

Thymalfasin for Malignant Melanoma

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Positive results from large 488-patient, randomized Phase II clinical trial in Stage IV melanoma

- Achieved primary tumor response endpoint
- Improved overall survival by up to 4.2 months in normal LDH patients

Synthetic preparation of naturally occurring peptide thymalfasin

- Direct anticancer and immunomodulatory activities

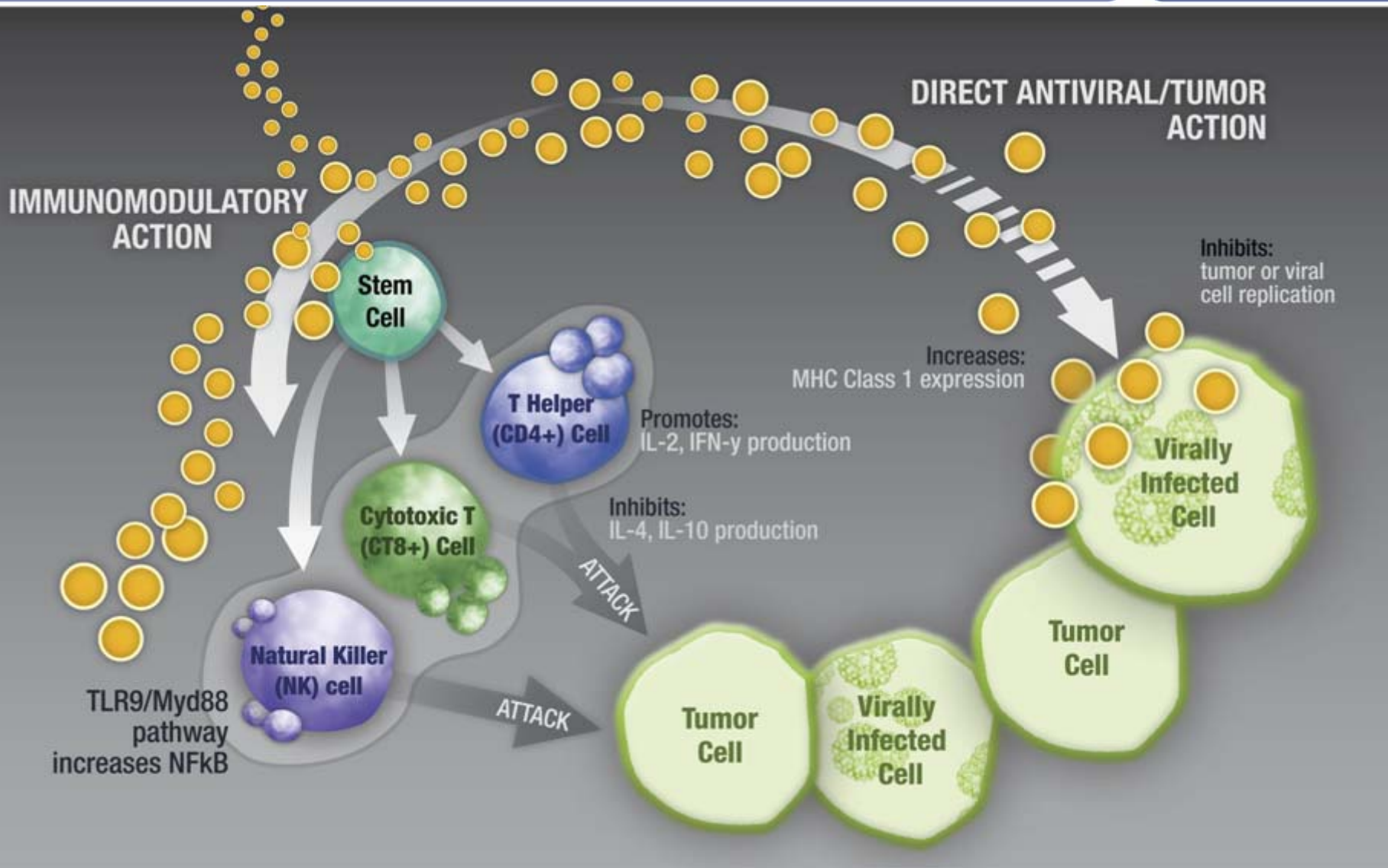
Approved for HBV, HCV and/or as a vaccine adjuvant in more than 30 countries, primarily in Asia and Latin America

- Safely used by more than 100,000 patients, incl. more than 2,000 patients in clinical trials in the US and Europe

Special Protocol Assessment approved by FDA

- Plan to initiate a Phase 3 registration trial in place

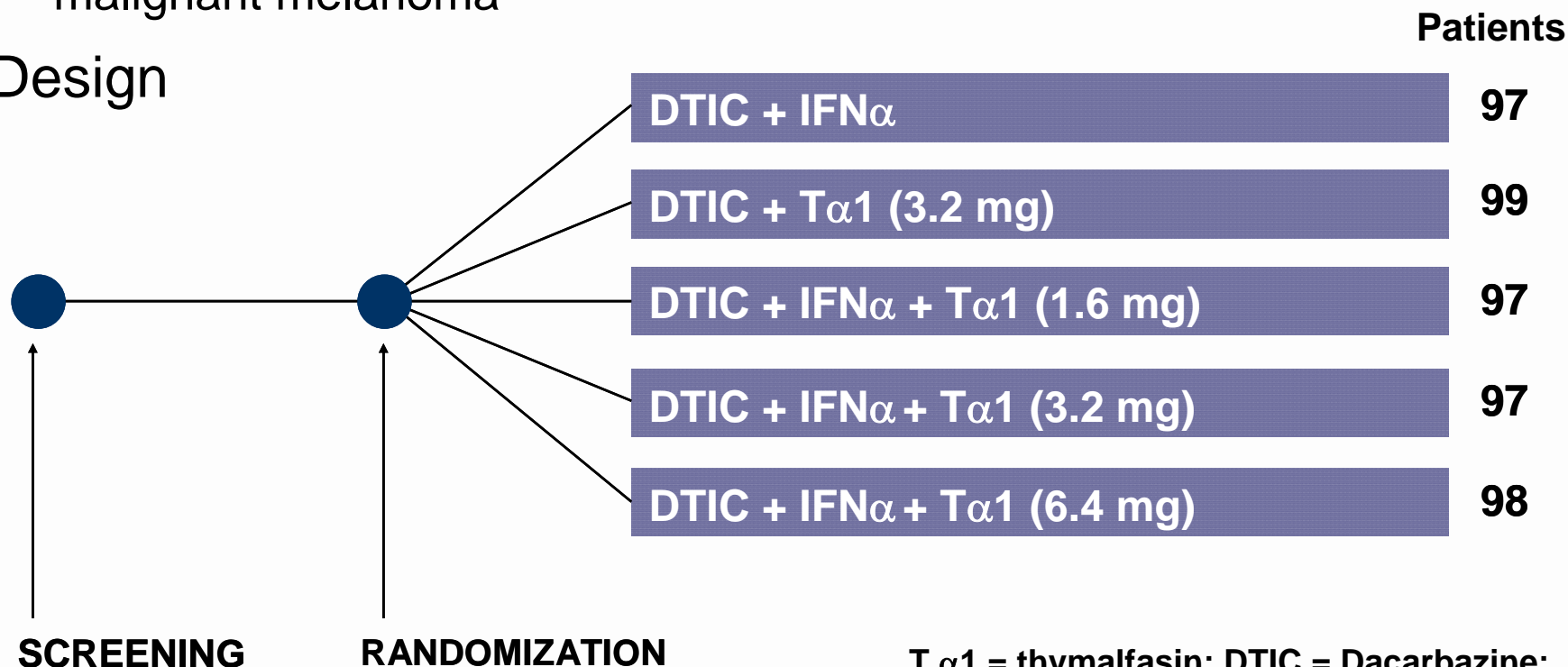
SciClone and Sigma-Tau are seeking a development / commercial partner



Objective

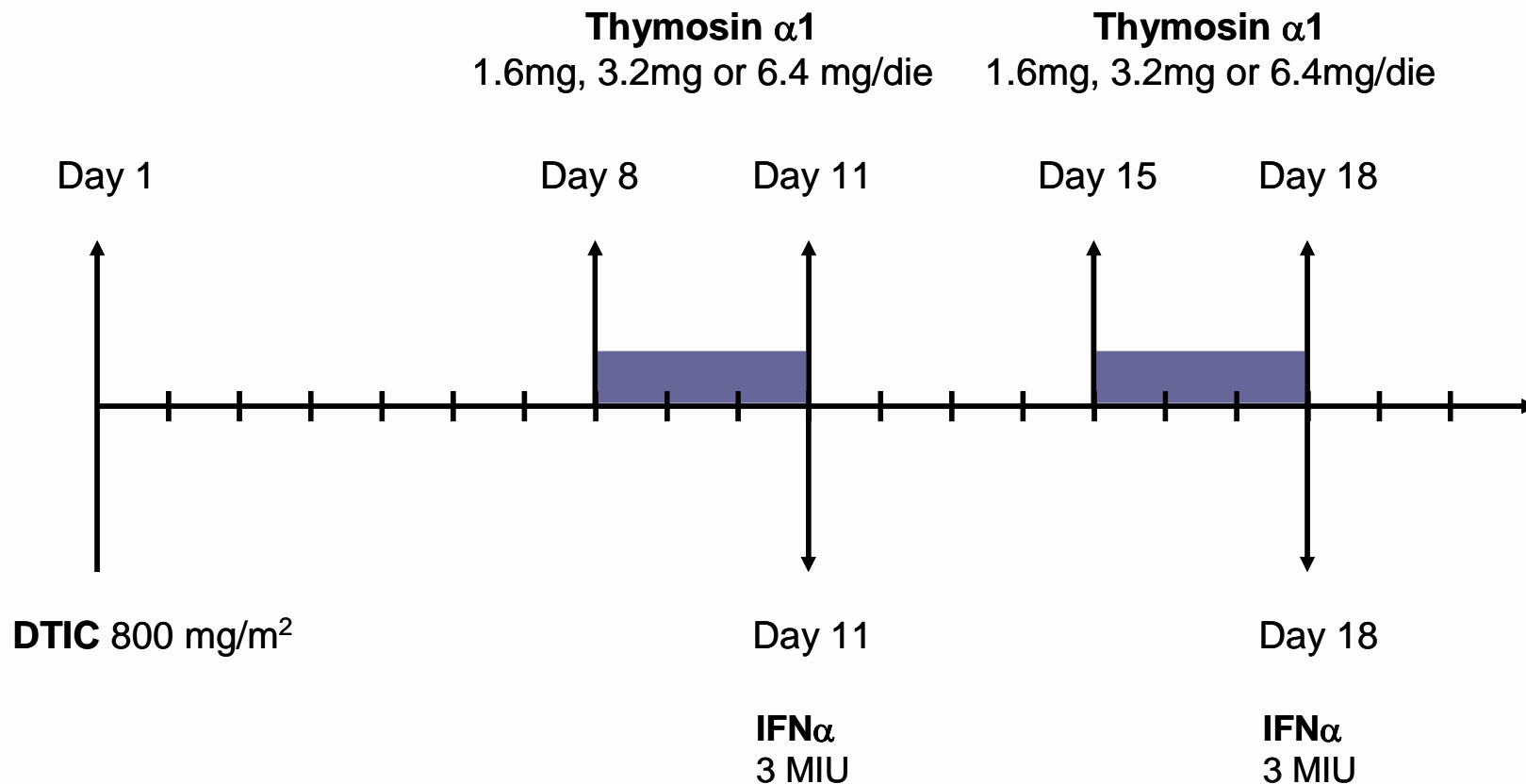
- A dose-finding study to establish the most appropriate thymalfasin-based treatment combination in patients with advanced stage malignant melanoma

Design



T α 1 = thymalfasin; DTIC = Dacarbazine;
IFN α = Interferon alpha

Phase II Treatment Cycle



Thymosin α 1 = thymalfasin; DTIC = Dacarbazine; IFN α = Interferon alpha

BASELINE CHARACTERISTICS		DIT 1.6 (N=97)	DIT 3.2 (N=97)	DIT 6.4 (N=98)	DT 3.2 (N=99)	TOTAL THYMOSIN (N=391)	DI (N=97)
Age (years)	Mean	54	54	56	56	55	57
	Median	57	54	57	56	56	57
Gender (%)	Male	61	48	54	62	56	43
	Female	39	52	46	38	44	57
ECOG PS (%)	PS = 0	74	68	77	73	73	70
	PS = 1	25	32	23	27	27	30
Prior treatment (%)	Immunotherapy	18	12	19	13	16	18
	Chemotherapy	1	0	2	0	1	2
	Radiotherapy	14	15	15	5	13	11
Disease site (%)	M1a	12	11	15	13	13	12
	M1b	24	25	22	24	24	26
	M1c	64	64	62	63	63	62
LDH level, (%)	Low/Normal	64	60	65	63	63	65
	Elevated	36	40	35	37	37	35
Number of Metast Sites (%)	</=2	63	59	65	58	61	53
	>2	37	41	35	42	39	47
Liver Metastases (%)		36	44	40	31	38	39

	DIT 1.6 (N=97)	DIT 3.2 (N=97)	DIT 6.4 (N=98)	DT 3.2 (N=99)	Total T (N=391)	Control (N=95)
Median overall survival (months)	9.26	8.57	10.32	9.3	9.36	6.64
Median progression- free survival (months)	1.87	1.84	1.84	2.04	1.87	1.84
Overall tumor response (n (%))	7 (7.2%)	10 (10.3%)	6 (6.1%)	12 (12.1%)	35 (9.0%)	4 (4.1%)

Conclusions:

- Overall survival increased by up to 3.7 months
- Overall response rate increased up to 3-fold

N = evaluable patients; D = Dacarbazine; I = Interferon alpha; T = thymalfasin; Tot T = all thymalfasin arms; OS = Overall Survival; PFS = Progression-free Survival; ITT = Intent-to-Treat Population

	DIT 1.6 (N=97)	DIT 3.2 (N=97)	DIT 6.4 (N=98)	DT 3.2 (N=99)	Total T (N=391)	Control (N=95)
Hazard Ratio	0.807	0.826	0.745	0.841	0.798	Reference
% Reduction in Risk of Death	19.3	17.4	25.5	15.9	20.2	Reference

Conclusions:

- Relative risk of death reduced by 20.2% (average)
- Relative risk of death reduced by 25.5% for DIT 6.4

N = evaluable patients; D = Dacarbazine; I = Interferon alpha; T = thymalfasin; Tot T = all thymalfasin arms; ITT = Intent-to-Treat Population

	DIT 1.6 (N=71)	DIT 3.2 (N=67)	DIT 6.4 (N=67)	DT 3.2 (N=68)	Tot T (N=273)	DI (N=68)
Median overall survival (months)	12.52	11.99	12.65	13.63	12.55	9.4
Median progression free survival (months)	1.99	2.94	2.63	3.58	2.63	1.94

Conclusions:

- Overall survival increased by up to 4.2 months in normal LDH patients
- Progression-free survival increased from 1.9 months to 2.6 months (average of all thymalfasin arms)

* The level of lactate dehydrogenase (LDH) is a strong prognostic factor for survival, and subjects with elevated LDH levels do not appear to respond as well to treatment as do subjects with normal LDH levels; normal LDH is defined as LDH $\leq 1.2 \times$ ULN (Upper Limit of Normal)

N = evaluable patients; D = Dacarbazine; I = Interferon alpha; T = thymalfasin; Tot T = all thymalfasin arms; OS = Overall Survival; PFS = Progression-free Survival

Hazard Ratios & Reduction of Death – Normal LDH Population

	DIT 1.6 (N=71)	DIT 3.2 (N=67)	DIT 6.4 (N=67)	DT 3.2 (N=68)	Tot T (N=273)	DI (N=68)
Hazard Ratio	0.782	0.744	0.676*	0.726	0.728*	Reference
% Reduction in Risk of Death	21.8	25.6	32.4	27.4	27.2	Reference

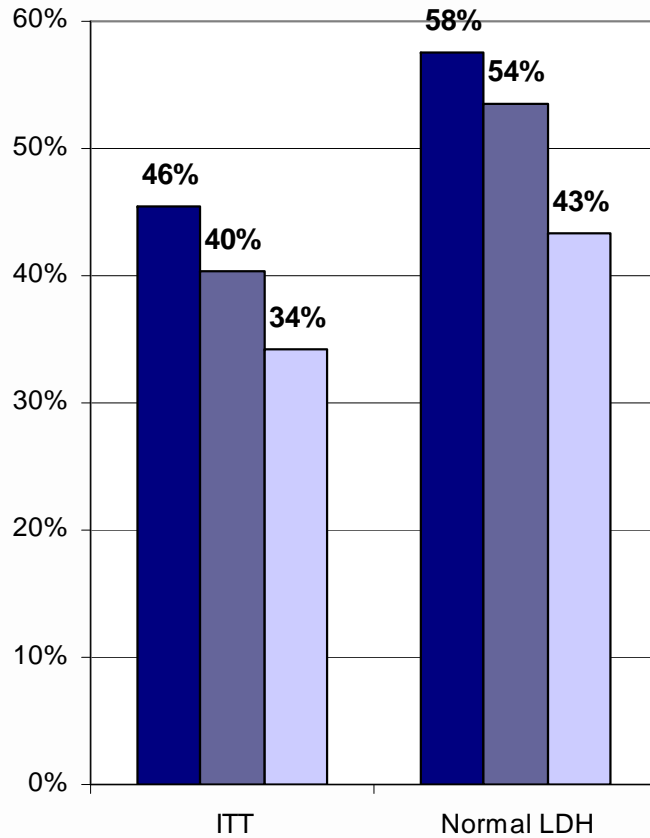
* significant at the 0.05 level

Conclusions:

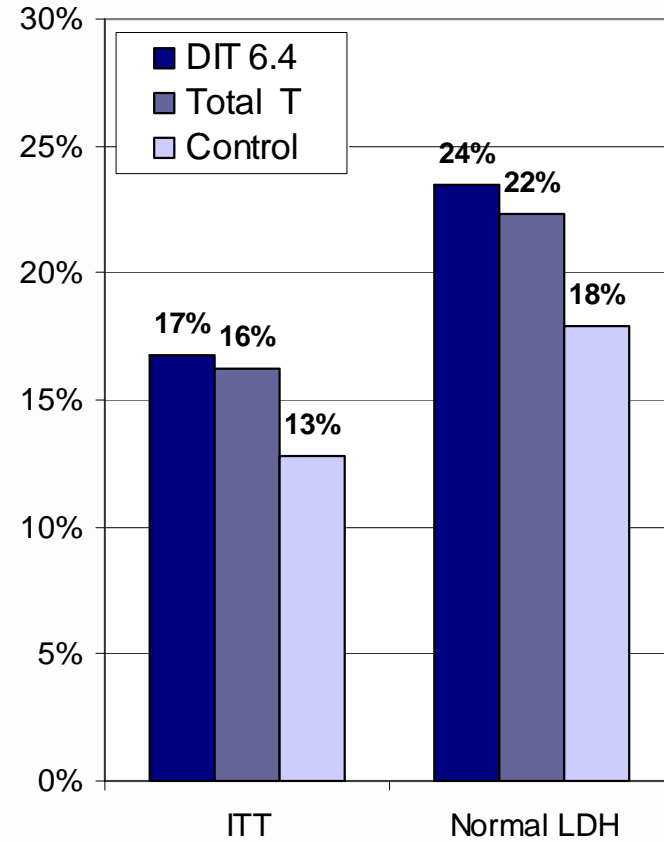
- Relative risk of death reduced by 27.2% (average)
- Relative risk of death reduced by 32.4% for DIT 6.4
- Relative risk of death diminishes with dose going up

N = evaluable patients; D = Dacarbazine; I = Interferon alpha; T = thymalfasin; Tot T = all thymalfasin arms; ITT = Intent-to-Treat Population

1-Year Overall Survival



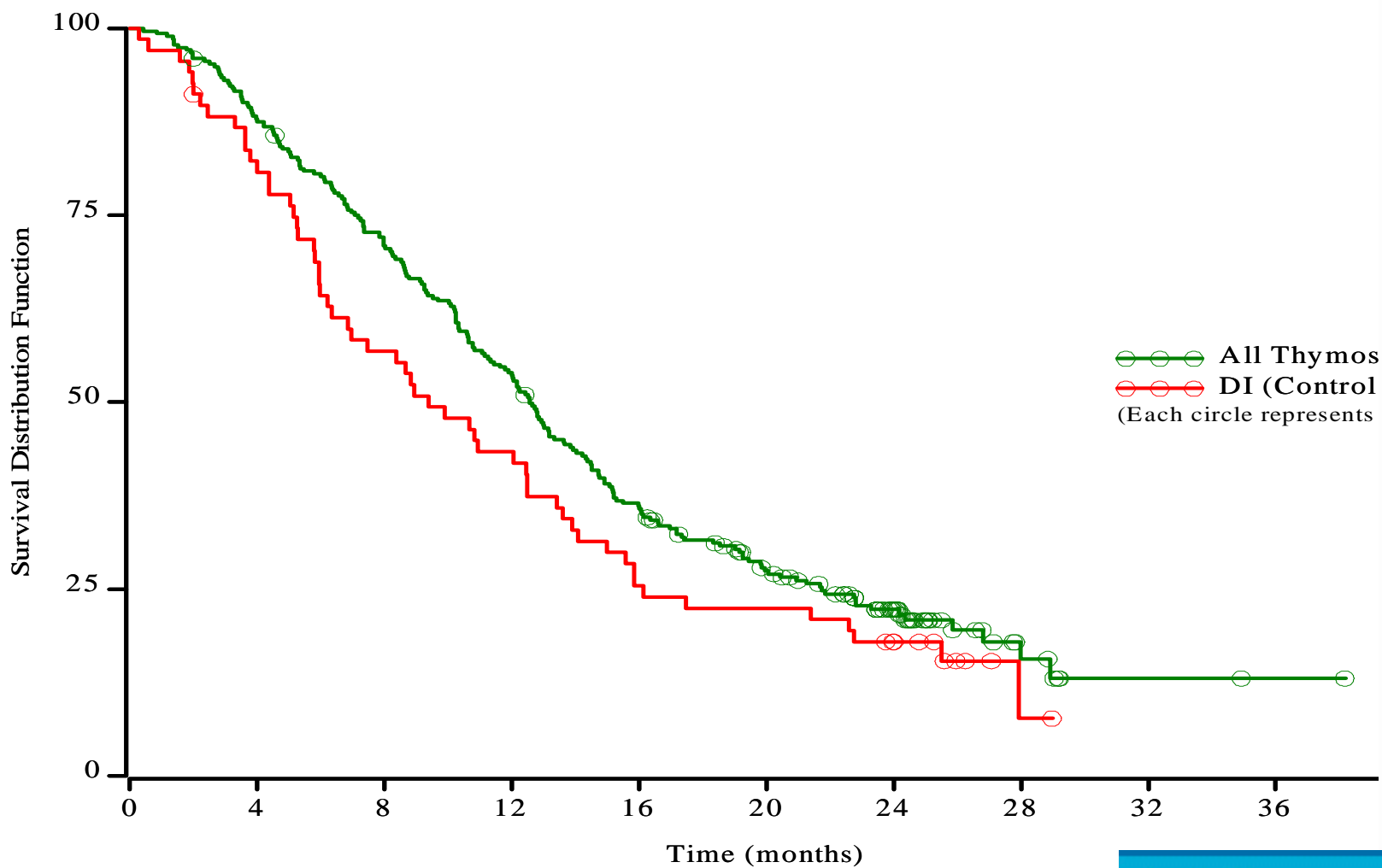
2-Year Overall Survival



N = evaluable patients; D = Dacarbazine; I = Interferon alpha; T = thymalfasin; Tot T = all thymalfasin arms; ITT = Intent-to-Treat Population; normal LDH is defined as LDH $\leq 1.2 \times$ ULN (Upper Limit of Normal)

Overall Survival in Normal LDH Patients

Overall Survival in Subjects with LDH ≤ 1.2 times ULN



	DIT 1.6 (N=97)	DIT 3.2 (N=97)	DIT 6.4 (N=98)	DT 3.2 (N=98)	Total T (N=390)	Control (N=95)
Patients with AEs (n (%))	91 (94%)	91 (94%)	88 (90%)	91 (93%)	361 (93%)	88 (93%)
Not related	79 (81%)	82 (85%)	82 (84%)	83 (85%)	326 (84%)	77 (81%)
Related	58 (60%)	64 (66%)	49 (50%)	40 (41%)	211 (54%)	46 (59%)
Patients with SAEs* (n (%))	71 (73%)	67 (69%)	75 (76%)	74 (75%)	287 (74%)	72 (76%)
Not related	66 (68%)	64 (66%)	71 (72%)	66 (67%)	267 (68%)	65 (68%)
Related	8 (8%)	9 (9%)	6 (6%)	12 (12%)	35 (9%)	13 (14%)

Conclusion:

- No additional toxicities observed with the addition of thymalfasin

Number of patients with Adverse Events (non-Serious AEs) and Serious Adverse Events (SAEs); N = evaluable patients; T = thymalfasin; D = Dacarbazine; I = Interferon alpha

- The addition of Thymalfasin to standard dacarbazine treatment with or without interferon alpha resulted in a reduction in the risk of mortality and disease progression in patients with advanced stage malignant melanoma
- The risk of mortality and disease progression was further reduced in patients with normal LDH levels
- The 6.4 dose appears most promising based on the hazard ratio and % reduction in the risk of death analyses
- Interferon alpha has a minimal effect on efficacy, if any, but adds toxicities to the combination regimen
- Data on Overall Survival support the conduct of a Phase III trial, particularly in the population with normal LDH

- Prospective, double-blind, multicenter, Phase 3 study of DTIC plus thymalfasin compared to DTIC plus placebo in patients with Stage IV melanoma
- Approximately 1050 patients will be randomized
- 120 sites worldwide including sites in the U.S., Canada, Argentina, Europe, New Zealand and Australia
- Subjects will be allocated to one of several strata defined by country and stage of disease (M1a/M1b vs. M1c) at baseline
- Within each stratum, subjects will be randomized in a 1:1 ratio to one of 2 treatment arms, as follows:
 - DTIC plus thymalfasin
 - DTIC plus placebo

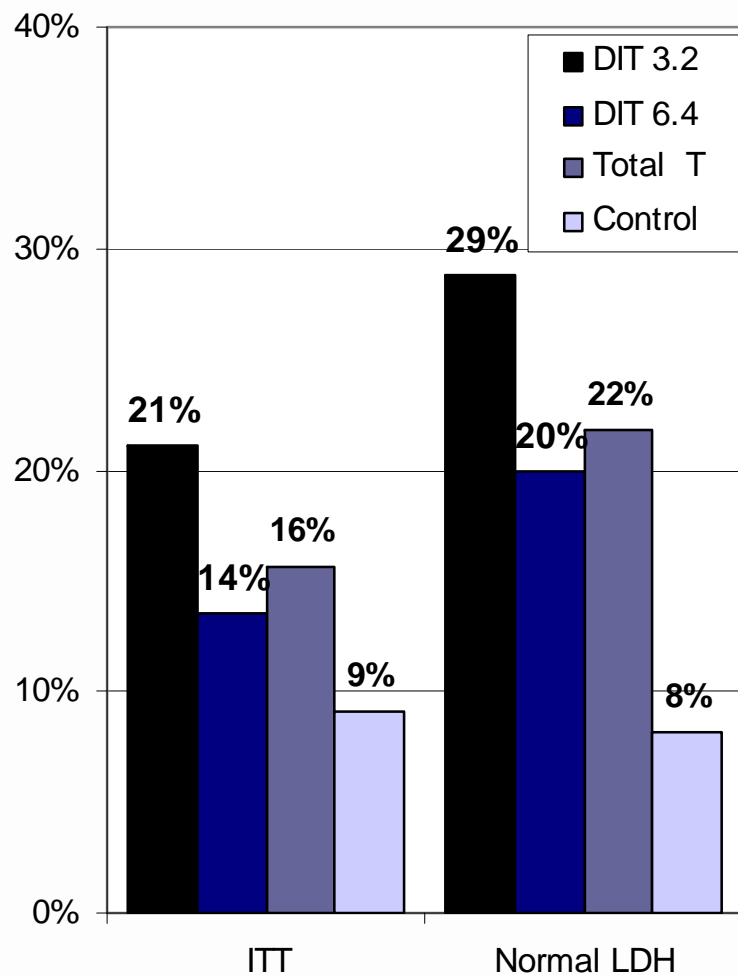
Efficacious	<p>Demonstrated similar or superior efficacy compared to other compounds currently in later-stage clinical development</p> <ul style="list-style-type: none">• Overall survival increased by up to 4.2 months in the normal LDH population
Safe	<p>No toxicities observed in several clinical studies in the US and Europe in more than 2,000 patients</p> <ul style="list-style-type: none">• Safely used in more than 100,000 patients in China and other countries
Combo Therapy	<p>Shown to be synergistic with other emerging therapies</p> <ul style="list-style-type: none">• Could become part of future combination regimens
Adjuvant Therapy	<p>Has potential utility in the adjuvant setting (Stage II/III)</p> <ul style="list-style-type: none">• Biggest target population in melanoma• Potential to replace interferon

Immunomodulatory Effects

- Activates Toll-like Receptor 9 and triggers innate immune response
- Increases lymphocytic infiltration to sites of disease and secretion of chemotactic cytokines which facilitate infiltration
- Increases maturation and differentiation of dendritic cells and up-regulates anti-tumor T cells
- Enhances secretion of thymopoietic cytokines including IFN α , IL-7, and IL-15

Direct Effects on Cancer Cells

- Increases the expression of antigen presenting molecules, such as MHC Class I and II surface marker proteins, which enable the identification and elimination of cancer cells
- Inhibits the growth of cancer cells and stimulates apoptosis of human cancer cells
- Enhances the expression of tumor-associated antigens



6-Month
Progression-
free Survival

D = Dacarbazine; I = Interferon alpha; T = thymalfasin; Total T = all thymalfasin arms; ITT = Intent-to-Treat Population; normal LDH is defined as LDH ≤ 1.2*ULN (Upper Limit of Normal)

Duration of Response – ITT Population

Response Duration	DIT 1.6 (N=97)	DIT 3.2 (N=97)	DIT 6.4 (N=98)	DT 3.2 (N=99)	Total T (N=391)	Control (N=97)
Number of CR/PR	7	10	6	12	35	4
Median duration (months)	7.4	8.3	7.9	7.7	7.6	6.3
25° percentile (months)	3.7	5.8	4.4	3.9	4.4	4.5
75° percentile (months)	12.9	11.2	12.7	14.9	12	8.2
Minimum	3.5	4.3	3.9	1.9	1.9	4.4
Maximum	23.2	17.2	17	20.7	23.2	8.4

D = Dacarbazine; I = Interferon alpha; T = thymalfasin; Total T = all thymalfasin arms; ITT = Intent-to-Treat Population