

5.1.2 Effect of Study Treatment on Tumour Cell Apoptosis

Overall, the rate of apoptosis was low throughout the trial and there were no significant differences between baseline and end of treatment apoptosis levels within and between treatment groups (Table 3). Given the established positive correlation between Ki67 and apoptosis (Figure 7), the growth index defined as percent Ki67-expression divided by percent Caspase-3 expression was analysed. There was a greater suppression in the growth index in the combination arm (75.2%) compared to anastrozole alone 55.9% (Table 4), (Figure 8).

	Anastrozole (n = 33)	Pictilisib plus Anastrozole (n = 56)	Relative Risk (combination/ anastrozole)	p-Value
The geometric mean baseline Casp-3 expression [% (95% CI)]	0.14% (0.10%-0.18%)	0.15% (0.11%-0.19%)	NS	NS
The geometric mean EOT Casp-3 expression [% (95% CI)]	0.14% (0.11%-0.18%)	0.14% (0.10%-0.19%)	NS	3NS

Table 3: Induction of apoptosis with anastrozole or anastrozole plus pictilisib. Geometric mean Ki67 suppression is defined as  $\text{Ln}(\text{Ki67Day15}) - \text{Ln}(\text{Ki67baseline})$ ; the ratio (combination/ anastrozole) of geometric mean Ki67 suppression is provided with 95% CI. Geometric mean end-of-treatment (EOT) Ki67 expression is defined as  $\text{Ln}(\text{Ki67Day15})$ ; individual EOT anti-proliferative response  $R_{\text{Ki67-Day15}}$  is defined as  $\text{Ln}(\text{Ki67Day15}) \leq 2$ ; individual anti-proliferative response  $R\Delta\text{Ki67}$  is defined as a  $\geq 50\%$  fall in Ki67 expression between baseline and Day 15.

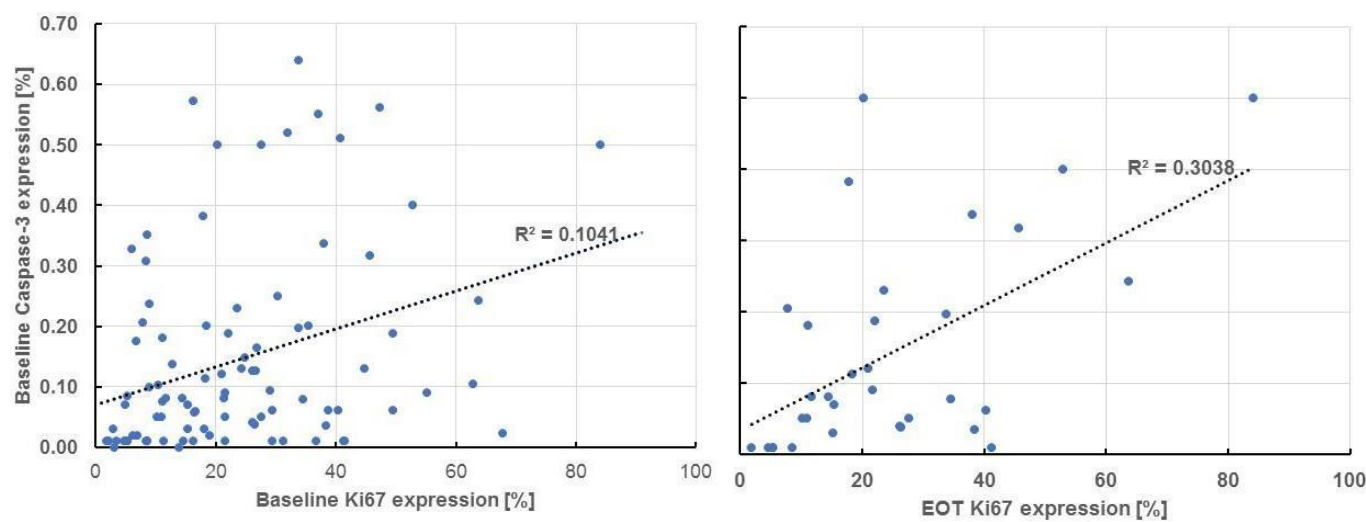
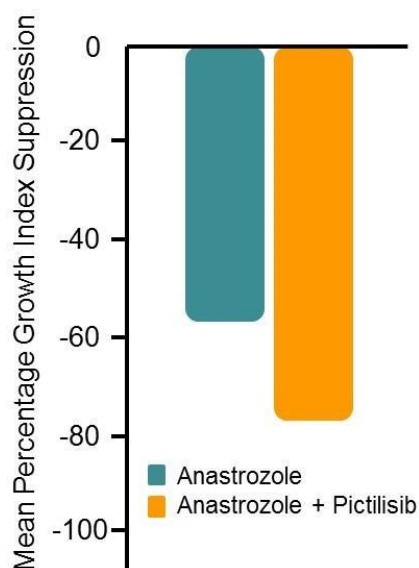


Figure 7: Relationship between Ki67(%) and apoptosis (%) before and after 2 weeks of treatment irrespective of treatment arm.

	Anastrozole (n = 33)	Pictilisib plus Anastrozole (n = 56)	Relative Risk (combination/ anastrozole)	p-Value
The geometric mean baseline growth index [% (95% CI)]	433.2 (190.0-676.4)	635.5 (381.2-889.8)	NS	NS
The geometric mean EOT growth index [% (95% CI)]	190.9 (71.5-310.3)	157.5 (93.0-222.1)	NS	NS
The mean relative growth index suppression [% (95% CI)]	55.9 (4.4-270.7)	75.2 (25.3-191.8)	NS	NS

**Table 4: Treatment-associated change in growth index (GI), defined as Ki67[%]/Caspase-3[%], with anastrozole or anastrozole plus pictilisib**



**Figure 8: Mean percentage Growth Index suppression**