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Therapy focus – Potential for progress in mesothelioma is on the horizon

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The rare but aggressive cancer mesothelioma has proven largely resistant to the tumour-fighting mechanisms of novel agents. However, hopes are high that in the next couple of weeks the new checkpoint inhibitors will make their mark in another intractable disease, with Merck & Co due to present data on Keytruda in this setting at the approaching AACR conference.

Demonstrating a significant impact on survival would be a huge step forward – mesothelioma kills most patients within a year of diagnosis. This fact and the disease's relative obscurity compared with other tumour types has not helped encourage commercial research, although a look at the pipeline reveals a handful of other agents that should also yield data in the coming months (see table below).

Mesothelioma is caused in the vast majority of cases by exposure to asbestos, and comprises tumours that grow in the thin layer of cells lining internal organs. Around three quarters of these arise in the lung in the form of pleural mesothelioma, although peritoneal and pericardial tumours also occur, in the abdominal cavity and heart lining respectively.

Surgery, radiotherapy and chemotherapy are the treatment options available but, because the disease is frequently discovered late, prognosis tends to be poor. The only agent so far to show a survival benefit in malignant disease is Lilly’s Alimta, approved back in 2004 in patients unsuitable for surgery. Adding Alimta to cisplatin prolonged survival by around three months, to 12.1 months.

It is clear that this disease presents a huge problem to novel therapies, and many have failed to show much impact. For example Molmed’s vascular targeting agent NGR-hTNF failed to prolong the survival of patients previously treated with Alimta, in a phase III study that reported last year.

An encouraging signal was seen in a subgroup with particularly aggressive disease, however, and the Italian biotech might still pursue a filing, pending data from a second study. These are due in the second half of the year from a maintenance trial, and will likely determine the fate of the compound.

Selected novel agents for mesothelioma in the pipeline				
	Project	**Company**	**Pharma class**	**Trial ID (enrolment)**
Phase III	NGR-hTNF	MolMed	CD13 APN inhibitor	NCT01098266 (360); NCT01358084 (100)
Phase II	Keytruda	Merck & Co	Anti-PD-1 MAb	NCT02054806/Keynote-28 (unknown)
	VS-6063 (defactinib)	Verastem	FAK inhibitor	NCT01870609/Command (372); NCT02004028 (20)
	Tremelimumab	AstraZeneca	Anti-CTLA4 MAb	NCT01843374 (564)
	Ofev	Boehringer Ingelheim	TKI	NCT01907100 (86)
	INNO-305	Memorial Sloan-Kettering (CytRx abandoned)	Anti-WT1 vaccine	NCT01265433 (78); NCT01890980 (39)
	Yondelis	Grupo Zeltia (Mario Negri Institute study)	Cell cycle inhibitor	NCT02194231/Atreus (79)
	MORAb-009 (amatuximab)	Eisai	Anti-mesothelin MAb	NCT02357147 (610, not yet recruiting)
Phase I/II	ADI-PEG 20	Polaris Group	Arginine inhibitor	NCT02029690 (47); NCT01279967 (70)
	Anti-mesothelin CAR therapy	NCI	CAR-T cell therapy	NCT01583686 (136)
	Seprehvir	VIRTTU Biologics	Oncolytic virus	NCT01721018 (12)
Phase I	CRS-207	Aduro BioTech	Mesothelin cancer vaccine	NCT01675765 (40)
	CART-meso	Unniversity of Pennsylvania	CAR-T cell therapy	NCT02159716 (24)
	LY3023414	Eli Lilly	PI3K & mTOR inhibitor	NCT01655225 (130)
	Ganetespib	Synta (UCL/Cancer Research sponsored)	Hsp90 inhibitor	NCT01590160 (24)
	CB-839	Calithera Biosciences	Glutaminase inhibitor	NCT02071862 (165)

Hopes for Keytruda are no doubt high given the strong track record of the anti-PD-1 antibodies. It is also notable that Merck's presentation has been given prominent billing at the AACR.

Preliminary data from the Keynote-028 study will be revealed on April 19; the expansive, 320-subject, phase I trial is recruiting patients with various forms of PD-1-positive solid tumours. The malignant pleural mesothelioma subset has been selected as a late-breaking presentation. Still, with nothing known about how big this subgroup is, or indeed the outcome, its relevance is hard to judge.

AstraZeneca is also pursuing an immuno-oncology approach here: last year it expanded a phase II trial of its anti-CTLA-4 antibody tremelimumab so it could file for approval on any positive readout. Data are expected towards the end of the year.

Verastem, which is working on one of the higher-profile targeted agents in this area, VS-6063, should also soon report progress. The FAK inhibitor works by blocking enzymes that are particularly active in mesothelioma. An interim analysis from the phase II Command trial is due in the second quarter; prespecified efficacy analyses and safety data will be examined and a decision made whether to stop the study early for futility, continue as planned or enrich the population.

Other active mid-stage projects include Boehringer’s Ofev; a phase II study appears to have been completed although results have not been presented. And Eisai recently unveiled plans for a large study of amatuximab in combination with chemotherapy. This represents a bold move considering that the anti-mesothelin antibody

has already been abandoned in several other tumour types.

Earlier work

Closely watched early-stage projects in the commercial world include Polaris's arginine inhibitor ADI-PEG 20. The US company started a phase I chemo-combination trial last November, in the wake of a larger phase II conducted by a UK hospital that showed a reduction in the risk of disease progression.

And Aduro, which attracted attention recently by signing a big deal with Novartis over its "Sting" immuno-oncology platform, also has a mesothelioma project in the clinic based on another platform, called LADD. The technology, which genetically engineers the bacterium *Listeria monocytogenes* into a therapeutic agent, created a project called CRS-207, and should generate phase I data next year.

Outside the commercial sphere much work is being done by academic centres or government-run agencies, frequently with novel drugs that are no longer being considered by their commercial owners.

For example Memorial Sloan-Kettering is particularly active with two studies of a WT-1-targeting cancer vaccine; the project was abandoned by CytRx in 2008. And in the UK a 24-patient trial is under way with Synta's troubled Hsp90 inhibitor ganetespib, in combination with platinum-based chemotherapy.

Also of note is work in the red-hot CAR-T space. The NCI is funding a 136-patient trial of a construct it has engineered to contain the gene for anti-mesothelin, while Novartis and its partners at the University of Pennsylvania have started a 24-patient trial of what they refer to as MesoCART. Both are recruiting patients with various types of mesothelin-expressing cancers, including mesothelioma.

Much of this work remains early, however, in both the academic and commercial spheres. It is perhaps fortunate that mesothelioma remains rare – around 3,000 cases are diagnosed in the US each year, it is estimated – and incidence is falling in many developed nations, reflecting the declining use of asbestos.

But there is still substantial room for improvements in treatment options, and in the coming year the likelihood of these emerging soon will become clearer.

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