1. The agent below is an example of what type of anticancer agent? Explain (using sentences) the mechanism of this type of anticancer agent? It is no longer on the market but it is presently being studied for an interesting cancer use. What is this use and what is its value?
2. The agent below is another useful macrolide antibiotic. It can generate reactive oxygen species (ROS), yet it does not contain a quinone or hydroquinone structure. Explain how it generates ROS.
3. The agent below (Enzalutamide) was recently approved (in 2012) for prostate cancer, specifically metastatic castrate resistant prostate cancer (mCRPC). Explain its mechanism(s) of action. It is generally well tolerated, but does have a unique and worrisome toxicity. What is this toxicity?

![Enzalutamide molecule]

4. Tamoxifen, shown below, is an old but still useful anti-estrogen agent. It can be metabolized to an important metabolite that is active. What is the name of this metabolite? What enzyme is most important to its formation? With an arrow, show the site of this important metabolism.

![Tamoxifen molecule]
5. The tyrosine kinase (TK) inhibitor shown below was very recently approved (in 2012) for Ph+ leukemias. Name the agent. It appears to lack an important toxicity common to TK inhibitors. Name this toxicity. Finally, can this agent be used to treat patients whose tumors have the T315-I mutation? (Yes or No)

6. Explain the mechanism of action of bevacizumab. How is it different than most other antibodies used to treat cancer? What is it commonly used to treat? Would you expect a HAMA response and why or why not?
Answers:

1. The agent shown is a macrolide antibiotic and because it contains a specifically sized planar region as well as bulky groups, it can intercalate into DNA. The planar portion intercalates between base pairs while the bulky sugar groups fit into the DNA grooves. This drug is being studied for inhibition of metastases which is of value because most cancer patients die from the problems associated with cancer spreading to other tissues rather than the primary cancer itself.

2. Although the formation of reactive oxygen species is usually mediated via quinone structures, this specific agent can chelate iron atoms which can mediate electron transfer to molecular oxygen as well. This agent, called bleomycin, is used in Hodgkin’s lymphoma but is also used to treat NHL, squamous head and neck cancer and testicular cancer.

3. This agent is an androgen receptor antagonist in that it will bind to the androgen receptor and prevent proper translocation of the receptor to the nucleus. In addition, it can down-regulate and possibly degrade the androgen receptor protein itself. Although it is generally well tolerated in patients, it can cause seizures.

4. The important active metabolite is known as endoxifen and this conversion is mediated by CYP2D6. Refer to the structure below for the site of metabolism marked by a red arrow.

![Structure diagram]

5. The important toxicity associated with tyrosine kinase inhibitors is QT prolongation which can result in fatal arrhythmia. The agent shown in the question is bosutinib and it cannot be used to treat tumors with the T315I mutation.
6. Most antibodies target specific proteins on cell surfaces however bevacizumab instead targets vascular endothelial growth factor (VEGF) to prevent it from binding to VEGF-receptors on cancer cells and promoting growth. It is generally used to treat colorectal cancer alongside a number of other agents. As the suffix “-umab” suggests, this antibody is fully human so one would not expect a HAMA response to occur because there is no murine protein to trigger the response.