**Supplementary Table S1. Genotypes of indicated genes and 17-AAG $IC_{50}$ in 6 CRC cell lines**

| Cell line | *KRAS* | *BRAF* | *PIK3CA* | *p53* | *FBW7* | 17-AAG $IC_{50}$ |
|---|---|---|---|---|---|---|
| **HCT116** | p.G13D | WT | p.H1047R | WT | WT | 0.31 |
| **Lim2405** | WT | p.V600E | WT | WT | WT | 0.46 |
| **RKO** | WT | p.V600E | p.H1047R | WT | WT | 0.30 |
| **SW48** | WT | WT | p.G914R | WT | p.R658Q | 1.35 |
| **LOVO** | p.G13D | WT | WT | WT | p.R505C | 1.28 |
| **HCT-8** | p.G13D | WT | p.E545K | WT | p.R658Q | 3.07 |

**Supplementary figure legend**

**Supplementary Fig. S1. Induction of proapoptotic Bcl-2 family proteins by 17-AAG in *FBW7*-mutant CRC cells.** Western blotting of indicated proapoptotic Bcl-2 family proteins in *FBW7*-mutant SW48 and LoVo cells treated with 1 μM 17-AAG at indicated time points.

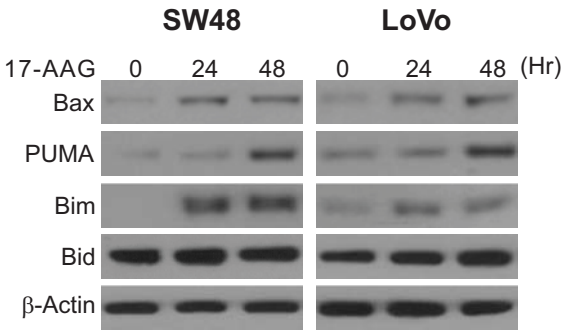
**Supplementary Fig. S2. FBW7 is critical for cell death and Mcl-1 degradation induced by Hsp90 inhibitors in CRC cells. (A)** WT and *FBW7*-KO DLD1 cells treated with 1 μM 17-AAG for 48 hr were analyzed for apoptosis by counting condensed and fragmented nuclei. **(B)** Western blotting of Mcl-1 in WT and *FBW7*-KO DLD1 cells treated with 1 μM 17-AAG or 0.25 μM 17-DMAG at indicated time points. **(C)** 17-AAG sensitivity of WT and *FBW7*-KO DLD1 cells with or without HA-tagged FBW7 transient transfection or *Mcl-1* knockdown, which was analyzed by western blotting (left panel). **(D)** Western blotting of transiently transfected HA-tagged R505C mutant FBW7 in the presence or absence of transfected Flag-tagged WT FBW7 in SW48 cells. **(E)** 17-AAG sensitivity of *FBW7*-mutant SW48 cells with transient transfection of HA-tagged WT FBW7 or R505C mutant, which was analyzed by western blotting (left panel). **(F)** 17-AAG sensitivity of *FBW7*-KO DLD1 cells transiently transfected with HA-tagged WT FBW7 or indicated mutants (R465C, R479Q or R505C). Transfected FBW7 was analyzed by western blotting (left panel). In (B)-(F), western blotting was performed on untreated cells at 24 hr after transfection. In (C), (E) and (F), 17-AAG sensitivity was analyzed by MTS assay on cells treated with 17-AAG at indicated concentrations for 72 hr. Results in (A), (C), (E) and (F) were expressed as means ± s.d. of three independent experiments.

**Supplementary Fig. S3. Mcl-1 degradation induced by Hsp90 inhibitors. (A)** Western blotting of Mcl-1 in HCT116 cells treated with 0.25 μM 17-DMAG at indicated time points. **(B)** Western blotting of Mcl-1 in HCT116 cells treated with 17-AAG or 17-DMAG at indicated concentrations

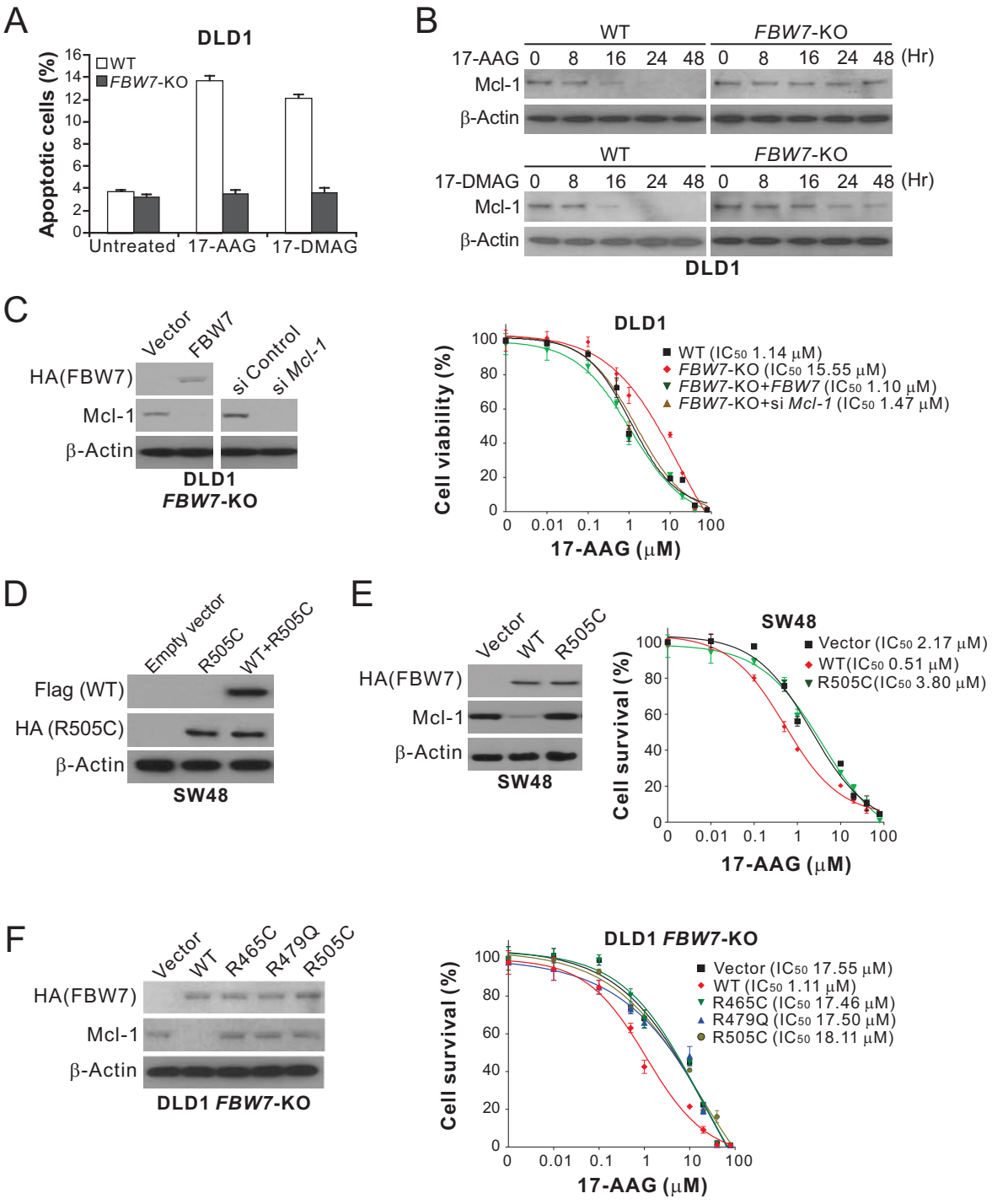
for 24 hr. **(C)** *Mcl-1* mRNA expression in HCT116 cells treated with 1 μM 17-AAG at the indicated time points was analyzed by RT-PCR followed by gel electrophoresis (upper panel), or by real-time RT-PCR (lower panel). *β-Actin* was used as a control for normalization. Results were expressed as means ± s.d. of three independent experiments. **(D)** Western blotting of indicated proteins in HCT116 cells transfected with control or *GSK3β* siRNA, and then treated with 1 μM 17-AAG for 48 hr.

**Supplementary Fig. S4. Analysis of non-apoptotic death pathways in *Mcl-1*-KI cells treated with 5-fluorouracil. (A)** WT and *Mcl-1*-KI HCT116 cells with or without 1-hr pretreatment with the necroptosis inhibitor necrosulfonamide (NSA; 5 μM)) were treated with 5-fluorouracil (5-FU; 50 μg/ml) for 48 hr. Non-apoptotic cell death was analyzed by quantification of propidium iodide (PI) positive and annexin V negative cells by flow cytometry. Results were expressed as means ± s.d. of three independent experiments. **(B)** WT and *Mcl-1*-KI HCT116 cells treated with 5-FU (50 μg/ml) for 48 hr were analyzed for autophagy by western blotting of LC3II accumulation and p62 degradation.

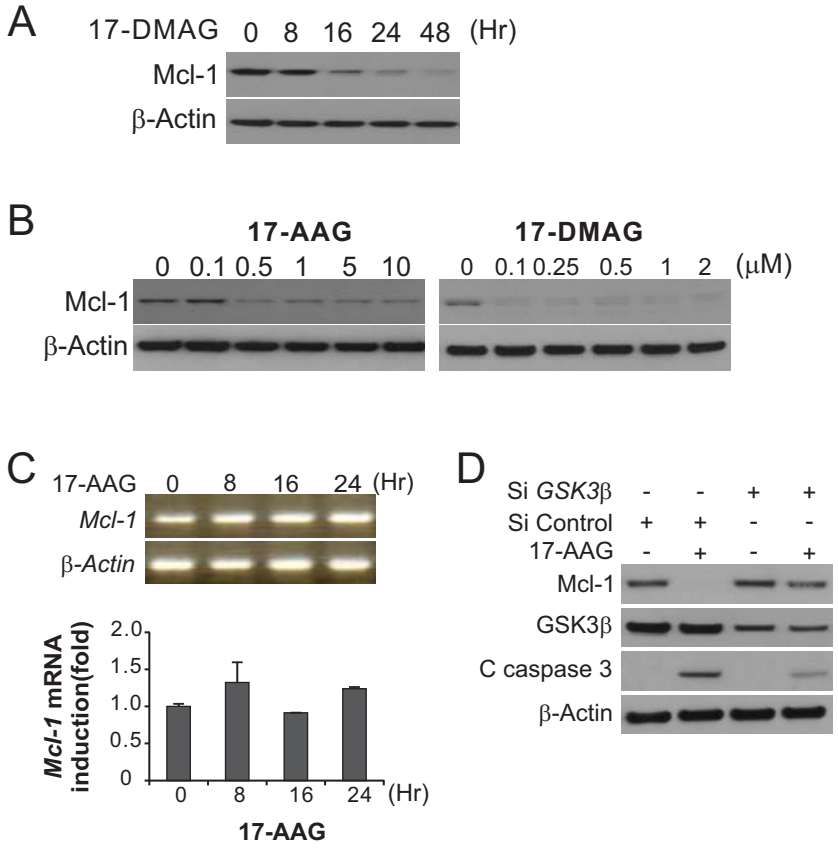
Supplementary Fig. S1



# Supplementary Fig. S2



Supplementary Fig. S3



Supplementary Fig. S4