A Phase I/II Study of Pexa-Vec Oncolytic Virus in Combination with Immune Checkpoint Inhibition in Refractory Colorectal Cancer: An Interim Safety Report

Abstract #646

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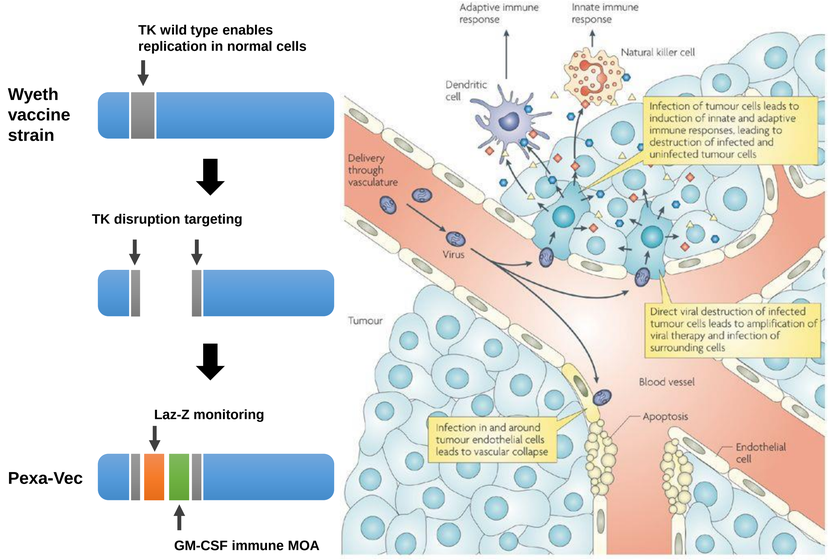
ABSTRACT

Background: The efficacy of immune checkpoint inhibitor has been limited to small portion of colorectal cancer (CRC) patients whose tumors with mismatch repair (MMR) gene abnormalities. There is an urgent need for patients with MMR proficient (pMMR) tumors. Oncolytic immunotherapy represents a novel therapeutic platform for the treatment of cancer with unique activity compared to conventional chemotherapy. The trial is to evaluate if the combination of Pexa-Vec oncolytic virus (Pex) with immune checkpoint inhibition enhance antitumor immunity.

Methods: Patients with microsatellite-stable and MSI-H mCRC refractory to PD-1 monotherapy were enrolled. Patients received either Arm A treated with Pex + Durvalumabor Arm B with Pex + Durvalumab and Tremelimumab. Each arm had two dose levels (DL) of Pex, 3 x 10^8 pfu in DL1 and at 10^9 pfu in DL2, every 2 weeks for total 4 doses. The first dose of Pex was administered on Day -12, followed by three more dose administration on Days 2, 16 and 30 in combination with the immune checkpoint inhibition. The primary endpoint is response rate, safety, tolerability and feasibility of these combination therapy in refractory metastatic CRC.

Pexa-Vec Design and Cancer Target



Study Design and Schedule

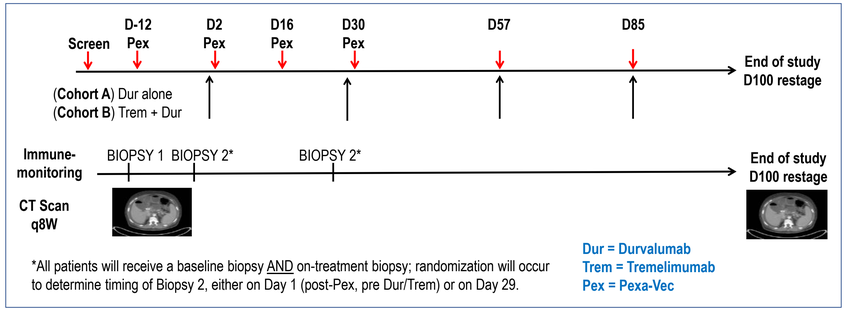
- MSS/pMMR mCRC: fail, be intolerant or refuses: 5FU, oxaliplatin, irinotecan-based chemotherapy
- MSI-h/dMMR mCRC: documented refractory to anti-PD1/PDL1

Cohort A
DL1: Dur 1500mg q28d, Pex 3x10^8/pfu (N=3-6)
DL1: Dur 1500mg q28d, Pex 1x10^9/pfu (N=3-10)

Cohort A
DL1: Trem 75mg/Dur 1500mg q28d, Pex 3x10^8 pfu (N=3-6)
DL1: Trem 75mg/Dur 1500mg Iq28d, Pex 1x10^9 pfu (N=3-10)

Primary Endpoints
Safety, tolerability and feasibility

Secondary Endpoints
RR, 5-month PFS, OS



Key Inclusion Criteria

- Patients with MSS/pMMR mCRC must fail, be intolerant or refuses: 5FU, oxaliplatin, irinotecan-based chemotherapy
- Patients with KRAS wild type mCRC must fail, be intolerant of or refused cetuximab or panitumumab-based chemotherapy.
- Patients with MSI-h/dMMR mCRC must have domumented refractory to anti-PD1/PDL1
- Patients must have at least one focus of metastatic disease that is amenable to pre- and on-treatment biopsy and be willing to undergo this.
- Patients must have acceptable organ and marrow function

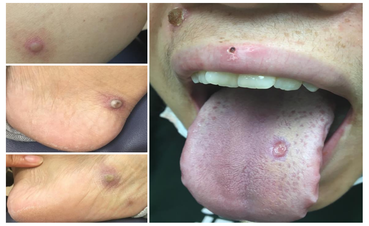
References

Breitbach et al. *Nature* 2011, Kirn et al. *Nat Rev Cancer* 2009, Breitbach et al. *Cancer Res* 2013, Kirn et al. *Science Transl Med* 2013

Interim Safety Events

Events \ Grades / Patients	DL1 patients			DL2 patients								
	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11	#12
Fever	**3**	2	**3**	**3**	2	**3**	2	1	2	**3**	**3**	2
Hypotension	1		2	2	1	2	1	2	1		2	1
Chills	1	1	1	2		1	2		2	2	2	
Fatigue	1	1		1		1	1	2				2
Papulopustular rash				1	1	1	1	1	1	1		
Sinus tachycardia			1					2	1		1	
Vomiting			1				1	1	1			
Nausea			1			1	1	1	1	1		
Flu like symptoms	1						1	2				
Headache			1				1	2				
Pain	1											
Hypertension							2					
Elevated ALT	2						1		1		1	
Elevated AST	2											
Elevated ALP	2						1				1	
Elevated bilirubin	1											
Lymphopenia	1				1	**4**						1
Neutropenia								**3**	1			
Anemia					2		2		1		1	
Hyperuricemia			1					1				
Hyponatremia			1	1			1				1	
Hypophosphatemia			2									
Hypomagnesemia								1				
Hypoalbuminemia						2	1					
Elevated lipase	1		1									
Elevated amylase										1		
Increased Creatinine					2							

The patient developed a pustular lesion on the feet, calf, face and tongue intravenous injection with Pexa-Vec (1x10^9 pfu)



Conclusions

Pexa-Vec in combination with Durvalumab showed a favorable safety profile.