Finding new vulnerabilities of cancer cells for therapeutic benefit.

Rene Bernards
The Netherlands Cancer Institute, Amsterdam, The Netherlands

Many of the newer cancer drugs target oncogenic “driver” mutations to which the cancer is addicted. Consequently, inhibition of these oncogenic signals by specific drugs delivers therapeutic benefit. However, resistance to these targeted therapies is almost invariably inevitable due to tumor heterogeneity. With conventional chemotherapies, resistance can be delayed by combining drugs. A variation on this theme is also seen with targeted therapies, where inhibition of multiple components of an activated signaling pathway delivers more clinical benefit. For instance, co-inhibition of both BRAF and MEK kinases in BRAF mutant melanoma results in superior responses as compared to BRAF inhibition alone. To find optimal combinations of targeted cancer drugs, synthetic lethality screens can help to guide the choice of drugs. As one example, my laboratory has found, through a synthetic lethality genetic screen, that co-inhibition of both BRAF and EGFR in BRAF mutant colon cancer is very effective. Such a combination is counter-intuitive, given that EGFR functions upstream of oncogenic BRAF in signaling.

In my lecture, I will focus on two new concepts in the treatment of cancer. First, I will discuss how we can identify acquired vulnerabilities of drug-resistant cancers. Based on the notion that every acquired strength (i.e. drug resistance) must have an associated weakness, we have searched for acquired vulnerabilities when BRAF mutant melanomas become resistant to the combination of BRAF and MEK inhibitors. Our pre-clinical findings indicate a major acquired sensitivity of such drug resistant melanomas for HDAC inhibitors. Initial results from a clinical trial in our center confirm our pre-clinical findings.

Second, I will discuss how we can use sequential drug treatment to deliver a “one-two punch” lethal blow to cancer cells. In this scenario, we use the first drug to expose a major new vulnerability of the cancer cells that is subsequently targeted by the second drug. Examples of effective sequential drug treatments based on the induction of senescence in cancer cells will be presented.