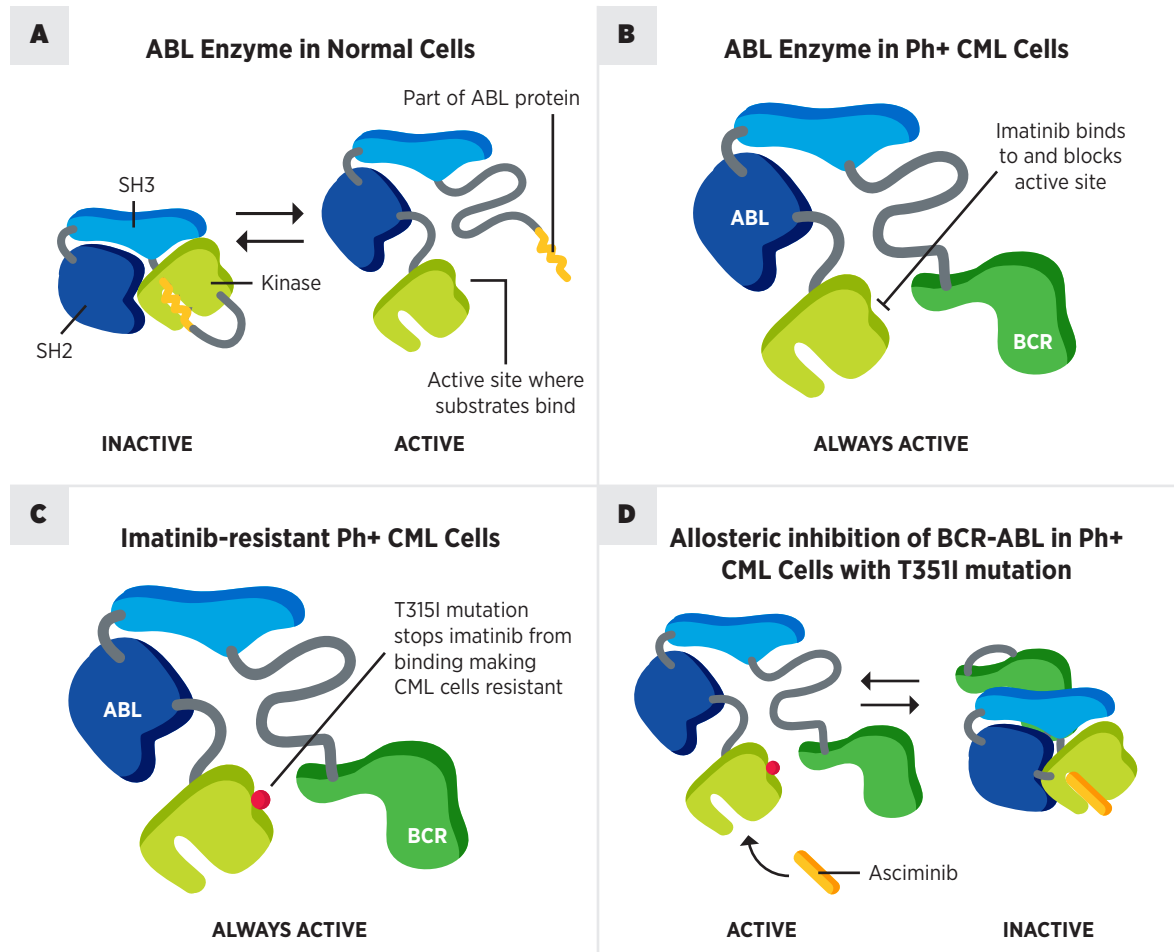


FIGURE 10

How Does Asciminib Work?



In normal cells, the activity of the ABL enzyme is regulated by cues from outside the cell. Typically, ABL enzyme is present in normal cells in an inactive form, in which one part of the protein is “locked” into another part of the protein as a “key” and prevents substrates from binding to the enzyme. When a cell receives cues to perform certain functions, such as divide, the ABL enzyme acquires an active form which allows substrates to bind to the enzyme, ultimately helping cells proliferate (**Panel A**).

In Philadelphia chromosome positive (Ph+) CML cells, the portion of the ABL protein that controls the self-regulation is replaced by the BCR protein, thus keeping the ABL enzyme in an active form at all times. As a result, Ph+ CML cells divide and proliferate

uncontrollably. The drug imatinib (Gleevec) inhibits the activity of the ABL protein even when the “lock and key” mechanism that keeps the ABL protein inactive in normal cells is lost in Ph+ CML cells (**Panel B**).

Unfortunately, the BCR-ABL protein in Ph+ CML cells acquires mutations, such as T315I, that prevent imatinib from binding to and inhibiting the activity of the protein, thus making the cancer cells resistant to treatment with imatinib (**Panel C**).

Asciminib utilizes the naturally occurring “lock and key” mechanism to inactivate BCR-ABL protein, thus overcoming the imatinib resistance of Ph+ CML cells and restoring inhibition of BCR-ABL1 kinase activity (**Panel D**).