AUTHORS' REPLY

(Not) too early to say, “no targeting of mitosis!”

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We appreciate Dr Katsumi Kitagawa's comments and interest in our article: Mitosis is not a key target of microtubule agents in patient tumors. *Nat. Rev. Clin. Oncol.* **8**, 244–250¹ (Too early to say, “no targeting of mitosis!” *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2010.228-c1)².

The main points of our article were these: first, although microtubule targeting agents (MTAs) have been successful as cancer therapeutics, to date, the clinical results from mitosis-specific agents have been disappointing despite clear evidence of their ability to affect mitosis in patients, as evidenced by their principal toxicity, neutropenia. Second, MTAs can target critical microtubule functions in cells while they are in mitosis as well as critical cellular functions in other phases of the cell cycle, where many cells spend more than 98% of their time. By comparison, mitosis-specific agents can only target cells in mitosis, and this occurs infrequently in patient tumors. Finally, we concluded that MTAs are successful because they target both mitotic and non-mitotic microtubule functions.

In cell culture, xenografts and in humans, mitosis in normal or cancer cells is uniformly fast, lasting on average about 1 h. By contrast, one can find marked differences in the rates of cell growth when comparing human tumors with xenografts or cells in culture, with tumors having rates that are relatively slower. In our article, we did not suggest that a tumor's growth rate is defined by mitotic frequency, but it is true that cells in mitosis are uncommon in human tumors (Table 1). Slow-growing tumors present fewer mitotic cells as targets for mitotic agents compared with rapidly doubling cells in culture and xenografts. We agree with Dr Kitagawa² that the net increase in the size of a tumor in xenografts and in human cancers is the result of concomitant cell death and cell replication. While both of these events occur in patient tumors, losses from cell death do not contribute substantially to the ‘sum’ value.^{3–5} In addition, although the growth rate of a tumor

will determine the survival of a patient, the number of mitotic cells in human tumors is less than 1% and for a chemotherapy to be successful it must target both dividing and non-dividing transformed cells.

We thank Dr Kitagawa² for raising the possibility of a dysfunctional mitotic spindle checkpoint in breast cancers. In our article,¹ we showed biopsies obtained from four patients with metastatic breast cancer following ixabepilone treatment, which support data from other studies showing that both mitosis and mitotic arrest occur infrequently in patient tumors. We acknowledge the possibility that breast cancer cells might not arrest in mitosis if their checkpoint function is impaired, but this would be unlikely to be the case in these patients without specific family histories of breast cancer. Regardless of the mitotic spindle checkpoint activity of a tumor, the success of MTAs in the therapy of breast cancer further supports the paradigm that MTAs lead to cell death not only by causing mitotic arrest followed by apoptosis, but primarily by compromising essential cell functions in non-mitotic tumor cells.

Finally, it is true that only three proteins involved in mitosis have been targeted by drugs in the 23 clinical trials discussed in the paper,¹ and that two of those were kinases, with the third an ATP-driven mitosis-specific kinesin unrelated to kinases. Nonetheless, our point is that any protein whose function is restricted to mitosis, and whose function in mitosis is essential, will only provide a drug target in the few cells that are in mitosis. Treated cells may or may not arrest in mitosis, and damage during mitotic transit may indeed not be manifest until later. But, for any of this to happen mitotic cells have to be present during drug treatment, and the low frequency of mitosis in tumors indicates this is not the case for many cells. By contrast, microtubules are present in all cells in all phases of the cell cycle, presenting a target for MTAs in all cells. MTAs can, without doubt, poison mitosis when they encounter it, but they can

Table 1 | Mitotic index in patient samples

Tumor type	Mitotic index (mitosis/ 1,000 tumor cells)
Breast cancer	5 (mean) ⁶ 1.2 (mean) ⁷ 1–5 (median) ⁸ 2 (mean) ⁹ 5.8 (mean) ¹⁰
Ovary granulosa	0.2 (median) ¹¹
Uterine cervical	9 (mean) ¹²
Prostate cancer	15 (mean) ¹³

also poison interphase microtubule functions such as intracellular trafficking and signaling in non-mitotic cells that make up the bulk of the cells in patient tumors.

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Competing interests

The authors declare no competing interests.

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