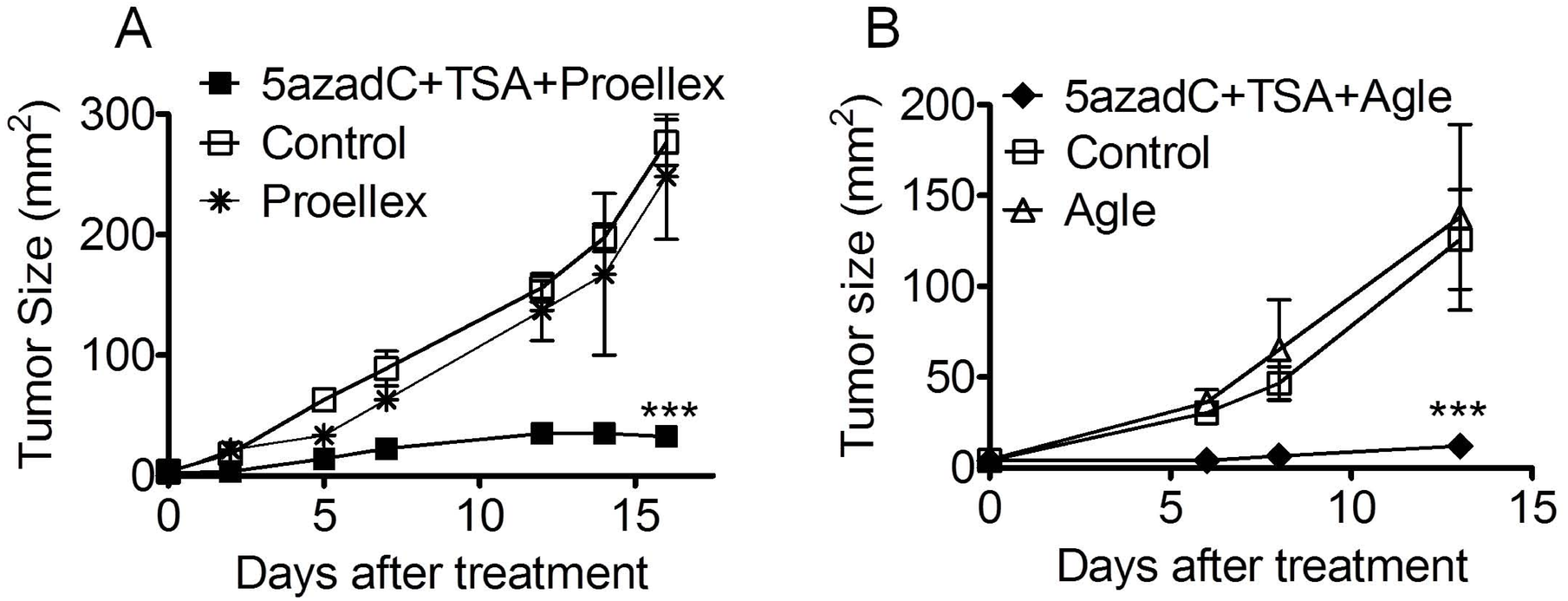
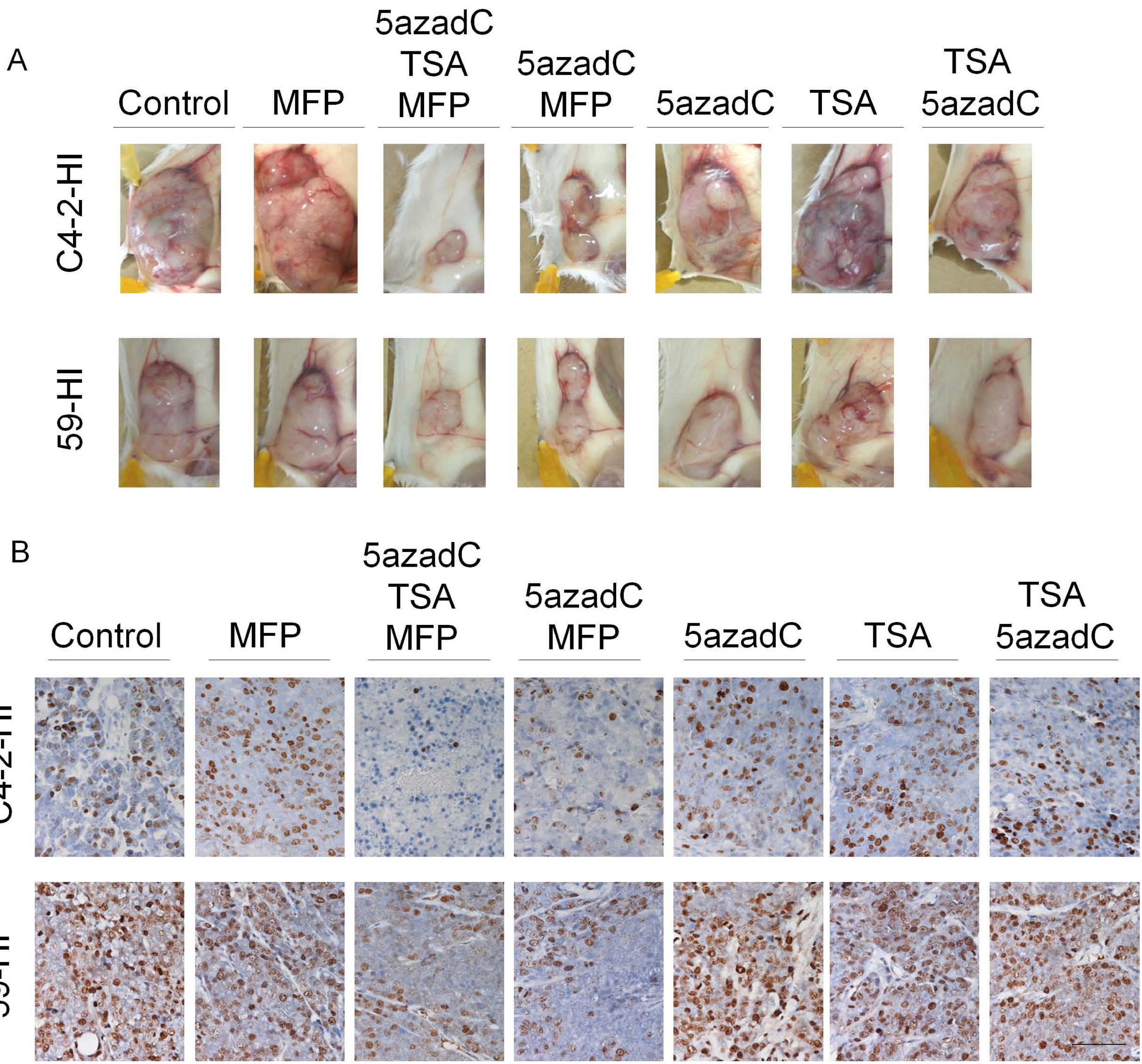


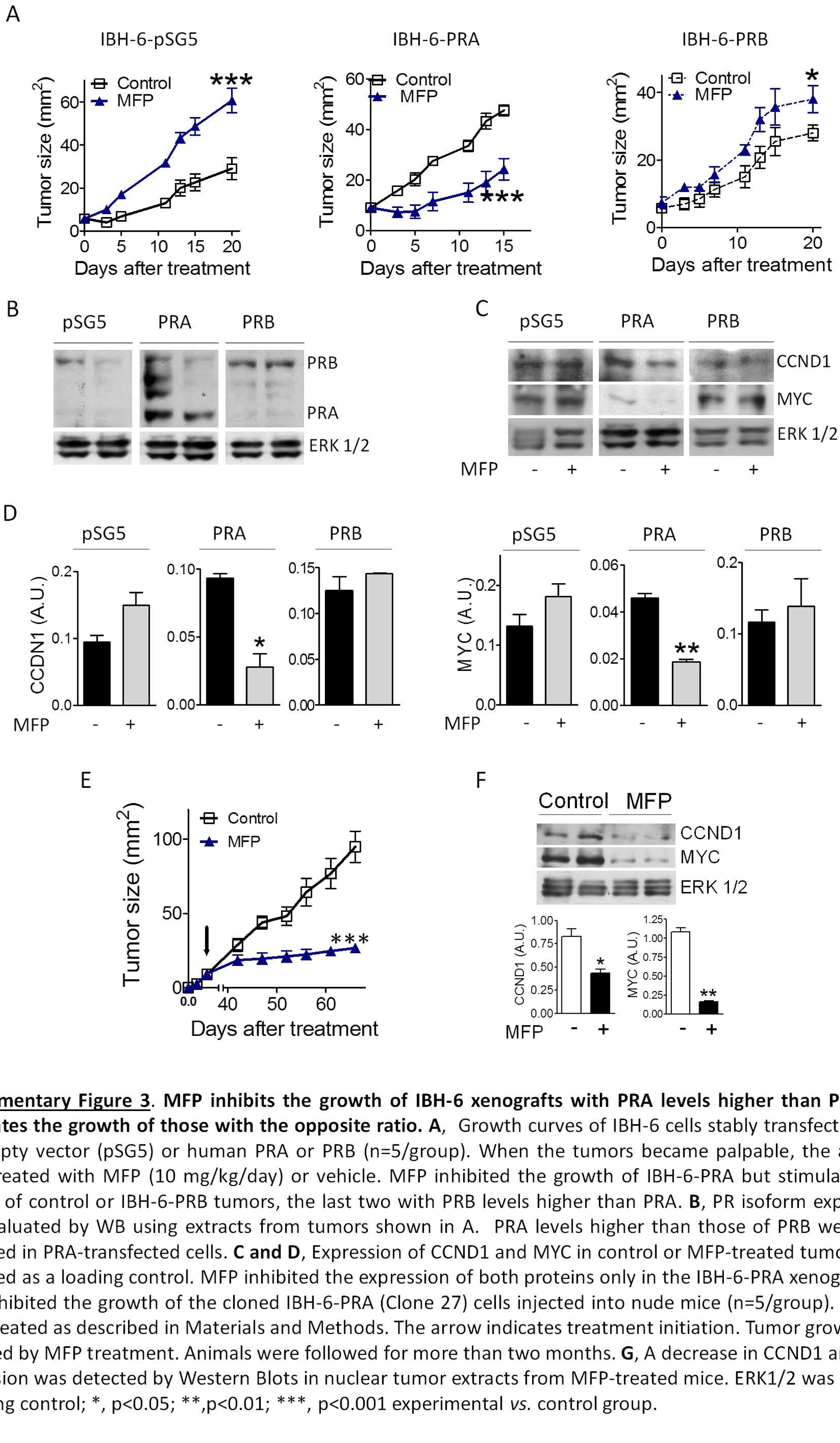
Supplementary Figure 1. DNMT and HDAC inhibitors restore antiprogestin responsiveness in constitutively MFP-resistant tumors. C4-2-HI tumors growing in BALB/c mice were treated as described in Materials and Methods with 5azadC and/ or TSA and/ or Proellex (A) or Aglepristone (B). Tumor growth was inhibited only in mice treated with the DNMT and the HDAC inhibitors in the presence of antiprogestins. Growth curves of groups treated with 5azadC and/ or TSA can be observed in Figure 2A. ***: $p<0.001$ *vs.* all other groups.

Wargon *et al.*, Supplementary Figure 2,



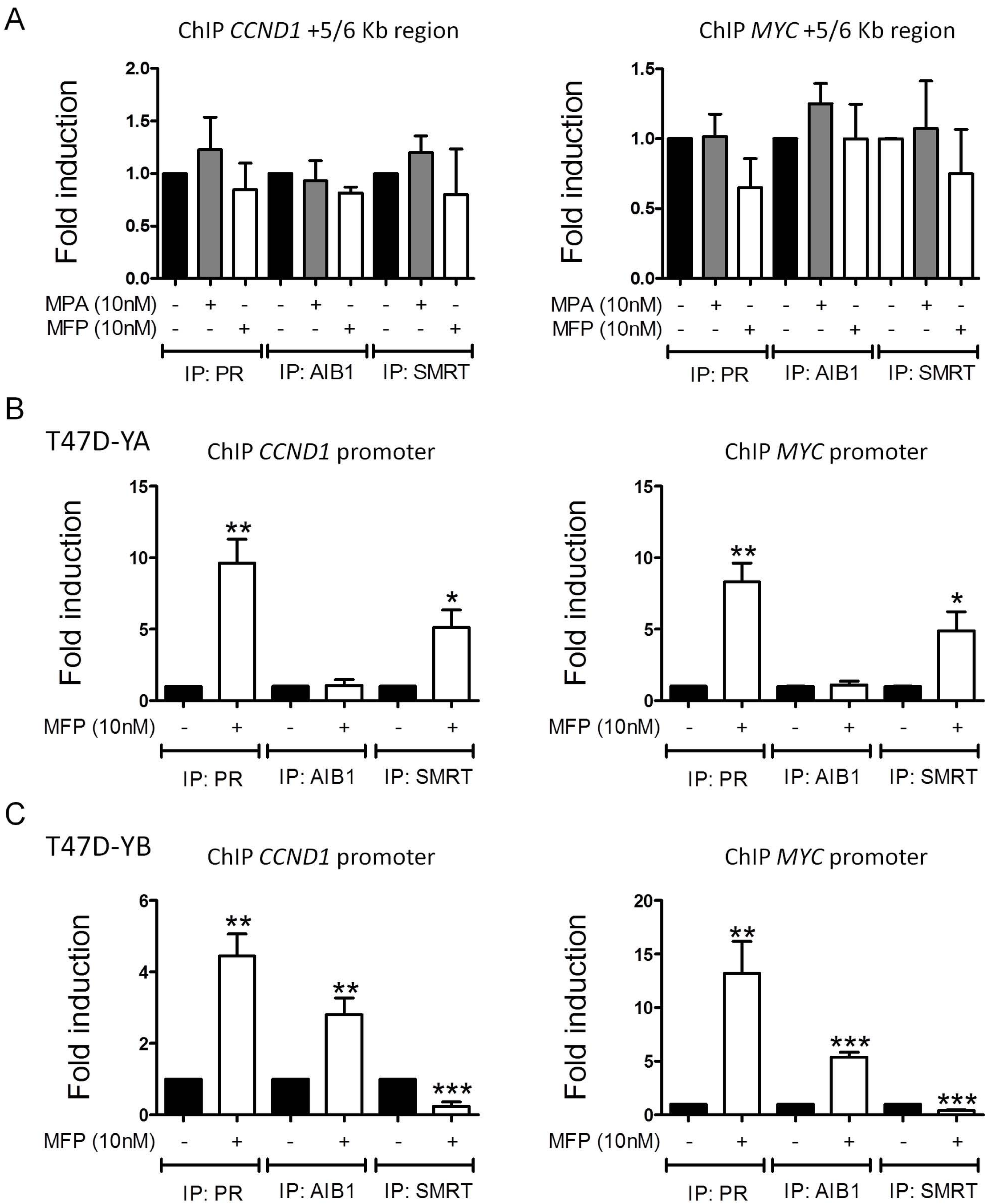
Supplementary Figure 2. Treatment of constitutive MFP-resistant tumors *in vivo* with 5azadC, TSA and/or MFP. Tumors were treated as described in Materials and Methods and in Legend to Figure 2 and a representative image of one tumor of each group in shown in A. Ki67 expression was evaluated by immunohistochemistry to evaluate the proliferative state of the tumors. A representative image of each group in shown in B and the average of the percentage number of stained nuclei/total nuclei in the different tumors is shown in Figure 2 B. Scale bar=100 μm.

Wargon *et al.*, Supplementary Fig. 3

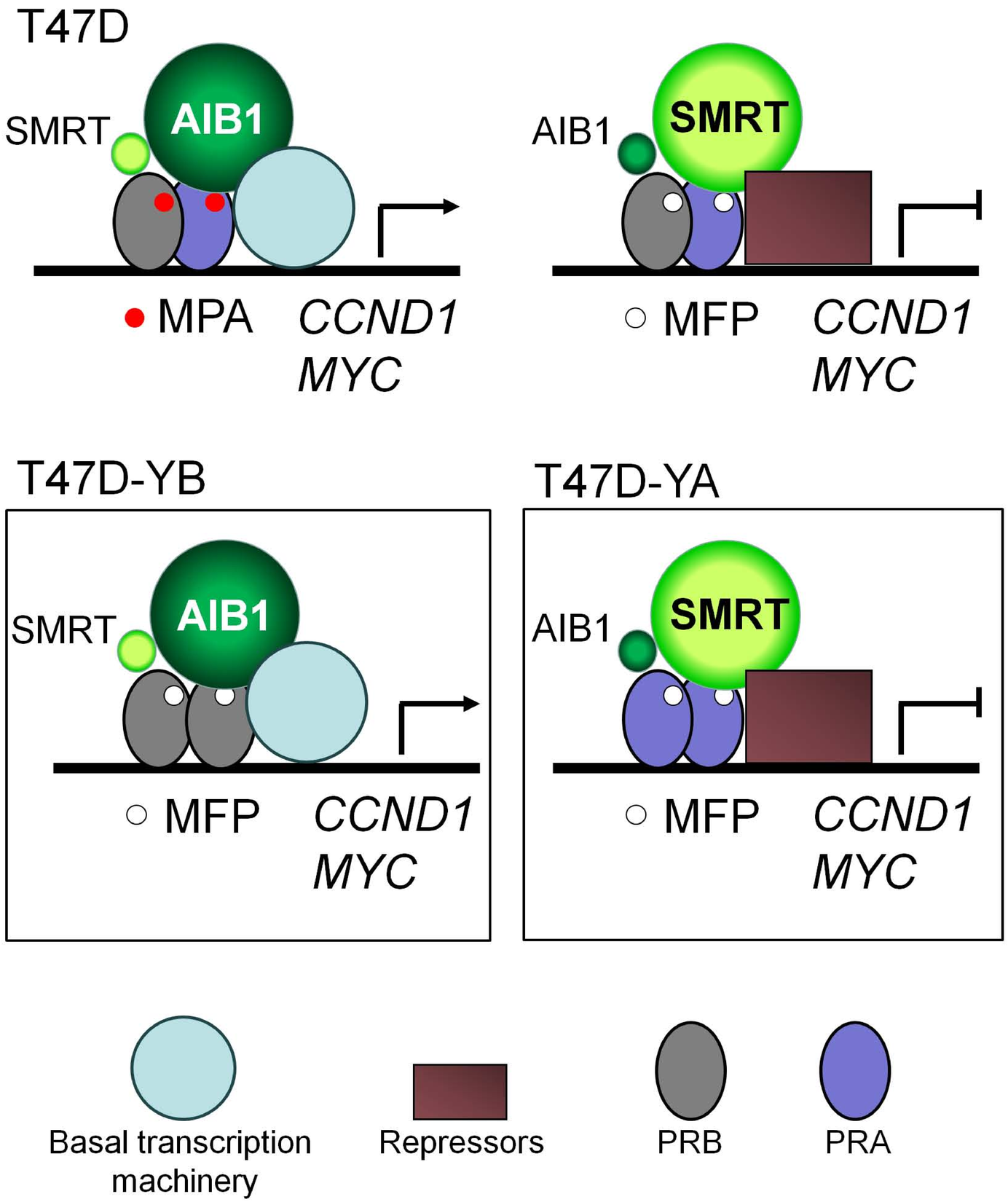


<u>Supplementary Figure 3</u>. MFP inhibits the growth of IBH-6 xenografts with PRA levels higher than PRB and stimulates the growth of those with the opposite ratio. A, Growth curves of IBH-6 cells stably transfected with the empty vector (pSG5) or human PRA or PRB (n=5/group). When the tumors became palpable, the animals were treated with MFP (10 mg/kg/day) or vehicle. MFP inhibited the growth of IBH-6-PRA but stimulated the growth of control or IBH-6-PRB tumors, the last two with PRB levels higher than PRA. **B**, PR isoform expression was evaluated by WB using extracts from tumors shown in A. PRA levels higher than those of PRB were only observed in PRA-transfected cells. **C and D**, Expression of CCND1 and MYC in control or MFP-treated tumors. ERK was used as a loading control. MFP inhibited the expression of both proteins only in the IBH-6-PRA xenografts. **F**, MFP inhibited the growth of the cloned IBH-6-PRA (Clone 27) cells injected into nude mice (n=5/group). Tumors were treated as described in Materials and Methods. The arrow indicates treatment initiation. Tumor growth was inhibited by MFP treatment. Animals were followed for more than two months. **G**, A decrease in CCND1 and MYC expression was detected by Western Blots in nuclear tumor extracts from MFP-treated mice. ERK1/2 was used as a loading control; *, $p<0.05$; **,$p<0.01$; ***, $p<0.001$ experimental *vs.* control group.

Wargon *et al*., Supplementary Figure 4



Supplementary Figure 4. **A**, T47D cells were incubated with MPA or MFP and processed for ChIP/qPCR analysis as described in Figure 6B. PR and cofactors recruitment was evaluated at the +5/6 Kb region in both gene promoters shown in Figure 6B using specific primers (Supplementary Table 1). These positions at the*CCND1* and *MYC* genes were used as a negative control regions of PR and cofactors occupancy. T47D-YA (B) and T47D-YB (C) cells were treated with MFP for 45 min and processed for ChIP/qPCR studies to detect the presence of PR, AIB1 and SMRT in both gene promoters as described in Figure 6B. ChIP/qPCR and data analysis were carried out as detailed in Materials and Methods. SMRT was recruited with PR at the *CCND1* and *MYC* promoters in T47D-YA MFP-treated cells whereas AIB1 was recruited with PR at the same sites in T47D-YB MFP-treated cells.



Supplementary Figure 5. Proposed model of PR actions after MPA or MFP incubation in breast cancer cells. In T47D cells, MFP inhibits *CCND1*/*MYC* transcription and cell proliferation by increasing SMRT recruitment to the PRE sites at the *CCND1* and *MYC* promoters (top, right). On the other hand, MPA recruits the coactivator AIB1 at the same sites (top, left), increasing *CCND1*/*MYC* transcription and cell proliferation. Co-localization assays performed with C4-HI cells suggest a similar regulation as in T47D cells. However, in a PRB-dominant context, such as in C4-2-HI or in T47D-YB cells, MFP activates PR and favors the interaction of PR with AIB1, instead of SMRT, supporting cell survival (bottom, left). In T47D-YA cells, MFP inhibits cell proliferation increasing the recruitment of SMRT and PR to gene target promoters (bottom, right). It may be speculated that the stimulatory effect that MFP exerts on tumor cells depends on the amount of PR A/B homodimers and heterodimers. See the text for more details.