Evaluate Vantage

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Growth of anti-PD1 therapy threatens traditional second line chemo in NSCLC

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Pfizer and Merck KGaA's decision to push avelumab into phase III in second-line non-small cell lung cancer brings a fifth anti-PD-1/PDL-1 agent into late-stage trials for this large and fiercely competitive cancer indication.

And with positive data already reported for Bristol-Myers Squibb's Opdivo and Merck's Keytruda, the lead agents in the class, it now seems a fair bet that checkpoint inhibition will cause a tectonic shift in the NSCLC treatment landscape. All of this will surely mean considerable disruption to the commercial plans for a handful of small companies with more traditional approaches in late-stage trials for second-line NSCLC (see table below).

Last week Bristol-Myers stopped early the CheckMate 057 phase III trial of Opdivo versus docetaxel in second-line non-squamous NSCLC, after the study's data monitoring committee concluded that it had met its endpoint of demonstrating superior overall survival. The result mirrored the CheckMate 017 study of Opdivo in squamous NSCLC, which led to the product's approval in record time.

Playing catch up

Merck has, meanwhile, just filed Keytruda for NSCLC in patients who have progressed on or after platinum-containing chemotherapy or a targeted therapy for EGFR or ALK mutations. The submission was based on data from its Keynote-001 study, which enrolled PDL-1 positive patients.

The question now is whether the regulator will approve Keytruda for all NSCLC patients or only the PDL-1-positive subgroup; there is a good chance the two lead agents end up with broadly similar labels in this condition (*AACR – Keytruda set for lung cancer approval but restrictions unclear, April 20, 2015*).

Meanwhile the Javelin Lung 200 study, just announced by Pfizer and Merck KGaA, tests avelumab directly against docetaxel and recruits only PDL-1-positive patients.

The growing herd of phase III challengers in the space also includes Roche's study of its PDL-1 antibody, MPDL3280A, in second/third-line NSCLC. More interestingly, the group is also pursuing no fewer than five studies of the agent in first-line treatment. These latter studies test the drug in combination with all of the current first-line chemo combinations, such as carboplatin/paclitaxel, gemcitabine and pemetrexed.

AstraZeneca is running three phase III studies with its PD-1 antibody, MEDI4736, including one that combines the project with the CTLA-4 antibody tremelimumab in various NSCLC settings. One of these, Pacific, examines first-line maintenance, and data are expected next year.

Old school

Docetaxel has enjoyed its position as the standard of care for second-line NSCLC for nearly 10 years but it seems certain to see this usurped by Opdivo/Keytruda later this year.

The drug has also been joined by two new chemotherapy agents – Boehringer Ingelheim's Vargatef and Lilly's Cyramza – which received approvals in recent months. However, both of these new agents are likely to struggle to make commercial inroads, given their incremental survival benefit compared with Keytruda and Opdivo.

The landscape could shift even more for traditional chemotherapeutic approaches if one or more anti-PD-1/PD-L1 antibodies posts positive first-line data. Any agent tested against, or in combination with, docetaxel might find itself relegated to what will by that point have become a much later line of therapy.

Creating niches

The commercial implications of the approval of checkpoint inhibitors in NSCLC are also compounded by the fact that the market is becoming increasingly fragmented. It is now commonplace to profile patients for

specific driver mutations.

Those with EGFR mutations have for some time received Roche's Tarceva first line and could in the future go on to new agents that target the T790M mutation, such as Clovis's rociletinib and AstraZeneca's AZD9291. Similarly, ALK-positive NSCLC patients could expect to be put on Pfizer's Xalkori, followed by Novartis's Zykadia.

A strategic solution in this environment could be to target specific high-responder subgroups, as has been done with AstraZeneca/Array's selumetinib. This targets second-line NSCLC patients, but specifically those who are KRAS-positive. However Synta failed to show an expected advantage in mutant KRAS with its HSP90 inhibitor ganetespib and instead chose, somewhat controversially, to select chemo-sensitive patients based on time from diagnosis for its Galaxy 2 phase III study.

Despite the peculiar challenges in NSCLC, the size of the patient pool means that there are still a number of companies with phase II studies under way and aggressive plans to move into late-stage trials. These include Zeltia with lurbinectedin, Threshold and Merck KGaA with evofosphamide and Merrimack with MM-121, specifically targeting Heregulin-positive patients.

These companies might be fortunate in being able to make a go/no-go decision when the new standard is clearer.

Second-line NSCLC treatments in phase III

Company	Product	Pharma class	Study (enrollment)	NCT ID
BMS	Opdivo/Nivolumab	PD-1 MAb	CheckMate 153 (780)	NCT02066636
			CheckMate 017 (264)	NCT01642004
			CheckMate 057 (574)	NCT01673867
Merck	Keytruda/pembrolizumab	PD-1 MAb	KEYNOTE-010 (920)	NCT01905657
Roche	MPDL3280A	PD-L1 MAb	OAK (1,100)	NCT02008227
AstraZeneca	MEDI4736	PD-1 MAb	PACFIC (702)	NCT02125461
			ARCTIC (900)	NCT02352948
Pfizer/Merck KGaA	Avelumab	PD-1 MAb	JAVELIN Lung 200 (650)	NCT02395172
Peregrine	Bavituximab	Anti-PS MAb	SUNRISE (582)	NCT01999673
NewLink Genetics	HyperAcute-Lung (tergenpumatucel-L)	Cancer vaccine	- (240)	NCT01774578
Oncogenex	Custirsen	Clusterin antisense	ENSPIRIT (1,100)	NCT01630733
AstraZeneca/Array	Selumetinib	MEK inhibitor	SELECT-1 (634)	NCT01933932
Synta	Ganetespib	Hsp90 inhibitor	GALAXY 2 (850)	NCT01798485

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