Summary of the Conclusion of the ADIUVO Phase 3 Trial and Observation Study

[Adjuvant mitotane versus surveillance in low-grade, localised adrenocortical carcinoma (ADIUVO): an international, multicentre, open label, randomised, phase 3 trial and observational study]

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The results of this important research study were published online in The Lancet on 21 August, 2023.

ADIUVO was a multicentre phase 3 trial with 23 participating centres across seven countries. Its purpose was to assess how effective and safe mitotane is when given to patients after complete surgical removal of an adrenocortical carcinoma (***ACC) that was considered to be at low risk of recurrence***. The study did ***not*** look at patients with an ACC that was at high risk of recurrence or that had already spread to elsewhere in the body.

The study ran between October 2008 and December 2018 and had two 'arms':

1. The Phase 3, open-label, parallel, randomised Clinical Trial of mitotane in 91 post-surgery ACC patients with low risk of recurrence, where 45 patients, were randomly assigned to mitotane and 46 to surveillance alone, and
2. An Observational Study of 95 patients who refused the randomisation of the trial but agreed on data collection by the European Network for the Study of Adrenal Tumours (ENSAT). Of these 95 patients, 42 received mitotane and 53 underwent surveillance alone.

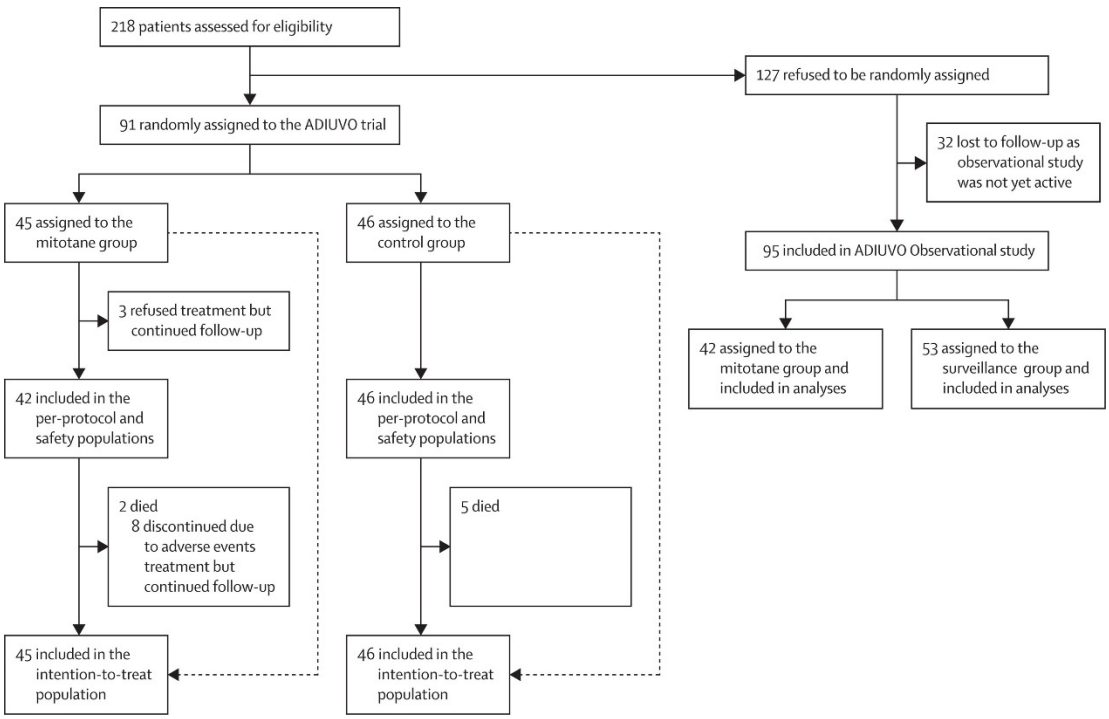

Diagram: trial profile

The Ki67 index is currently used to assess how aggressive and likely to spread ACC (and some other cancers) are. In this study, the participants had to have a Ki67 of less than 10% (average 5%), and no sign of cancer spread on scans.

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Results

In the Clinical Trial arm, the team saw no significant difference in the 5-year recurrence-free survival rates between those receiving mitotane and those who weren't (79% vs 75% respectively). All 42 of those who received mitotane (3 patients in the mitotane arm refused the treatment) suffered mild or moderate side-effects, resulting in 8 discontinuing treatment after an average of 6 months.

They also didn't find any significant difference in recurrence-free survival between those on mitotane who reached the 'therapeutic level', and those who didn't, nor between those who reached the 'therapeutic level' within 3 months, and those who didn't.

In the Observational Study arm, the team saw no significant difference in the 5-year recurrence-free survival rates between those receiving mitotane and those who weren't (74% and 72% respectively).

The team had hoped to be able to look at overall survival rates; however, due to slow recruitment to the trial resulting in its early discontinuation, this wasn't possible. This meant that they could not properly determine whether or not mitotane would have been effective in these patients with lower risk of recurrence.

'..the ADIUVO findings provide insufficient evidence of mitotane efficacy and suggest that active surveillance is the most adequate concept for patients with low-grade, localised adrenocortical carcinoma'.

Comment

This study shows just how difficult it is to undertake research into such rare diseases and cancers. Despite what seems to the average person to be a long time-frame, the trial ended early due to insufficient recruitment and the authors acknowledge the limitations.

Nevertheless, given the lack of significant difference between the two groups (mitotane and no mitotane), the conclusion of the study was that there is not enough evidence to show that mitotane is useful in this group, and that, in fact, active surveillance was *'the most adequate concept for patients with low-grade, localised adrenocortical carcinoma'.*

A Final Warning

The authors wrote that, *'the results of the ADIUVO trial should not be generalised to patients with adrenocortical carcinoma at standard or high risk of recurrence for whom adjuvant mitotane treatment should still be considered standard of care.'*

- Click here to read the full Lancet article.