

ASCO 2018 Take-Home

Cancer therapy stalwarts blaze trail for immunotherapy

Immunotherapy and precision medicine were the big themes of the American Society for Clinical Oncology (“ASCO”) 2018 meeting in Chicago.

With over 1,000 clinical trials running, there has been an explosion in efforts to identify benefits of immune checkpoint inhibitor (“ICI”) combinations. Although, combining ICIs with the myriad of next generation immunotherapies has yet to deliver, as highlighted by the failure of Incyte’s much vaunted epacadostat, combination with oncology stalwarts including chemo- and radiotherapy has provided benefits.

The potential benefits of gene-based profiling were well illustrated by data presented for the TAILORx phase III trial, demonstrating that 70% of women with the most common form of breast cancer could be spared chemotherapy. While the consensus is that biomarkers will play an increasing role in guiding therapy, the jury is still out on many of the key markers, and the tests required are likely to be multiple and complex, requiring specialist and eventually algorithmic interpretation.

New drugs disappoint

Following the initial success of ICIs in melanoma, cancer drug development has focussed on the development of drugs that can boost ICI effects. These are largely drugs that either unleash / rev up the immune system or ‘heat’ up the tumour, priming it for immune attack. Of these, few were as much anticipated as the IDO1 inhibitors, led by Incyte’s tumour priming epacadostat. The recent failure of epacadostat / ICI combo in phase III was the subject of vigorous debate during the ASCO meeting.

Much discussion focussed on the early positive I / II data, which was the basis of the phase III for epacadostat, and frequently the basis for the initiation of phase III in immuno-oncology.

Such problems could be avoided by randomised phase II trials. However, given the ICI bandwagon, checking that the new drug is actually having its desired priming effect on the tumour / immune system in patients would be a useful start for those attempting to assess programme value. An approach used in a series of early studies presented using a Class I histone deacetylase (“HDAC”) inhibitor entinostat / ICI combination in lung cancer, melanoma and colon cancer, showed correlations between increasing tumour inflammatory biomarkers and anti-tumour activity.

LAG-3 Standout

While much attention is on next generation LAG-3 ICI’s focussed on taking the immune brake off, the posters presented by ASX- and NASDAQ-listed Immutep focussed on how a synthetic LAG-3-based fusion protein opens the immune throttle. A first-in-class activator of key immune antigen presenting cells’, in phase II, eftilagmod has been shown to have a 47% overall response rate and 87% disease control rate in metastatic breast cancer.

While commercial impetus is for novel combinations, ICI combos with existing chemo- and radiotherapy stalwarts are yielding real benefits



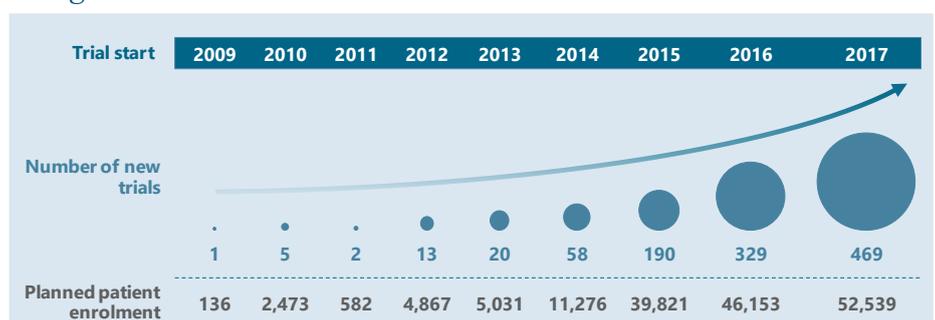
Chris Redhead



Martin Bruninger

CHECKPOINT COMBO BANDWAGON

Excitement over ICI combinations is driving a bandwagon of ill thought out and / or redundant trials.



Source: Cancer Research Institute

Combination with cancer stalwarts

While there is clearly a commercial impetus to create novel proprietary combinations, clinical evidence suggests that old stalwarts such as chemo- and radiotherapy ("RT") have major roles to play.

Merck leads with chemo-combo

Despite failure of its collaboration with Incyte on the epacadostat / ICI combo, Merck & Co continues to consolidate its position in first-line Non-small-cell lung cancer ("NSCLC"). While data was presented demonstrating the superiority of pembrolizumab alone over standard chemotherapy, Merck has already shown that, combined with chemo, the drug can generate response rates of over 50%. These and other data suggest that chemo has a big role to play, particularly as data accumulates over optimised timing and magnitude of dosing.

Radiotherapy old and new

There is a strong rationale for combining RT with immuno-therapy given RT's well-documented immuno-stimulatory effects. While studies need to be performed to optimise both dose and sequence, abscopal effects on sites distal to the site of radiation in combination ICIs can be dramatic.

Of a number of studies involving immune therapy and RT, one small

phase II study combining pembrolizumab with essentially palliative RT in patients with advanced metastatic breast cancer showed dramatic results (image below). Three responding patients experienced a 100% response in distal metastases.

Although current combinations largely involve external beam radiation, we are also excited at the prospect of ICI combination with the new generation of molecular targeted therapies.

Precision needs integration

A gene panel sparing 70% of women from unnecessary chemo for breast cancer reveals the potential of molecular-based precision medicine. Consensus from the meeting suggests that we are some way from a precision medicine utopia. Discussion around the meeting suggests there may be few consistent immunological markers.

The heterogeneity of tumours and the complexity of the immune system means that, outside a collection of relatively rare mutation-driven cancers, therapy will be guided by the integration of a complex mix of data, collected through molecular diagnostics, imaging and clinical analysis. Interpretation may frequently be beyond the scope of regular physicians requiring specialised guidance or algorithms.

ASCO TAKE HOME



COMBINATION GOLD-RUSH

Rush to identify novel immuno-combinations yet to deliver

Commercial impetus for proprietary combinations

A bandwagon of ill-thought out and / or redundant studies

Need to look for evidence of appropriate drug action before moving forwards

Tangible progress being made combining ICIs with chemo- and radiotherapy cancer stalwarts

PRECISION MEDICINE COMPLEX

Tumour gene screens yield treatment benefits in some cancer

No real sign of universal immuno-therapy markers

Precision in cancer care likely to be driven by complex multiple diagnostics

Interpretation and therapeutic decision making likely driven by specialist guidance or algorithms

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RADIANT IN COMBINATION

Impact of combining pembrolizumab and radiotherapy in advanced metastatic breast cancer.

