Report from the Princess Margaret Cancer Conference

Immunotherapy

DR. KIM CHI AND DR. TAK MAK DEBATE THE PROSPECT OF DOUBLING OS

Summarized by Dr. Marcus Butler, MD, FRCPC, and Dr. Philippe Bedard, MD, FRCPC, Princess Margaret Cancer Centre

To close their February conference, organizers invited Dr. Tak Mak, Director of the Campbell Family Cancer Research Institute, and Professor of Medical Biophysics at the University of Toronto, and Dr. Kim Chi, Professor of Medicine at the University of British Columbia, and Staff Medical Oncologist at the British Columbia Cancer Agency, to debate the following resolution:

“This house believes that immunotherapy will double cancer-specific survival, compared to molecular targeted therapies, in the next 10 years.”

Dr. Mak argued the “Pro” side in support of the resolution, with Dr. Marcus Butler assuming the rebuttal. Dr. Chi argued the “Contra” side, with Dr. Philippe Bédard rebutting. Summarized here are the main arguments on each side.

**PRO: Yes, immunotherapy will double cancer-specific survival, compared to molecular targeted therapies, in the next 10 years.**

In his opening statement, Dr. Tak Mak graciously reviewed the many successes in drug development over the past two decades, resulting in drugs that target deranged molecular pathways present within the tumour cell. By inhibiting these drivers of the cancer phenotype, targeted therapies are able to thwart cancer cell proliferation and survival and result in antitumour activity that is beneficial to patients. In fact, Dr. Mak commended the work of his esteemed colleagues, Drs. Kim Chi and Philippe Bedard, both of whom are world-class leaders in the clinical development of novel anticancer agents. Dr. Mak then stated that, despite past successes, the future for molecular targeting of these drivers of cancer growth...
is not bright. New approaches are needed, and immunotherapy has been proven to induce long-lasting, durable survival benefit. Dr. Mak forcefully mentioned that in comparison to molecularly targeted drugs, which often provide brief therapeutic benefit, the long-lasting benefits of tumour immunotherapy will double cancer-specific survival for the following reasons:

1. **Regulatory approval for targeted drugs has “hit the wall”**
Dr. Mak reviewed the approvals for new drugs over the past two decades and observed that while some successes have been achieved, the predicted avalanche of novel targeted therapies has not occurred. In fact, Dr. Mak observed that, in many instances, successful targeted therapies such as erlotinib actually bring modest improvements in overall survival (OS). While OS is improved by a couple of months in patients with advanced lung cancer, the drug has no impact on survival at 2 years. Dr. Mak explained that this is a commonly observed problem for all molecularly targeted therapies, and results from the “sharpshooting” approach. Sharpshooting drugs attempt to identify a specific driver that induces tumour growth and then focus on this target for inhibition. The problem is that resistance inevitably develops as other molecular derangements surface and evolve. The sharpshooting approach becomes a game of “Whack-a-Mole,” where as soon as one oncologic pathway is inhibited, a second is activated and resistance develops. Since there are “more paths to developing tumour than there are stars in the sky,” Dr. Mak observed, a therapeutic approach based solely on understanding driver mutations and treating with targeted therapies is doomed to failure.

2. **Cart before the horse**
Dr. Mak proposed a new strategy based on understanding the cancer phenotype instead of the derangements that lead to the development of the cancer. His goal is to develop therapies that are not based on oncogenes or tumour suppressors, but rather on characteristics that are intrinsic to the cancer phenotype: aneuploidy, the metabolic state of the cancer, and the fact that tumours are immunogenic and can be targets of an effective antitumour response.

3. **Only the beginning**
Dr. Mak reviewed the impressive results with immune-based therapies in the last few years and considers that these are only the beginning. Now that basic immunologic concepts such as immune checkpoints are understood, effective, relevant and long-lasting therapies for cancer are within our grasp. Anti-CTLA-4 blockade with ipilimumab, for instance, has resulted in a doubling of long-term survival for patients with metastatic melanoma. Importantly, this survival benefit is truly long-lasting, and patients alive at 3 years continue to be disease-free for a decade. Dr. Mak pointed to recent results with anti-PD-1 and anti-PD-L1 antibodies, where cancers of various types benefit from these drugs. Moreover, combinations of anti-CTLA-4 and anti-PD-1 are achieving even higher response rates. Dr. Mak concluded that cancer can develop through signal dysregulation of multiple pathways and that targeting each of these pathways is not feasible, due to the toxicity of targeted therapies. On the other hand, the immune system is exquisitely able to target abnormal cells. Each of us has up to 1,000,000,000,000,000 possible T-cell receptors, and you cannot get more personalized than your own T-cells.

**CONTRA:** No, immunotherapy will not double cancer-specific survival, compared to molecular targeted therapies, in the next 10 years.

In his opening statement, Dr. Chi compared himself to David facing a Goliath in the field of immunology. Dr. Mak, who first discovered the T-cell receptor and is one of Canada’s most distinguished scientists. He opened by reminding us that, despite the recent hype, the promise of immunotherapy for cancer is not new, as small studies of interleukin-2 (IL-2) in metastatic renal cell carcinoma more than 2 decades ago demonstrated durable response with a “long tail” on the survival curve. However, immunotherapy (interferon-alpha) was shown to be markedly inferior to targeted therapy (sunitinib) against metastatic renal cell carcinoma in a definitive randomized phase III trial. Likewise, multiple large phase III trials of antitumour vaccines for non-small cell lung cancer (NSCLC) and other solid tumours have failed to demonstrate a survival benefit. Dr. Chi proceeded to challenge the specific motion put before the house on the basis of 3 arguments:

1. **The number of tumour types that respond to immunotherapy is low**
Dr. Chi reminded us that activity with PD-1/PD-L1 targeted antibodies has largely been observed in high-mutation-rate solid tumours, such as NSCLC, melanoma, renal cell carcinoma and bladder cancer, with the potential to generate a large pool of neoantigens that can be recognized as foreign by the host immune system. In aggregate, these malignancies characterized by short survival involve a smaller burden of patients affected by metastatic disease in Canada (25,975 person-years), compared with 3 prevalent types of cancer (prostate, breast and colorectal) characterized by longer survival (53,200 person-years), where minimal activity has been observed with immunotherapy.

2. **Within a tumour type, the number of patients that benefit is modest**
Dr. Chi put forth that the response rate reported with PD-1/PD-L1 targeted antibody therapy is lower than that seen with highly effective targeted therapies. He provided the example of melanoma, where the response rate with nivolumab is 31% (and 40% with nivolumab and ipilimumab combined), compared with 81% for the BRAF inhibitor vemurafenib in BRAF-mutant melanoma. Similarly, the response rate to nivolumab in renal cell carcinoma is 22%, compared with 28% to 40% for VEGFR tyrosine kinase inhibitors such as sunitinib and cabozantinib. He provided
the example of castrate-resistant prostate cancer, which has not been shown to be a tumour type sensitive to immunotherapy, in which the response rate with the targeted treatment abiraterone is 59%, and prostate-specific antigen (PSA) response rate is 79%.

3. Targeted therapies and chemotherapy have already doubled survival and will continue to do so

Dr. Chi wrapped up his opening statement by challenging the position that further advances could not be achieved with targeted treatments. He provided a list of 35 novel targeted treatments that have been approved within the last few years. These therapeutic advances have led to significant improvements in cancer-specific survival across a range of tumour types in Canada. Looking to the future, he provided the example of prostate cancer, where advances in our understanding of disease biology and new medicinal chemistry techniques have produced exciting new targeted drugs now in clinical testing against long-standing targets that are known to be key drivers of this disease, such as androgen receptors and cMyc.

REBUTTAL TO DR. CHI

Dr. Butler provided a rebuttal to the arguments put forward by Dr. Chi, observing that the benefits of molecular targeted therapies in clinical studies are measured in months of additional survival and do not improve long-term cancer-specific survival. In contrast, immune therapies do result in meaningful long-term survival. While clinical data are dominated by the inhibition of just 2 immune checkpoint blocking agents, anti-CTLA-4 and PD-1, there are multiple new agents currently in the clinic such as TIL, CAR T cells, TCR T cells, anti-TIM3, BLTA4, VISTA, LAG-3, GITR, CD137, CD27 etc. The development of immunotherapy agents is accelerating at a breakneck pace. For example, pembrolizumab achieved FDA approval just 3 years after it had been first tested in a cancer patient. Clearly, within 10 years, many new immunotherapy agents will be available to patients. Moreover, Dr. Butler observed that immune therapy agents such as PD-1 blocking antibodies have shown activity in various common cancers, such that many cancer patients will possibly be treatable with any one immune-based therapy. Importantly, it is now being demonstrated that immunotherapy agents have utility in preventing recurrence of disease when used in the adjuvant setting. Encouraging data from the EORTC have shown that recurrence-free survival is statistically improved with the use of ipilimumab in the adjuvant treatment of melanoma. Dr. Butler noted that many targeted therapies, such as BRAF inhibition, are associated with an enhancement of the immune response to the tumour, raising the possibility that targeted therapies might indeed derive some of their activity through induction of an immune response. Dr. Butler concluded that 1) only immunotherapy can provide long-term cancer-specific survival benefit; 2) within the next 10 years, several new agents will come into use in the clinic to provide additional benefit; and 3) these new agents will be successfully deployed in the clinic, as progress will not be limited by availability of funds or enthusiasm.

REBUTTAL TO DR. MAK

Dr. Bedard provided a rebuttal to the 3 arguments put forward by Dr. Mak and Dr. Butler, challenging the position that immunotherapy produces durable disease control, and possibly even cure, in responding patients with metastatic disease. He argued that outside of the CTLA-4 targeted antibody ipilimumab in metastatic melanoma, there is little evidence that PD-1/PD-L1 targeted antibodies can produce durable disease control. He provided the example of a recent analysis of patients with metastatic melanoma who initially responded to nivolumab in a phase I trial, many of whom subsequently progressed and did not respond to rechallenge with nivolumab. He noted that even in tumour types where antitumour activity has been observed with PD-1/PD-L1 therapeutic antibodies, only a minority of patients (10% to 40%) respond, predominantly in tumour types that account for a small fraction of cancer-related deaths in Canada. He argued that successful immunotargeting of these “noninflamed” tumours that do not respond to PD-1/PD-L1 monotherapy is extremely challenging: the large number of potential combination approaches with immunostimulatory agents and immune checkpoint inhibitors will take a long time to test in clinical trials. Moreover, combination immune therapies for these “noninflamed” tumours may be too poorly tolerated to test in the adjuvant setting, which is required to significantly improve cancer-related survival. A significant burden of immune-related adverse events has been observed with the nivolumab and ipilimumab combination.