Myeloma XI trial for newly diagnosed multiple myeloma (NDMM); Long term second primary malignancy (SPM) incidence in the context of lenalidomide maintenance.

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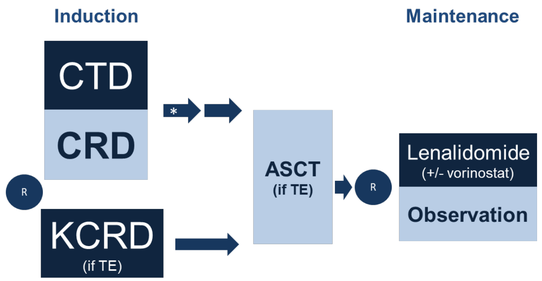
Background

As a consequence of improved treatment patients with multiple myeloma are living longer. Long term co-morbidity may include the risk of developing a second primary malignancy (SPM). Early trials of long-term lenalidomide reported an increased incidence of second primary malignancy (SPM), particularly AML and MDS (1-3). Later, meta-analysis suggested the link to be secondary to lenalidomide in combination with melphalan (4).

We have previously reported on SPM incidence in the context of this trial and shown that haematological SPM (hSPM) incidence was not increased in association with lenalidomide (5). Here we present a long-term analysis of SPM incidence in patients who have received maintenance therapy versus observation in the context of the Myeloma XI trial

Myeloma XI

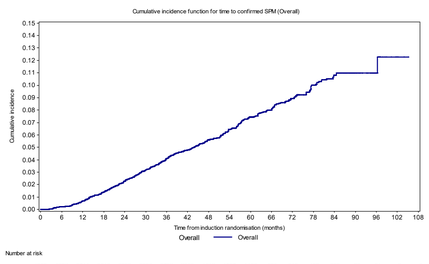
Myeloma XI is a phase III, randomised, multi-centre, parallel-group design, open-label trial comparing thalidomide, lenalidomide, carfilzomib and bortezomib induction combinations and lenalidomide ± vorinostat as maintenance in newly diagnosed myeloma patients (n=4358). The trial includes both transplant eligible (TE) and non-eligible (TNE) pathways.



CTD, cyclophosphamide, thalidomide, dexamethasone; CRD, cyclophosphamide, lenalidomide, dexamethasone; KCRD, carfilzomib plus CRD. *Patients receiving triplet induction with a suboptimal response to induction (<VGPR) were eligible for intensification. Patients with PR/MR were randomised to CVD (cyclophosphamide, bortezomib and dexamethasone) or no further therapy prior to ASCT. Patients with SD/PD all received CVD.

Overall SPM incidence

4358 patients were randomised to treatment with a further 1971 patients being randomised to either lenalidomide maintenance or active observation

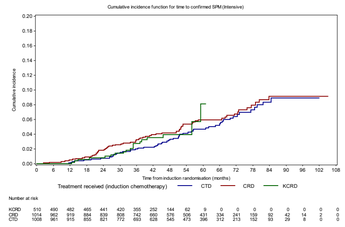


Overall cumulative incidence
3 year – 4.1%
5 years – 7.4%
7 years – 10.8%

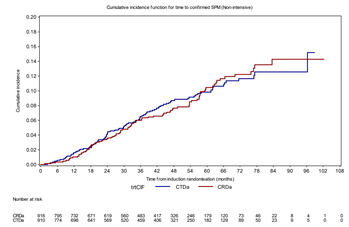
1. Attal, M., *et al., Lenalidomide maintenance after stem-cell transplantation for multiple myeloma.* N Engl J Med, 2012. **366**(19): p. 1782-91.
2. Palumbo, A., *et al., Continuous lenalidomide treatment for newly diagnosed multiple myeloma.* N Engl J Med, 2012. **366**(19): p. 1759-69.
3. McCarthy, P.L., *et al., Lenalidomide after stem-cell transplantation for multiple myeloma.* N Engl J Med, 2012. **366**(19): p. 1770-81.
4. Palumbo, A., *et al., Second primary malignancies with lenalidomide therapy for newly diagnosed myeloma: a meta-analysis of individual patient data.* Lancet Oncol, 2014. **15**(3): p. 333-42.
5. Jones JR *et al. Second malignancies in the context of lenalidomide treatment: an analysis of 2732 myeloma patients enrolled to the Myeloma XI trial.* Blood Cancer Journal, 2016. 6, e506.

SPM incidence according to pathway and induction therapy received

TE pathway – induction therapy

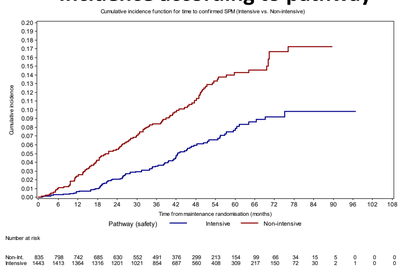


TNE pathway – induction therapy



- **SPM incidence was well matched in each pathway suggesting that the induction treatment received did not impact on the likelihood of SPM development.**

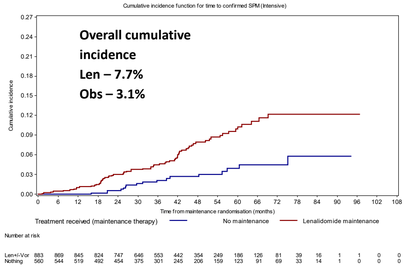
Incidence according to pathway



- **Incidence in the TNE pathway was greatest with 180 patients developing an SPM with an overall incidence of 9.8%. 138 patients in the TE pathway developed an SPM with an overall incidence of 5.5%**

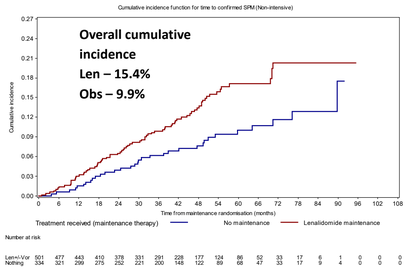
SPM incidence according to maintenance randomisation

Transplant eligible



- **85 TE patients developed an SPM post maintenance randomisation, 68 of them received lenalidomide.**
- **Overall incidence of 7.7% in patients receiving lenalidomide and 3.1% in patients being observed.**

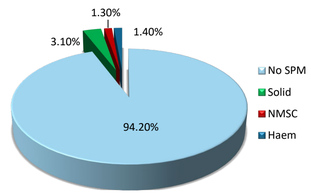
Transplant non-eligible



- **110 TNE patients developed an SPM post maintenance randomisation, 77 of them received lenalidomide.**
- **Overall incidence of 15.4% in patients receiving lenalidomide and 9.9% in patients being observed.**

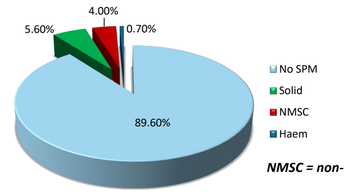
Proportion of patients who developed an SPM and breakdown of cases

Proportion of patients who developed an SPM in the TE pathway



- **94.20% of patients in the TE pathway have not developed an SPM**
- **Solid tumours occurred in 3.1%**
- **Haematological second malignancies were rare, seen in 1.4% of patients (n=35/2532)**

Proportion of patients who developed an SPM in the TNE pathway



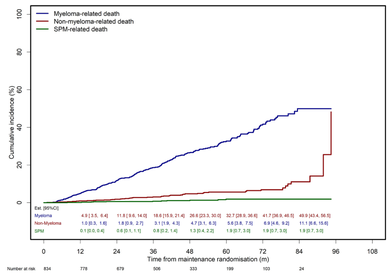
- **89.6% of patients in the TNE pathway have not developed an SPM**
- **Solid tumours occurred in 5.6%**
- **Haematological second malignancies were very rare, seen in 0.7% of patients (n=13/1826)**

NMSC = non-melanoma skin cancer

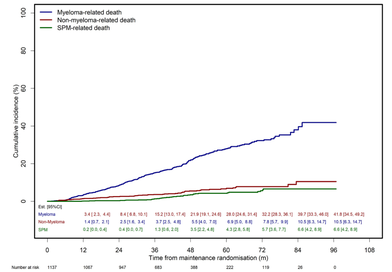
- **These data suggest that advanced age/frailty are greater risk factors for the development of second malignancies than the intensity of the treatment used.**

Cause of death according to maintenance strategy (TE and TNE combined)

Cause of death – observation



Cause of death – lenalidomide



- **In patients undergoing active observation or receiving lenalidomide maintenance the incidence of death due to SPMs was low. Most deaths in both groups were due to myeloma.**

Conclusions

- **Haematological SPM incidence is low in all patient groups including those receiving lenalidomide maintenance.**
- **The highest incidence of SPM (all types) is seen in transplant non-eligible patients receiving lenalidomide maintenance. This suggests that advanced age is an important risk factor**
- **Low risk non-melanoma skin cancers form a large proportion of SPM cases**
- **Death due to second malignancy is rare with most patients dying of advanced myeloma or other causes.**

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Conflicts

JJ has received honoraria and research funding from Celgene