Supplementary Materials 3:

Dual role of TNF and LTα in carcinogenesis as implicated by studies in mice

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Table S3. Recent clinical trials on cancer treatment involving TNF administration or its blockade

Type of cancer	Target cytokine/ cytokine receptor	Drug/ treatment	Additional drugs/ treatments	Outcome	Ref.	NCT trial number and year of study start
Melanoma	TNF	rhTNF	Melphalan, ILP	• Phase III trial: The addition of TNF to melphalan did not demonstrate a significant enhancement of short-term response rates over melphalan alone by the 3-month follow-up. • TNF plus melphalan was associated with a higher complication rate.	[1]	NCT00003789 (1999)
			Melphalan, IFNγ , hyperthermic ILP	• Phase III trial: ILP with TNF/IFNγ/melphalan is more effective (CR rate was 72%) then ILP with only melphalan (CR rate was 58%). • ILP with TNF/IFNγ/melphalan can be safely performed with mostly mild side effects.	[2,3]	NCT00001296 (1992)
		L19TNF (recombinant fusion protein that consists of fully human recombinant monoclonal antibody (L19) and the human TNF)	L19IL2	• Phase II trial: Intralesional injection of L19-IL2 and L19-TNF slowed down metastases progression. • Treatment was well tolerated, with mostly mild side effects limited to injection site.	[4]	NCT02076633 (2012)
Colorectal Cancer	TNF		No	• Phase I/II trial: No objective tumor responses. • The maximally tolerated dose (MTD) was not reached. Intravenous L19-TNF was safe up to 13 μg/kg.	[5]	NCT01253837 (2007)

Colorectal Cancer, Head and Neck Cancer, Kidney Cancer	TNF	NGR-hTNF (CNGRC peptide-TNF conjugate)	No	• Phase I trial: No objective responses were observed. • NGR-hTNF was well tolerated. The MTD was 45 μg/m^2.	[6]	NCT00098943 (2004)
Diffuse large B-cell lymphoma	TNF		Rituximab, doxorubicin, cyclophosphamide, vincristine, prednisone	• Phase II trial: Fast and prominent tumor regression was observed in 9 of the 12 assessed patients. NGR-hTNF selectively increased vascular permeability in tumoral/peritumoral areas. • The NGR-hTNF/R-CHOP* combination was well tolerated.	[7]	NCT03536039 (2016)
Hematological cancers	Anti-TNF, anti-LTα_3	Etanercept (fusion protein that consists of extracellular binding domain of the 75kD TNFR2 and the constant portion of human IgG1)	Methylpredni-solone	• Phase II trial: Etanercept in combination with corticosteroids (methylprednisolone) was associated with high response rates and overall survival in children with IPS. • Etanercept was well tolerated.	[8]	NCT00309907 (2006)
Myelodysplastic Syndromes	Anti-TNF, anti-LTα_3		Azacitidine	• Phase I/II trial: Etanercept increased the response rate and the duration of response observed with azacitidine therapy. • Most of the side effects were qualified as mild.	[9]	NCT00118287 (2005)
Non-melanoma Skin Cancer	TNF	L19TNF (recombinant fusion protein that consists of fully human recombinant monoclonal antibody (L19) and the human TNF)	L19IL2	–	NP	NCT04362722 (2020)
Melanoma	Anti-TNF	Certolizumab (PEGylated humanized antigen-binding fragment (Fab') of an anti-TNF monoclonal antibody) [10] Infliximab (chimeric monoclonal antibody)	Nivolumab, Ipilimumab	–	NP	NCT03293784 (2017)

TNF – tumor necrosis factor, rhTNF – recombinant human tumor necrosis factor, ILP – isolated limb perfusion, IFNγ – interferon-gamma, CR – complete responses, hTNF – human tumor necrosis factor, MTD – maximum tolerated dose, LTα_3 – lymphotoxin α, IPS - idiopathic pneumonia syndrome, NP – not published.

*R-CHOP is an acronym that stands for combination of drugs used in chemotherapy: R – Rituximab, C – Cyclophosphamide, H – Doxorubicin Hydrochloride (Hydroxydaunomycin), O – Vincristine Sulfate (Oncovin), P – Prednison.

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