Mirati Therapeutics Inc (MRTX) Sitravatinib Not Likely to Get Approved in 2023 Due to Severe Safety Issues

Summary: MRTX is using their drug Sitravatinib in combination with Nivolumab as second/third-line treatment of Non-Squamous Non-Small Cell Lung Cancer (NSCLC) in their phase 3 SAPPHIRE study[1], in comparison with chemotherapy Docetaxel. From existing clinical trial data and analysis of their drug principles, we state that phase 3 study is unable to produce convincing enough results to get Sitravatinib finally approved by FDA before year-end 2023, with safety problems being the biggest obstacle. This correlates with previous predictions (2018) based on the chemical structure of Sitravatinib (Oprea et al 2018).

Sitravatinib plays a secondary role to assist on the activity of Nivolumab

Nivolumab is an FDA-approved immunotherapy drug for different types of cancers including NSCLC. It is a type of checkpoint inhibitor (CPI). The basic function of CPI is to block the binding of checkpoint proteins to their partner proteins (PD-L1 to PD-1 for Nivolumab), which will free and release T-cells to fight against tumors[14].

Targeted therapies mainly aim at specific genes or proteins that help tumor cells to grow, either targeting the tissue environment that cancer cells grow in or cells related to cancer growth, like blood vessel cells[4]. That brings a problem that in general cases, if the actual cause of cancer is not determined, there will be immunosuppression symptoms that vary from person to person. As a result, it is reported that most NSCLC patients do not respond to single-agent CPI therapies. This fact motivates MRTX using Sitravatinib as a second/third-line treatment on specified groups of NSCLC patients who had experienced disease progression on CPI therapy before.

Sitravatinib is a small molecule drug. It belongs to the type of receptor tyrosine kinase (RTK) inhibitor with the effect of blocking the action of oncogenic kinases which lead to immunosuppression, and helping the immune system to overcome resistance to CPI therapy. It converts the immunosuppressive tumor microenvironment to an immune-supportive one to make tumors more likely to respond to CPI. The types of RTKs that Sitravatinib inhibits are TAM family receptors (TYRO3, Axl, MERTK) and Split family receptors (VEGFR2, KIT)[3].

Most similar studies of RTK inhibitor terminated at early stages

There have been several approved RTK inhibitor drugs for different mutations of NSCLC, like Alectinib, Ceritinib and Dacomitinib[3]. Also, there are combination therapy studies similar to the SAPPHIRE study of MRTX, with applying both tyrosine kinase inhibitors and other types of immunotherapies to NSCLC patients. But as shown in **Table 1**, most of these trials finally terminated at early stages of either phase 1 or phase 2, without directly leading to the drug approval by FDA[6] (statistical data from 2018).

Clinical Trial	Phase	Intervention	Status
NCT02574078/ CheckMate 370	I/II	Nivolumab + erlotinib (group D)/ crizotinib (group E)	Ongoing, not recruiting for group E
NCT01998126	I	Nivolumab/ipilimumab + erlotinib/crizotinib	Ongoing, not recruiting
NCT01454102/ CheckMate 012	I	Nivolumab + erlotinib (arm E)	Ongoing, not recruiting
NCT02393625	I	Nivolumab + ceritinib	Recruiting
NCT02039674/ KEYNOTE-021	I/II	Pembrolizumab + erlotinib (cohort E)/gefitinib (cohort F)	Ongoing, not recruiting
NCT02364609	I	Pembrolizumab + afatinib	Recruiting
NCT03157089/ LUX-Lung IO	II	Pembrolizumab + afatinib	Not yet open
NCT02511184	I	Pembrolizumab + crizotinib	Recruiting
NCT02013219	I	Atezolizumab + erlotinib/alectinib	Ongoing, not recruiting
NCT02584634/ Javelin Lung 101	Ib/II	Avelumab + crizotinib (group A)/ lorlatinib (group B)	Recruiting
NCT02088112	I	Durvalumab + gefitinib	Ongoing, not recruiting
NCT02898116	I/II	Durvalumab + ensartinib	Recruiting
NCT01998126	I	Ipilimumab + erlotinib/crizotinib	Ongoing, not recruiting
NCT02040064/ GEFTREM	I	Tremelimumab + gefitinib	Completed

Table 1: Clinical trials of immune checkpoint inhibitors in combination with EGFR/ALK tyrosine kinase inhibitors (TKIs) in advanced NSCLC.

Phase 3 SAPPHIRE study data analysis expected by mid-2023

The Phase 3 clinical trial started in July 2019, and is estimated to finish by July 2023. MRTX has planned to finish phase 3 final topline data analysis in Q2 2023[2]. From historical information, we made a prediction that the most probable conference for MRTX to release their phase 3 data is ASCO 2023 from June 2 to 6.

Phase 3 study was set to include 532 adult Non-Squamous NSCLC patients, who had already received prior treatment of PD-1/PD-L1 CPI therapy and platinum-based chemotherapy in combination or in sequence, with radiographic disease progression on or after treatment. Sitravatinib with Nivolumab is offered as a second/third-line treatment option to some patients, while the other patients take Docetaxel as the standard of care or active comparators[2].

The Primary Outcome Measure of phase 3 study is Overall Survival (OS), defined as time from date of randomization to date of death due to any cause. Secondary Outcome Measures are Adverse Events (AE), Objective Response Rate (ORR) and Progression-Free Survival (PFS)[2].

Sitravatinib does have certain level of improvement of Nivolumab on efficacy, and better outcomes than Docetaxel

MRTX has released some key results from their past clinical trials of the same study. However, there is no direct comparison on efficacy between different therapies from their existing data yet. So instead, we tried to seek data from other clinical trials with similar settings, comparing their combination therapy with single Nivolumab and Docetaxel, which is the active comparator selected from their phase 3 trial.

Apart from results from phase 2/3 clinical trial data released in September 2021 at ESMO conference[7], we also collected results from another study by Bristol-Myers comparing Nivolumab with Docetaxel, in which Non-Squamous NSCLC patients all received second/third-line treatments after progressive disease following multiple therapies as well[11]. Like the comparison results in **Table 2** exhibits, Nivolumab + Sitravatinib has some degree of improvement in OS and PFS measurements compared to Nivolumab alone, or to their selected baseline chemotherapy Docetaxel, while much fluctuation is discovered in OS data. And the results do not suggest an increase in ORR to Nivolumab.

	Nivolumab (N=292)	Docetaxel (N=290)	Nivolumab + Sitravatinib (N=68)
Median Overall Survival (OS)	12.19 months (95% CI 9.66-14.98)	9.36 months (95% CI 8.05-10.68)	14.9 months (95% CI 9.1-21.1)
Objective Response Rate (ORR)	19.5% (95% CI 15.4-24.5)	12.8% (95% CI 9.1-17.2)	18%
Median Progression-Free Survival (PFS)	2.33 months (95% CI 2.17-3.32)	4.44 months (95% CI 3.45-4.86)	5.7 months (95% CI 4.9-7.6)

Table 2: Efficacy comparison of Sitravatinib in combination with Nivolumab against Nivolumab and Docetaxel, in terms of primary/secondary outcome measures

With high adverse event rate, safety problem of Sitravatinib is more severe, comparing to limited improvements in efficacy

Along with the efficacy data, MRTX also posted safety data from their previous phase 2/3 clinical trial (**Table 3**). Several treatment-related adverse events (TRAE) were reported, with a few patients forced to discontinue their treatments because of severe adverse events[7].

	Nivolumab + Sitravatinib (120 mg) (N=68)	
Treatment-related adverse events (TRAE)	**Any grade**	**Grade ≥3**
Any TRAE	93%	66%
Diarrhea	62%	16%
Fatigue	52%	4%
Nausea	44%	2%
Hypertension	40%	22%
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Discontinuation due to TRAE	**After Nivolumab**	**After Sitravatinib**
	9%	21%

Table 3: Some safety data of Sitravatinib in combination with Nivolumab: treatment-related adverse event rates with several most common types of TRAE, and treatment discontinuation rates in both stages after receiving Nivolumab and Sitravatinib

During the combination therapy of Nivolumab and Sitravatinib, NSCLC patients received a dose of Nivolumab first, and then followed by a dose of Sitravatinib after a few days. From the TRAE rate data, nearly all 68 patients who received the treatment got some degree of TRAEs, and most of them got serious TRAEs with grade at least 3. Of all TRAEs, diarrhea was the most common type reported. As for the treatment discontinuation

data, at first there were 9 percent of patients discontinued their treatment due to TRAEs during the period between receiving doses of Nivolumab and Sitravatinib, but this number increased significantly after receiving Sitravatinib.

According to another comparison of data from their phase 2/3 clinical trial shown in **Table 4**, increasing the dosage of Sitravatinib could have even more evident effects on toxicity in this combination therapy[7]. Adding half of initial dosage of Sitravatinib from 80 mg to 120 mg resulted in double growth of TRAEs with grade at least 3.

	Nivolumab + Sitravatinib (80 mg) N=13		Nivolumab + Sitravatinib (120 mg) N=7	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Treatment-related adverse events (TRAE)	100%	31%	100%	71%

Table 4: Safety data of treatment-related adverse event rates with different dosages of Sitravatinib

Efficacy increase may result from treatment discontinuation

Another noteworthy point from the efficacy and safety results shown above is that the improvement in OS does not appear along with the increase of ORR. This leads us to hypothesize that the increase in OS is likely due to the higher discontinuation rate after sitravatinib, which is 21% compared to 9% before. So, we assume that those 21% patients who discontinued their treatment with sitravatinib are more likely the ones with worse prognosis and shorter OS time. As a result, the average OS rate turns out to be higher, after eliminating these 21% patients, with ORR stays almost the same.

The active comparator Docetaxel is considered to have extremely high toxicity

MRTX used Docetaxel as the baseline treatment or active comparator in phase 3 SAPPHIRE study. Docetaxel is a chemotherapy drug for multiple metastatic and non-resectable tumor types[6]. It inhibits tumor cells in the mitotic spindle stage by binding β-tubulin protein, and reduces the expression of B-cell lymphoma 2 (Bcl-2) gene to Make tumor cells more readily to undergo apoptosis[9]. Docetaxel is the most widely used drug for second/third line NSCLC treatment. Though it has been applied to clinical usage for many years, safety remains as its main shortcoming. As **Table 5** reveals, in the clinical trial by Bristol-Myers mentioned above comparing Docetaxel with Nivolumab, there were 55 percent of NSCLC patients who got serious treatment-related adverse events with grade at least 3, while only 7 percent of patients for Nivolumab[10,11].

	Nivolumab (N=131)		Docetaxel (N=129)	
Treatment-related adverse events (TRAE)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Any TRAE	58%	7%	86%	55%
Neutropenia	1%	0	33%	30%
Fatigue	16%	1%	33%	8%
Nausea	12%	9%	23%	2%
Alopecia	0	0	22%	1%
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Table 5: Safety data of treatment-related adverse event rates in the clinical trial of Nivolumab comparing with Docetaxel, with several most common types of TRAE

This is a common situation in chemotherapies, since chemotherapy drugs are always hazardous due to their mechanism of damaging normal human cells. But from our discovery, it is possible to find a safer alternative for Docetaxel, like Pemetrexed.

Pemetrexed is another type of chemotherapy. It works by blocking the growth and multiplication of tumor cells by inhibiting the formation of nucleotides[12]. Same as Docetaxel, it is also widely used in second/third-line NSCLC treatments. **Figure 1** and **Table 6** show results from another clinical trial comparing Pemetrexed with Docetaxel in NSCLC patients previously treated with chemotherapy, on both efficacy and safety measurements[13]. Both Median Progression-Free Survival (MPFS) and Median Survival Time (MST) measurements yield close outcomes for Docetaxel and Pemetrexed. But Docetaxel has clearly more hematologic toxicity rate. We can conclude from the results that Pemetrexed has equivalent efficacy with Docetaxel, and is much safer in toxicity. Back to MRTX, as the combination therapy of Sitravatinib with Nivolumab also displays huge safety issue from analysis above, it should be less persuasive to state that the therapy is safe enough if they could beat Docetaxel on TRAE measurement, than beating Pemetrexed.

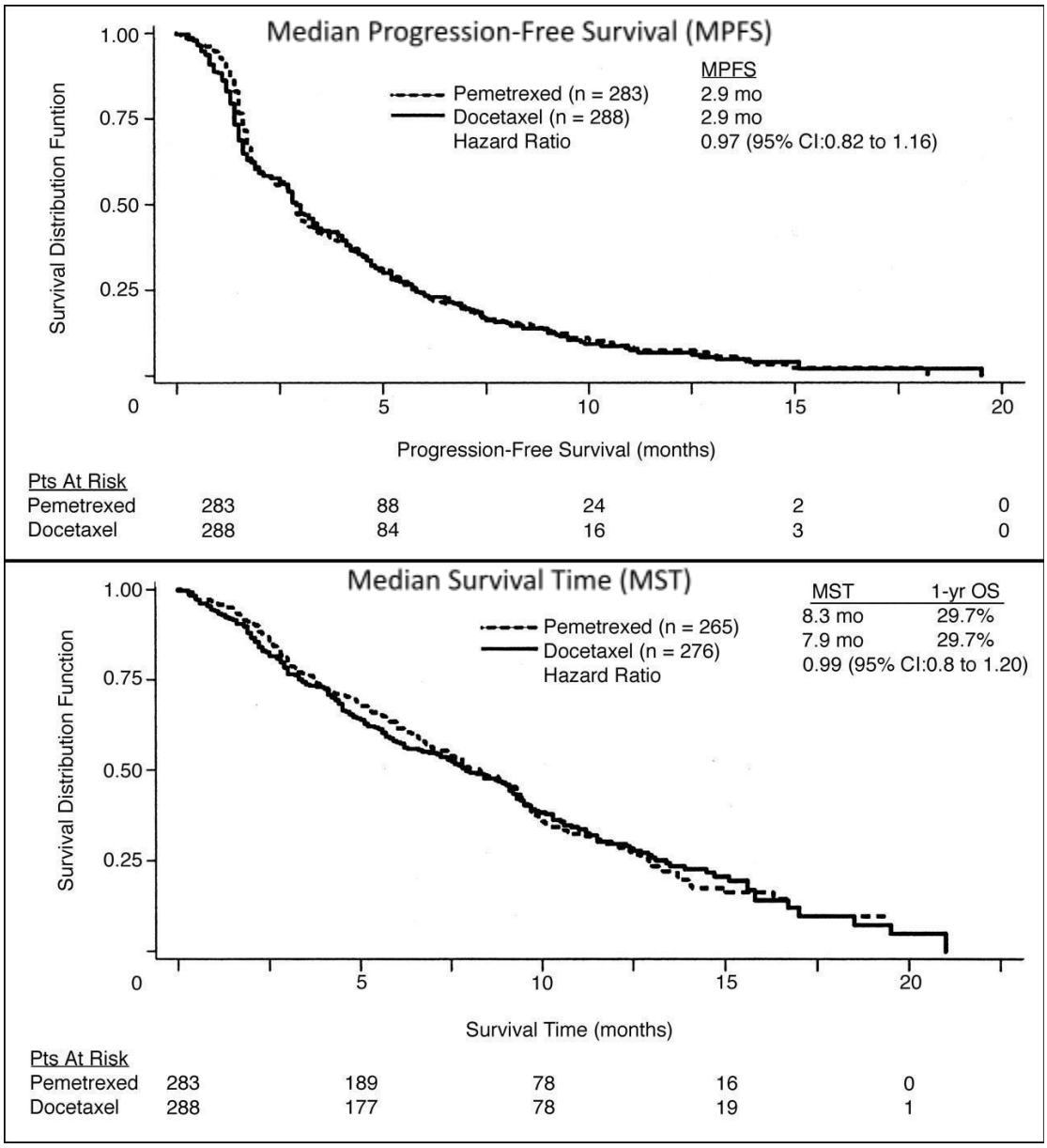

Figure 1: Comparison of Pemetrexed (Pem) with Docetaxel (Doc) on efficacy

Grade 3 and 4 Hematologic Toxicities

	% of Pemetrexed Patients (n = 265)	% of Docetaxel Patients (n = 276)	P*
Neutropenia	5.3	40.2	< .001
Febrile Neutropenia	1.9	12.7	< .001
Neutropenia with infection	0.0	3.3	.004
Anemia	4.2	4.3	.99
Thrombocytopenia	1.9	0.4	.116

NOTE. Toxicities graded using the National Cancer Institute Common Toxicity Criteria version 2.

*Fisher's exact test.

Table 6: Comparison of Pemetrexed (Pem) with Docetaxel (Doc) on safety

Conclusion

To sum up from all the information and analysis above, we hold a negative attitude towards the future success of Sitravatinib. The safety problem is severe enough to affect the continuation of the treatment process, which is the biggest issue Sitravatinib has. Plus, we did not find Sitravatinib with many outstanding points on efficacy, only limited improvement than Nivolumab alone. MRTX will be able to pass phase 3 of the SAPPHIRE study, because they were setting a relatively weak trial objective. Their choice of standard of care was Docetaxel, which also showed high toxicity. However, this does not indicate that Sitravatinib will get approved by FDA after phase 3 data analysis, as the drug is not competitive enough.

References

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Questions & Answers

1. What is the difference between Pemetrexed with Docetaxel?

   Pemetrexed and docetaxel have similar efficacy in treating advanced non-small cell lung cancer (NSCLC), but pemetrexed may have some advantages in terms of safety. Di (2014) found that pemetrexed was almost as effective as docetaxel in terms of overall response rate, survival time, progression-free survival, and disease control rate, but patients in the pemetrexed group had a significantly higher 3-year survival rate. Pemetrexed also led to lower rates of grade 3-4 hematological toxicity, including febrile neutropenia, neutropenia, and leukocytosis, as well as lower rates of non-hematological toxicities such as diarrhea and alopecia. Li (2012) found that pemetrexed had equivalent efficacy outcomes and better safety profiles compared to docetaxel in second-line therapy for advanced NSCLC in Chinese patients, and that patients over 60 may benefit more from pemetrexed. Zinner (2004) also found that pemetrexed had significant efficacy and a favorable toxicity profile in treating NSCLC, and that it was a useful agent in the treatment of thoracic malignancies. Fossella (2004) did not directly compare the efficacy of pemetrexed and docetaxel, but suggested that vitamin supplementation may affect docetaxel survival.

2. What is the cause of human body immunosuppression to targeted therapy?

   Immunosuppression can be caused by a variety of factors, including chemotherapy (Rasmussen 1982), pharmacologic immunosuppression (Barshes 2004), and activation of suppressor T cells after trauma (Munster 1976). Rosenblum 2012 discusses new targeted therapies for autoimmune disease that aim to restore the balance of effector and regulatory immune function, which is critical for avoiding autoimmunity. However, these therapies must be targeted to patients suffering from autoimmune disease while avoiding the pitfalls of general immunosuppression. Overall, the papers suggest that immunosuppression can be caused by a variety of factors and that targeted therapies are needed to avoid general immunosuppression.

3. In NSCLC treatments, is there any combination therapy with tyrosine kinase inhibitors and other immunotherapies that is over phase 3?

   According to a study published in Nature, the combination of tyrosine kinase inhibitors (TKIs) and immunotherapies has shown promising results in the treatment of non-small cell lung cancer (NSCLC). However, I could not find any information on whether this combination therapy has reached phase 3 clinical trials. In another study published in PubMed, the introduction of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) has improved the outlook for patients with advanced non-small-cell lung cancer (NSCLC) with EGFR+ mutations. However, most patients develop resistance, with the result that median progression-free survival (PFS) is 12 months.

Scenarios for Hyperforcasting

1. Optimistic (low probability): According to their phase 3 data released in June, the efficacy endpoints of SAPPHIRE are met, with acceptable toxicity. Sitravatinib makes significant progress, which is finally approved by the NDA at the end of 2023. Success of Sitravatinib marks a milestone in non-small cell lung cancer treatment, which facilitates more studies on activation of immune inhibitor therapy to start.

2. Pessimistic (high probability): Phase 3 trial of Sitravatinib plus Nivolumab does not show evident improvement on either primary or secondary outcome measurements, while adverse event rate is still severe. The trial ended with failure. Sitravatinib cannot make it to the market, and chemotherapy remains the first choice for most non-small cell lung cancer patients having suffered immunosuppression.