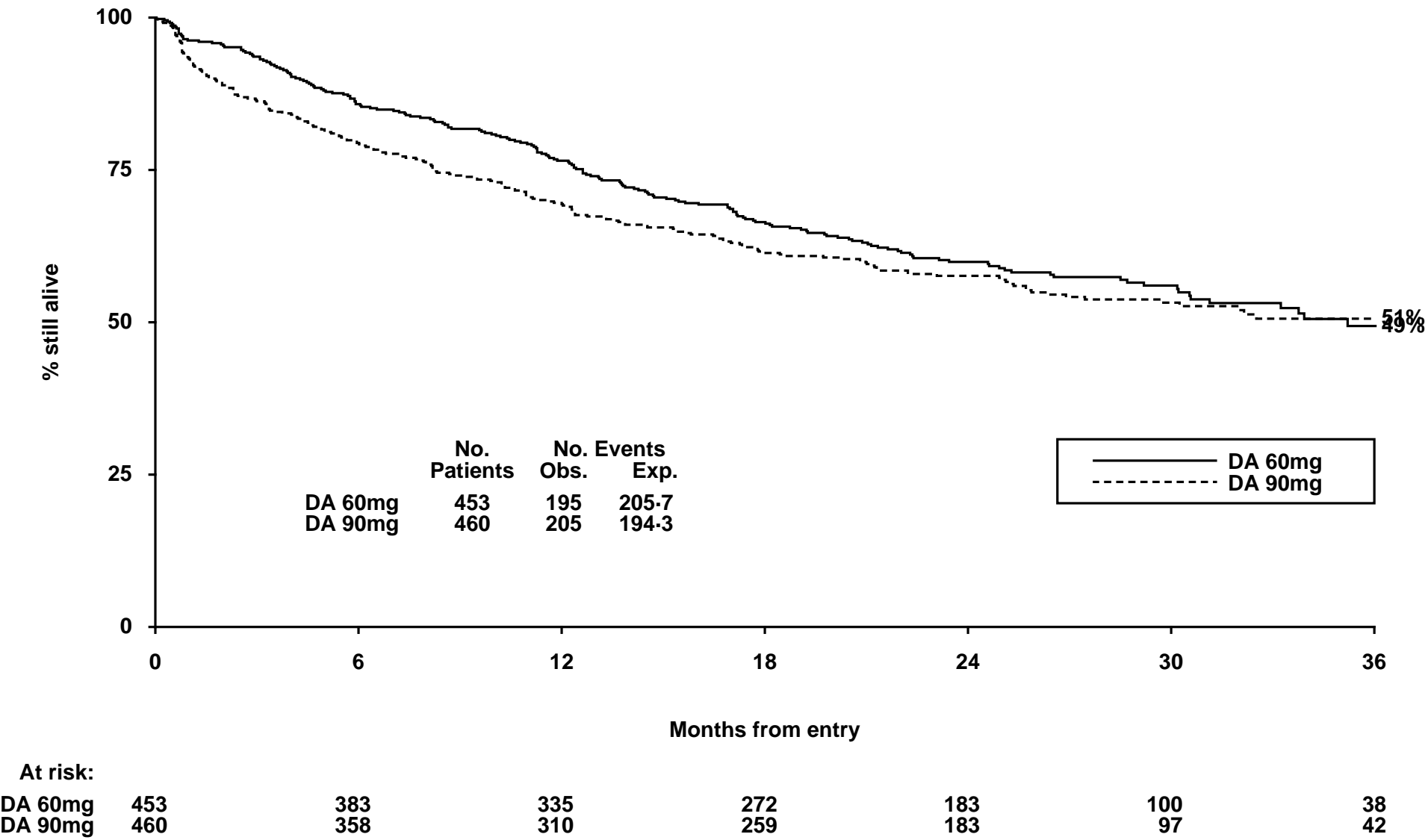


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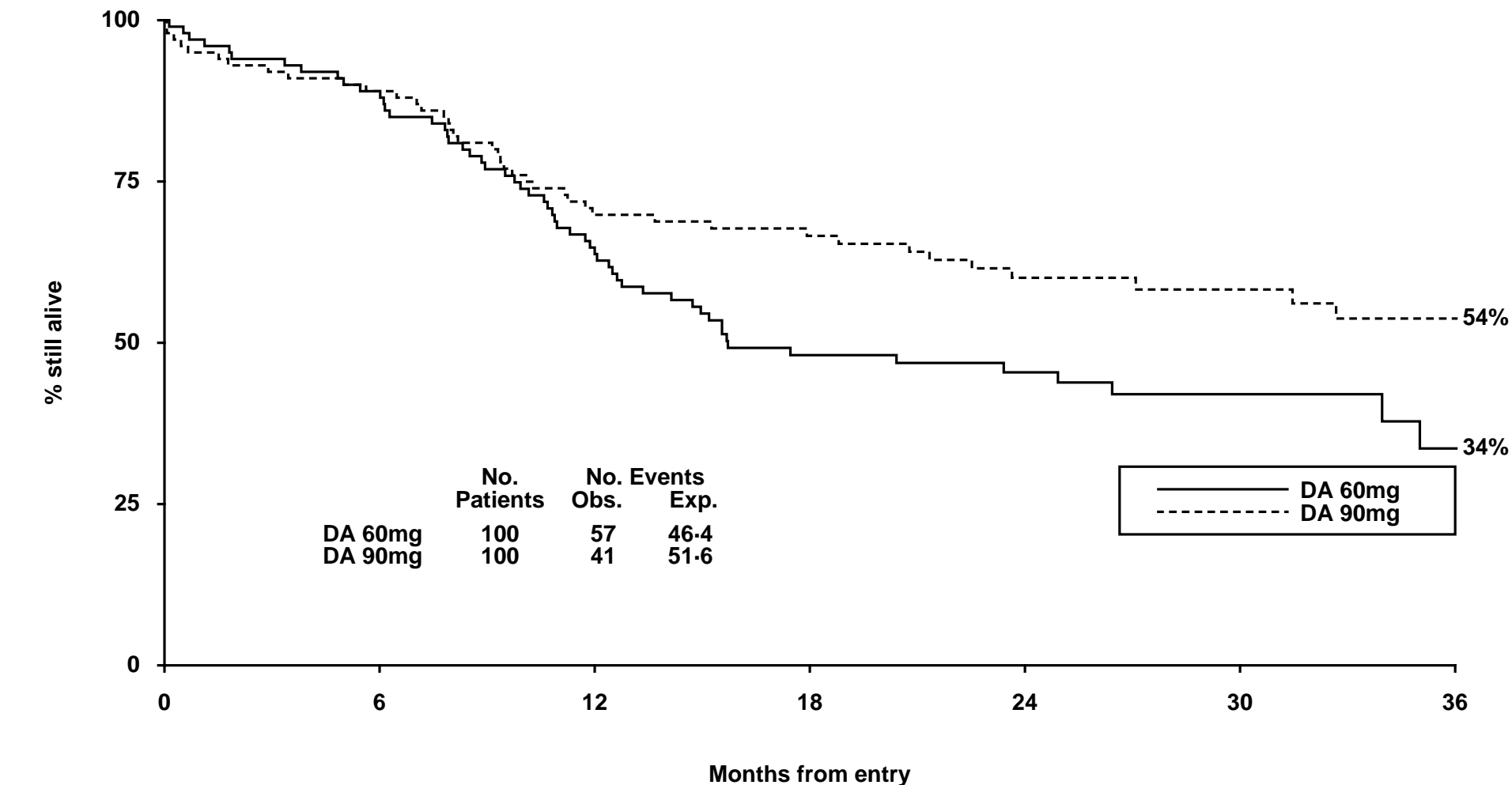
AML17: Overall Survival ITD Wild Type

Figure 2A



AML17: Overall Survival ITD Mutant

Figure 2B



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DA 90mg	100	89	68	57	40	29	11



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