Roche's closely watched TIGIT combo shows 2 checkpoint inhibitors could be better than 1

By Amirah Al Idrus |

May 13, 2020 5:00pm

Like PD-L1, TIGIT is an immune checkpoint that acts as a “brake” that stops T cells from attacking tumors. (Genentech)

The more checkpoint inhibitors the merrier—at least, that’s what Genentech is hoping to prove. Its PD-L1 blocker, Tecentriq, combined with its experimental anti-TIGIT antibody shrank tumors in 31% of patients with metastatic lung cancer—twice as many patients as Tecentriq alone. The findings could pave the way for an approach that makes checkpoint inhibitors work for more people.

The phase 2 results, to be presented at the virtual annual meeting of the American Society for Clinical Oncology, are the first clinical data for the TIGIT-targeting med tiragolumab. Dubbed Cityscape, the trial enrolled 135 patients with non-small cell lung cancer (NSCLC) that had spread locally or elsewhere in the body, and whose tumors expressed PD-L1.

At the first data analysis in June 2019, the Tecentriq-tiragolumab combo beat Tecentriq and placebo at shrinking tumors: 31.3% of patients versus 16.2%. It also kept cancer at bay for 5.4 months, compared with 3.6 months, slashing patients’ risk of cancer worsening or death by 43%.

Checkpoint inhibitors like Tecentriq, Merck & Co.’s Keytruda and Bristol Myers Squibb’s Opdivo have transformed treatment in certain cancers, but they don’t work for everyone—hence the glut of clinical trials testing combination approaches to see which drugs might boost their efficacy.

Like PD-L1, TIGIT is an immune checkpoint that acts as a “brake” to stops T cells from attacking tumors. Preclinical studies suggest that blocking both PD-L1 and TIGIT could work even better than targeting just one of them, Alan Sandler, Genentech’s global head of oncology product development, told FierceBiotech.

“The responses might be deeper and there might be more of them—there is more patient potential to benefit than either agent alone,” he said.

The combo worked best in a group of 58 patients with high PD-L1 levels in their tumors—the tiragolumab combination shrank cancers in more than half of them, while Tecentriq alone did so in only 17.2%. The response rates in patients with low PD-L1 levels were similar: 13.2% for the combo and 15.4% for the monotherapy.

When the data were checked again in December 2019, the combination had held its ground, nudging its response rate up to 37.3% compared to 20.6% for Tecentriq alone.

Genentech tested the tiragolumab combo in patients whose cancer couldn't be treated surgically or had spread to other areas in the body. The standard of care for these patients typically involves chemotherapy, a treatment that "served its role for a number of years," but comes with well-known side effects, Sandler said.

"Anytime you can allow patients to not receive chemotherapy and suffer from side effects… you're doing patients a service, particularly if you're getting the same or better results without the addition of chemotherapy," Sandler said.

Moving forward, Genentech already has two phase 3 studies of tiragolumab under way. The first pits the tiragolumab-Tecentriq combo against Tecentriq monotherapy in patients with PD-L1-positive NSCLC who have not received any cancer treatment. The second adds tiragolumab to Tecentriq and a pair of chemo drugs to see whether the cocktail can beat a Tecentriq-chemo combo in small-cell lung cancer that has grown or spread.

	ITT	
	PA	TA
n	68	67
ORR % (95% CI)	16.2 (6.7, 25.7)	31.3 (19.5, 43.2)
Odds ratio (95% CI)	2.57 (1.07, 6.14)*	
mPFS, months (95% CI)	3.6 (2.7, 4.4)	5.4 (4.2, NE)
HR (95% CI)	0.57 (0.37, 0.90)*	

Bristol's Opdivo-Yervoy-chemo trio cuts lung cancer death risk by up to 38%

By Carly Helfand |

May 13, 2020 5:00pm

“If you think about a community physician sitting in the office in the outpatient setting—I don’t think they think about a hazard ratio when they’re looking at a patient," Bristol Myers Squibb's chief medical officer, Samit Hirawat, said. (Bristol Myers Squibb)

When Bristol Myers Squibb said last October that its combination of Opdivo, Yervoy and chemo had topped solo chemo at lengthening patients’ lives, analysts and investors wondered whether the company’s three-drug regimen could spur a survival benefit on par with Merck’s market-leading Keytruda-chemo combo.

Spoiler alert: It didn't, strictly comparing the numbers between trials—but of course, that's a risky move investigators discourage. And the way BMS sees it, there are plenty of other factors at play.

With a median follow-up of 8.1 months, the combination of Opdivo, Yervoy and two cycles of chemo cut the risk of death by 31% in previously untreated lung cancer patients.

With longer follow-up—a minimum of 12.7 months—it kept that survival benefit going, regardless of patients’ levels of the PD-L1 biomarker. The cocktail pared down the risk of death by 38% in patients with PD-L1 levels below 1% and by 36% in patients with PD-L1 levels of 1% or more, BMS said ahead of the American Society of Clinical Oncology (ASCO) virtual annual meeting.

The chemo combo also showed it could provoke a response among 38% of patients compared with 25% for chemo alone and that it could keep 33% of patients progression-free at the one-year mark versus 18% for chemo. Both of those benefits reached the statistical significance threshold.

The overall survival marks are certainly ahead of the 21% death risk reduction Opdivo and Yervoy put up on their own in the Checkmate-227 trial, from which BMS unveiled three-year data Wednesday. The idea behind adding chemo to the two immuno-oncology drugs was to deliver a "fast initial response" to pair with the "durable longer-term benefit to patients" that Opdivo and Yervoy have already shown they can provide, Wolfe Research analyst Tim Anderson wrote in an October note to clients.

Still, that figure is not exactly the 51% showing that’s helped Merck dominate the lung cancer market with its Keytrudo-chemo pairing.

Of course, cross-trial comparisons are fraught with complications—and there are other things to consider, too, Samit Hirawat, BMS' chief medical officer, said.

For one, Bristol's regimen involves less chemo, which is difficult for many patients to tolerate. The three-drug study, called Checkmate-9LA, revealed an opportunity to prolong survival with a "limited amount of chemo," he said.

"If you think about a community physician sitting in the office in the outpatient setting—I don't think they think about a hazard ratio when they're looking at a patient, but rather they're looking at, 'What is the best that this patient should do, with what kind of therapy? What is the status of this patient? What can they tolerate in terms of chemo? What kind of side effects can they tolerate?'" Hirawat said.

But giving three drugs at once may come with its own set of side effect problems, and BMS won't release full safety data until its ASCO presentation later this month. The company did say in a release that "the safety profile of Opdivo plus Yervoy was consistent with previously reported studies in NSCLC, and no new safety signals were observed," but, as Anderson wrote in the October note, "It will only be once full results are presented" that a risk-benefit assessment "will be possible."

"Opdivo plus Yervoy by itself shows toxicity, and adding chemotherapy into the mix will only increase this. The commercial value of CM-9LA will therefore depend on the balance between the clinical benefit and the toxicity," he said, adding that bringing a third drug into the mix "also raises the cost of therapy somewhat."

Blueprint’s RET inhibitor pads its case ahead of FDA lung cancer decision

By Amirah Al Idrus |

May 13, 2020 5:00pm

Blueprint submitted pralsetinib for FDA approval as a treatment for RET fusion-positive NSCLC in the first quarter this year, and with a priority review tag, it could get a decision within six months. (Blueprint Medicines)

One year after its ASCO debut, Blueprint Medicines’ RET inhibitor continues to deliver. Echoing results presented last year from just 35 evaluable patients, pralsetinib shrank tumors in 61% of a difficult-to-treat group of lung cancer patients and curbed tumor growth in 95% of them.

The phase 2 data come from 116 patients with RET fusion-positive non-small cell lung cancer (NSCLC) that had spread, most of whom—nearly 70%—had tried platinum chemotherapy, while the remainder had not received any kind of treatment. Of the total population, 65% counted as responders, and the treatment eliminated tumors in seven patients, or 6%, the investigators wrote in the study abstract. Almost all (96%) saw some tumor shrinkage.

Those numbers were bolstered by the drug’s performance in the 26 patients who hadn’t been previously treated. Pralsetinib, also called BLU-667, shrank tumors in 100% of those patients. Nearly three-quarters of them had enough shrinkage to be responders.

At a median of nine months after treatment, the median duration of response had not yet been reached, suggesting the treatment’s effect on preventing cancer from growing or spreading could be long-lasting.

"With increased patient follow-up, these data reinforce the prolonged durability demonstrated by pralsetinib. In addition, pralsetinib data have shown a deepening of response with additional patients achieving complete responses," said Andrew Law, Blueprint's associate director of product communications, in an email.

Praseltinib also fared well in patients whose cancer had spread to the brain. It shrank brain tumors in seven of the nine patients whose brain metastases were large and defined enough to be seen on a CT scan or with an MRI, Blueprint reported at ASCO last year.

"In addition, no patients treated at the recommended 400 mg dose had progression due to new CNS involvement," Law said. Data presented late last year showed "durable CNS activity, with several patient cases showing ongoing CNS responses for more than 10 months."

The safety data come from 354 patients who have received pralsetinib, including those with thyroid cancer and other solid tumors. Most of the side effects were mild and the most common were elevated liver enzymes, anemia, constipation and hypertension.

Until recently, patients with RET mutations haven't benefited from a targeted therapy the way their peers with other mutations, like ALK or RAS, have. Instead, they routinely receive platinum chemotherapy along with "any number of drugs," said Blueprint Chief Medical Officer Andy Boral, M.D., in a previous interview. If a patient's disease gets worse, there aren't many options.

Blueprint submitted pralsetinib for FDA approval as a treatment for RET fusion-positive NSCLC in the first quarter this year, and with a priority review tag, it could get a decision within six months. Praseltinib won't be the first targeted treatment for patients with RET-mutated cancers, though—that distinction goes to Eli Lilly's Retevmo (selpercatinib), which scored approval last week.

Although Retevmo will beat pralsetinib to market, Chief Commercial Officer Christina Rossi said on a Blueprint conference call last week that she doesn't expect a significant lag between the two drugs' approvals. She also touted pralsetinib's complete response rates as something physicians have found "incredibly compelling" and potentially "differentiating."

Blueprint plans to follow this submission with a filing in RET-altered medullary thyroid cancer (MTC) later this year. Beyond that, the company wants to get into other RET-altered cancers and earlier lines of treatment.

Roche's Alecensa stays on top of Xalkori with long-term survival showing

By Carly Helfand |

May 13, 2020 5:00pm

Roche won first-line approval in ALK-positive non-small cell lung cancer for Alecensa in 2017. (Roche)

Roche made a splash at ASCO three years ago with data showing that its Alecensa could top Pfizer's Xalkori at keeping ALK-positive lung-cancer at bay. This time, it's back with long-term data showing it can best Xalkori at keeping patients alive, too.

At the five-year mark, 62.5% of previously untreated patients taking Alecensa were still alive, versus just 45.5% of the Xalkori group, Roche said ahead of the American Society of Clinical Oncology (ASCO) virtual annual meeting. That's a mark Alan Sandler, global head of oncology product development for solid tumors at Roche's Genentech, called "remarkable."

In terms of just how long Alecensa can keep people alive, the data aren't yet mature, and follow-up will continue until enough data accumulate to make the call. Still, the new showing—from the phase 3 Alex study—is "really the first real look that we've been able to take at survival," Sandler said, calling it "the ultimate endpoint" and one that's "deeply important" for physicians.

In this case, it's "just further evidence that what they've been doing is correct, and for those few who are not, maybe this gives them another reason to be using Alecensa," he said.

Survival data are also important to payers, and in some markets, they're "critical for strong reimbursement," said Cathi Ahearn, VP of global product strategy for Genentech's oncology business. "The more evidence that we can provide that this is providing benefit for patients, the stronger our evidence base becomes," she added.

The data follow a 2017 showing in which Alecensa proved it could beat Xalkori at cutting down the risk of disease worsening or death by more than 53%. The drug went on to win a front-line FDA nod that set up a head-to-head battle in the marketplace, where Alecensa racked up CHF 268 million ($276.5 million) in Q1 versus Xalkori's $149 million.

That presentation also unveiled a benefit in patients with brain metastases that was echoed in Wednesday's results. In patients with CNS metastases, Alecensa spurred a 42% death reduction compared with Xalkori.

In brain metastases, there's "clear evidence that it does work," Sandler said of the drug.

Bristol Myers Squibb, awaiting Opdivo-Yervoy approval, trumpets 3-year lung cancer survival win

By Carly Helfand |

May 13, 2020 5:00pm

Bristol Myers Squibb is waiting for an FDA decision on Opdivo and Yervoy in previously untreated lung cancer, due by May 15. (Bristol-Myers Squibb)

Just days away from an FDA decision that could finally bring Bristol Myers Squibb's Opdivo to previously untreated non-small cell lung cancer patients, the company's Opdivo-Yervoy combo has put up positive three-year data.

At that juncture, the duo showed it was still outperforming chemo when it came to helping patients live longer. The combo cut the risk of death by 21% among patients whose tumors tested positive for biomarker PD-L1, BMS said ahead of the American Society of Clinical Oncology (ASCO) virtual annual meeting, and 38% of those patients who responded to the combo were still seeing benefits at the three-year mark.

That last piece is key, especially considering that patients only received the combo treatment for two years. "Importantly, especially for those patients who get into a response," they see "a continuation of that response beyond that two-year treatment," said Samit Hirawat, BMS' chief medical officer.

The data come from Part 1 of the Checkmate-227 trial, which made headlines at last fall's European Society for Medical Oncology annual meeting when BMS unveiled the survival benefit.

But it also generated some disagreements among experts. Some heralded the results as "practice-changing," noting that the regimen provided a chemo-free option for patients.

Others, though, pointed out that chemo is no longer the treatment option to beat in newly diagnosed patients—that would be a combination of chemo and Opdivo's archrival, Keytruda from Merck, or Keytruda on its own for those who can't tolerate chemo.

Some of the skeptics said it would take more time—and more data—to really determine the appropriate place for Opdivo-Yervoy in the first-line setting, and that's part of what BMS is getting at with its latest update.

And that's where BMS encourages oncologists to look at Opdivo-Yervoy's track record in other cancers—particularly kidney cancer and melanoma, where it's shown it can keep survival going long-term.

“If you think about it, there’s continuous and growing evidence of dual (immuno-oncology agents) providing an overall benefit in terms of overall survival for these patients, and I think that’s the way to look at it from an overall perspective,” Hirawat said.

Of course, the New Jersey drugmaker can’t start making that pitch to doctors until it has an FDA approval, which could come at any time. The agency is due to make a decision by Friday after bestowing the pairing with a priority review back in January.

Across the pond, though, things haven’t gone so well on the regulatory side for the Opdivo-Yervoy combo. BMS pulled its application in February after reviewers at the European Medicines Agency's Committee for Medicinal Products for Human Use determined that multiple changes to the trial’s design had made it too difficult to evaluate the data.

If BMS can secure a green light, it’ll be counting on doctors’ familiarity with the combo—as well as new data from ASCO—to drive prescriptions.

“Fifty percent of oncology prescribers are already using this combo in other diseases. For them to continue to see the evolution of these data … I think will provide the confidence that ‘Yes, we can go ahead and start to use this once approved by the FDA,'” Hirawat said.

Quitting Smoking at Any Point Improves Lung Cancer Survival, Study Finds

By The ASCO Post Staff

Posted: 5/14/2020 12:11:00 PM

People who quit smoking at any time—even 2 years before a lung cancer diagnosis—improve their chances of survival after being diagnosed with the disease, according to the results of a large international study presented by Fares et al in a press briefing in advance of the ASCO20 Virtual Scientific Program (Abstract 1512).

While much is known about how smoking cessation affects the risk of developing lung cancer, there has been uncertainty about how soon after smoking cessation survival benefits start to accrue after a lifetime of smoking.

"This research shows that if you're a smoker and you quit, no matter when you quit, you will be more likely to survive after being diagnosed with lung cancer, compared to someone who continues smoking," said lead author **Aline Fusco Fares, MD**, a clinical research fellow at Princess Margaret Cancer Centre in Toronto. "The study's message is simple: quit smoking now."

About the Study

The researchers analyzed data from 17 International Lung Cancer Consortium (ILCCO) studies that included data on time to smoking cessation. The consortium is an international group of lung cancer researchers who aim to share comparable data from ongoing lung cancer case-control and cohort studies.

This analysis included 35,428 patients with lung cancer, of which 47.5% were current smokers, 30% were former smokers, and 22.5% had never smoked at the time of diagnosis.

Key Findings

The study results showed a decreased risk of death after lung cancer diagnosis for former smokers, including deaths from all causes.

"Although we can't say that all these deaths after a lung cancer diagnosis are specifically due to the disease, a proportion of them certainly are," said senior author **Geoffrey Liu, MSc, MD**, a clinician-scientist at the Princess Margaret Cancer Centre.

The researchers found that among all former smokers, among those who quit less than 2 years before, between 2 and 5 years before, and more than 5 years before a lung cancer diagnosis had, respectively, a 12%, 16%, and 20% reduced risk of death from all causes when compared to current smokers. The benefit seen from quitting smoking was slightly greater among those who had smoked at least 20 cigarettes per day for more than 30 years.

There was also a trend toward improved lung cancer–specific survival for those who quit smoking less than 2 years before and between 2 and 5 years prior to diagnosis. Improvement in lung

cancer–specific survival was statistically significant for those who quit smoking for more than 5 years prior to diagnosis.

Lung cancer screening offers an opportunity to encourage smokers to quit. With this in mind, the researchers next looked at long-term, heavy smokers—those who smoked more than 30 pack-years—as these smokers would likely be included in lung cancer screening recommendations. A pack-year is defined as the equivalent of 20 cigarettes (a standard pack of cigarettes) smoked every day for 1 year.

Long-term heavy smokers who quit less than 2 years before, between 2 and 5 years before, and more than 5 years before their lung cancer diagnosis had 14%, 17%, and 22% respective reduced risks of death from all causes, compared to current smokers. This effect was not as strong for those who smoked less than for < 30 pack-years; the reduction rate was significant only for those who had quit at least 5 years before diagnosis (23%).

“We saw a slightly bigger benefit to quitting among people who had smoked heavily for over 30 years compared with the overall population of former smokers. For long-term smokers, the benefits of quitting cannot be overstated,” said Dr. Liu.

Next Steps

The researchers plan to collaborate with local lung cancer screening programs to incorporate the findings from this study into a pilot program of smoking cessation counseling sessions.

“We’ve been encouraging people to quit smoking for a long time. These results add more weight to this public health message and provide additional incentive for smokers—particularly those who have smoked for many years—to quit. The improvements in survival seen even with quitting a short time before lung cancer diagnosis show that it’s never too late to stop smoking,” said ASCO President **Howard A. “Skip” Burris III, MD, FACP, FASCO**.

EMA Does Not Recommend Extending the Use of Pembrolizumab

Application concerned first-line treatment in patients with NSCLC and PD-L1 scores between 1 and 49%

Date: 11 May 2020

On 30 April 2020, the European Medicines Agency (EMA) announced that it has finalised its assessment of an application for the use of pembrolizumab (Keytruda) alone as a first-line treatment in patients with non-small cell lung cancer (NSCLC) and low levels of the protein PD-L1 (scores between 1 and 49%).

Currently pembrolizumab is only used alone as first-line treatment in patients with NSCLC and high levels of PD-L1 (scores of 50% and above).

Although EMA's Committee for Medicinal Products for Human Use (CHMP) did not recommend extending the use of Keytruda, it recommended that study data from the application be included in the medicine's product information.

Keytruda is a cancer medicine used to treat melanoma, NSCLC, classical Hodgkin lymphoma, urothelial cancer, head and neck squamous cell carcinoma, and renal cell carcinoma.

For NSCLC, Keytruda on its own can be used as a first-line treatment in patients whose tumours produce high levels of the PD-L1 protein (scores of 50% and above).

It contains the active substance pembrolizumab and is given as an infusion into a vein.

Merck Sharp & Dohme B.V. applied to extend the use of Keytruda alone and as a first-line treatment in patients who have NSCLC with lower levels of PD-L1 (scores between 1 and 49%).

The company presented results from a main study in 1,274 previously untreated patients with NSCLC that had PD-L1 scores of 1% and above. The study compared Keytruda on its own with chemotherapy consisted of carboplatin with paclitaxel or pemetrexed and looked at overall survival.

The CHMP noted that although the main study showed that Keytruda was effective when used alone as a first-line treatment in NSCLC patients with protein scores of 1% and above, the benefits were mainly seen in patients with higher levels of PD-L1. When patients with lower levels of PD-L1 were looked at separately, the results were inconclusive. For these reasons, the committee was of the opinion that the extension should not be granted.

In addition, the CHMP noted that a higher number of patients given Keytruda alone died early compared with those given chemotherapy, although a higher number of Keytruda patients also survived for longer.

The data from the main study will be included in the product information for Keytruda so that healthcare professionals have access to most up to date data on the effects of Keytruda in patients with NSCLC.

The company informed the Agency that there is no impact on patients in ongoing clinical trials or compassionate use programmes.

There are no consequences for Keytruda in its authorised uses

FDA Approves Selpercatinib for Lung and Thyroid Cancers with RET Gene Mutations or Fusions

Efficacy was evaluated in a multicentre, open-label, multi-cohort LIBRETTO-001 trial

Date: 12 May 2020

On 8 May 2020, the US Food and Drug Administration (FDA) granted accelerated approval to selpercatinib (RETEVMO, Eli Lilly and Company) for the following indications:

- Adult patients with metastatic *RET* fusion-positive non-small cell lung cancer (NSCLC);
- Adult and paediatric patients ≥12 years of age with advanced or metastatic *RET*-mutant medullary thyroid cancer (MTC) who require systemic therapy;
- Adult and paediatric patients ≥12 years of age with advanced or metastatic *RET* fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).

Efficacy was investigated in a multicentre, open-label, multi-cohort clinical trial (LIBRETTO-001) in patients whose tumours had *RET* alterations. Identification of *RET* gene alterations was prospectively determined in local laboratories using either next generation sequencing, polymerase chain reaction, or fluorescence *in situ* hybridisation. The main efficacy outcome measures were overall response rate (ORR) and response duration determined by a blinded independent review committee using RECIST v1.1.

Efficacy for *RET*-fusion-positive NSCLC was evaluated in 105 adult patients, previously treated with platinum chemotherapy. The ORR was 64% (95% confidence interval [CI] 54%, 73%); 81% of responding patients had responses lasting 6 months or longer. Efficacy was also evaluated in 39 patients who never received systemic treatment. The ORR for these patients was 85% (95% CI 70%, 94%); 58% of responding patients had responses lasting 6 months or longer.

Efficacy for advanced or metastatic *RET*-mutant MTC was investigated in adults and paediatric patients (≥12 years of age). The trial enrolled patients previously treated with cabozantinib, vandetanib, or both, and patients who had not received these drugs. The ORR for the 55 previously treated patients was 69% (95% CI 55%, 81%); 76% of responding patients had responses lasting 6 months or longer. Efficacy was also evaluated in 88 patients not previously treated with an approved therapy for MTC. The ORR for these patients was 73% (95% CI 62%, 82%); 61% of responding patients had responses lasting 6 months or longer.

Efficacy for *RET* fusion-positive thyroid cancer was evaluated in adults and paediatric patients (≥12 years of age). The trial enrolled 19 patients who were radioactive iodine-refractory (if appropriate) and had received another prior systemic treatment, and 8 patients who were RAI-refractory and had not received any additional therapy. The ORR for the 19 previously treated patients was 79% (95% CI 54%, 94%); 87% of responding patients had responses lasting 6 months or longer. Efficacy was also evaluated in 8 patients who received RAI and no other subsequent therapy. All 8 patients responded (95% CI 63%, 100%) and 75% had responses lasting 6 months or longer.

The most common adverse reactions, including laboratory abnormalities, (≥ 25%) were increased aspartate aminotransferase, increased alanine aminotransferase, increased glucose, decreased leukocytes, decreased albumin, decreased calcium, dry mouth, diarrhoea, increased creatinine, increased alkaline phosphatase, hypertension, fatigue, oedema, decreased platelets, increased total cholesterol, rash, decreased sodium, and constipation.

The recommended selpercatinib dose is weight based—120 mg for patients less than 50 kg, and 160 mg for those 50 kg or greater. Selpercatinib is taken orally twice daily with or without food; or with food when co-administered with a proton pump inhibitor.

Full prescribing information for RETEVMO is available here.

This review used the Assessment Aid, a voluntary submission from the applicant to facilitate the FDA's assessment. This application was approved 3 months prior to the FDA goal date.

This application was granted accelerated approval based on ORR and response duration. Continued approval may be contingent upon verification of clinical benefit in confirmatory trials.

This application was granted priority review, breakthrough therapy, and orphan drug designation.

Healthcare professionals should report all serious adverse events suspected to be associated with the use of any medicine and device to FDA's MedWatch Reporting System.

For assistance with single-patient INDs for investigational oncology products, healthcare professionals may contact FDA's Oncology Center of Excellence Project Facilitate

CheckMate-743 Trial of Nivolumab, Ipilimumab Meets Primary Endpoint in Mesothelioma Trial

Hannah Slater
April 21, 2020

The CheckMate-743 trial evaluating nivolumab (Opdivo) in combination with ipilimumab (Yervoy) in previously untreated malignant pleural mesothelioma met its primary endpoint of overall survival (OS), according to Bristol-Myers Squibb, the agent's developer.[1]

Based on a pre-specified interim analysis conducted by an independent data monitoring committee, the combination treatment was also found to result in a statistically significant and clinically meaningful improvement in OS compared to chemotherapy (pemetrexed and cisplatin or carboplatin). Additionally, the safety profile of nivolumab plus ipilimumab observed in the trial reflects the known safety profile of the combination.

"Malignant pleural mesothelioma is a devastating disease that has seen limited treatment advances over the past decade," Sabine Maier, MD, development lead of thoracic cancers at Bristol Myers Squibb, said in a press release. "These topline results from the CheckMate-743 trial demonstrate the potential of Opdivo plus Yervoy in previously untreated patients with malignant pleural mesothelioma and is another example of the established efficacy and safety of the dual immunotherapy combination seen in multiple tumor types."

"We would like to thank the patients who participated in this trial, as well as the investigators and site personnel for their perseverance during the conduct of this study and in delivering this important result for patients in the midst of the COVID-19 pandemic," Maier added. "We look forward to working with investigators to present the results at a future medical meeting, and to discussing them with health authorities."

Overall, 606 participants with unresectable pleural mesothelioma were randomized to either nivolumab plus ipilimumab or pemetrexed plus cisplatin or carboplatin. Patients randomized to the nivolumab plus ipilimumab combination were administered 3 mg/kg of nivolumab every 2 weeks and 1 mg/kg of ipilimumab every 6 weeks.[2]

Secondary endpoints for the trial included objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and efficacy measures according to PD-L1 expression level.

In the single-center, single-arm, phase II INITIATE trial researchers assessed nivolumab plus ipilimumab in patients with malignant pleural mesothelioma who progressed after at least 1 line of platinum-containing chemotherapy. The study enrolled patients between October 5, 2016, and August 3, 2017.

Participants were administered 240 mg of nivolumab every 2 weeks and 1 mg/kg of ipilimumab every 6 weeks up to 4 times. Only 34 of the 38 enrolled patients were evaluable for response assessment at 12 weeks, with 10 (29%) achieving a partial response and 13 (38%) demonstrating stable disease. This resulted in an overall disease control rate of 68% (95% CI, 50-83).

Notably, treatment-related adverse events (AEs) were reported in 33 (94%) patients. The most AEs were infusion-related reactions, skin disorders, and fatigue. Further, grade 3 treatment-related AEs were reported in 12 (34%) of 35 patients.

References:

1. Bristol Myers Squibb Announces Positive Topline Result from Pivotal Phase 3 Trial Evaluating Opdivo (nivolumab) plus Yervoy (ipilimumab) vs. Chemotherapy in Previously Untreated Malignant Pleural Mesothelioma. Published April 20, 2020. news.bms.com/press-release/corporatefinancial-news/bristol-myers-squibb-announces-positive-topline-result-pivotal. Accessed April 20, 2020.

2. Disselhorst MJ, Quispel-Janssen J, Lalezari F, et a. Ipilimumab and nivolumab in the treatment of recurrent malignant pleural mesothelioma (INITIATE): results of a prospective, single-arm, phase 2 trial. *Lancet*. doi:10.1016/S2213-2600(18)30420-X.

FDA Approves Capmatinib for Patients With Metastatic NSCLC With Confirmed *MET* Exon 14 Skipping

By The ASCO Post Staff

Posted: 5/6/2020 2:54:00 PM

Last Updated: 5/15/2020 1:56:13 PM

On May 6, 2020, the U.S. Food and Drug Administration (FDA) granted accelerated approval to capmatinib (Tabrecta) for adult patients with metastatic non–small cell lung cancer (NSCLC) whose tumors have a mutation that leads to mesenchymal-epithelial transition (*MET*) exon 14 skipping as detected by an FDA-approved test.

The FDA also approved the FoundationOne CDx assay as a companion diagnostic for capmatinib.

GEOMETRY *mono-1*

Efficacy was demonstrated in the GEOMETRY *mono-1* trial, a multicenter, nonrandomized, open-label, multicohort study enrolling 97 patients with metastatic NSCLC with confirmed *MET* exon 14 skipping. Patients received capmatinib at 400 mg orally twice daily until disease progression or unacceptable toxicity. The main efficacy outcome measures were overall response rate determined by a blinded independent review committee using Response Evaluation Criteria in Solid Tumors, version 1.1, and response duration.

Among the 28 treatment-naive patients, the overall response rate was 68% (95% confidence interval [CI] = 48%–84%) with a response duration of 12.6 months (95% CI = 5.5–25.3). Among the 69 previously treated patients, the overall response rate was 41% (95% CI = 29%–53%) with a response duration of 9.7 months (95% CI = 5.5–13.0).

The most common adverse reactions (in ≥ 20% of patients) were peripheral edema, nausea, fatigue, vomiting, dyspnea, and decreased appetite. Capmatinib can also cause interstitial lung

disease, hepatotoxicity, photosensitivity, and embryofetal toxicity. Based on a clear positive signal for phototoxicity in early laboratory studies in cells, patients may be more sensitive to sunlight and should be advised to take precautions to cover their skin, use sunscreen, and not tan while taking capmatinib.

The recommended capmatinib dose is 400 mg orally twice daily with or without food.

The content in this post has not been reviewed by the American Society of Clinical Oncology, Inc. (ASCO®) and does not necessarily reflect the ideas and opinions of ASCO®.

Reference:

Novartis announces MET inhibitor capmatinib (INC280), the first potential treatment for METex14 mutated advanced non-small cell lung cancer, granted priority FDA review [news release]. Basel. Published February 11, 2020. https://www.novartis.com/news/media-releases/novartis-announces-met-inhibitor-capmatinib-inc280-first-potential-treatment-metex14-mutated-advanced-non-small-cell-lung-cancer-granted-priority-fda-review. Accessed February 11, 2020.

Sintilimab Regimen Improves PFS in Frontline Squamous NSCLC

Jason M. Broderick @jasoncology

Published: Thursday, May 07, 2020

Adding the PD-1 inhibitor sintilimab injection (Tyvyt) to gemcitabine (Gemzar) and platinum-based chemotherapy improved progression-free survival (PFS) as a frontline treatment in patients with advanced or metastatic squamous non–small cell lung cancer (NSCLC), meeting the primary end point of the phase 3 Chinese ORIENT-12 trial.[1]

There were no new safety signals with sintilimab compared to previous research with the PD-1 inhibitor. The data from the trial will be shared at a future medical meeting, Innovent Biologics and Eli Lilly and Company, the codevelopers of sintilimab, stated in a press release.

"Lung cancer is the leading cause of cancer death (25.2%), of which NSCLC accounts for 80% to 85%, with about 35% of those patients having the squamous subtype. In the past 20 years, drug development to treat NSCLC has been mainly focused on nonsquamous NSCLC, while drug development of squamous NSCLC has been slower due to its lack of driving mutation and its unique epidemiological, histopathological and molecular characteristics," Caicun Zhou, MD, PhD, head of the Department of Oncology, Shanghai Pulmonary Hospital, stated in the press release.