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GI-5005 THERAPEUTIC VACCINE PLUS PEG-IFN/RIBAVIRIN IMPROVES END OF TREATMENT RESPONSE AT 48 WEEKS VERSUS PEG-IFN/RIBAVIRIN IN NAÏVE GENOTYPE 1 CHRONIC HCV PATIENTS

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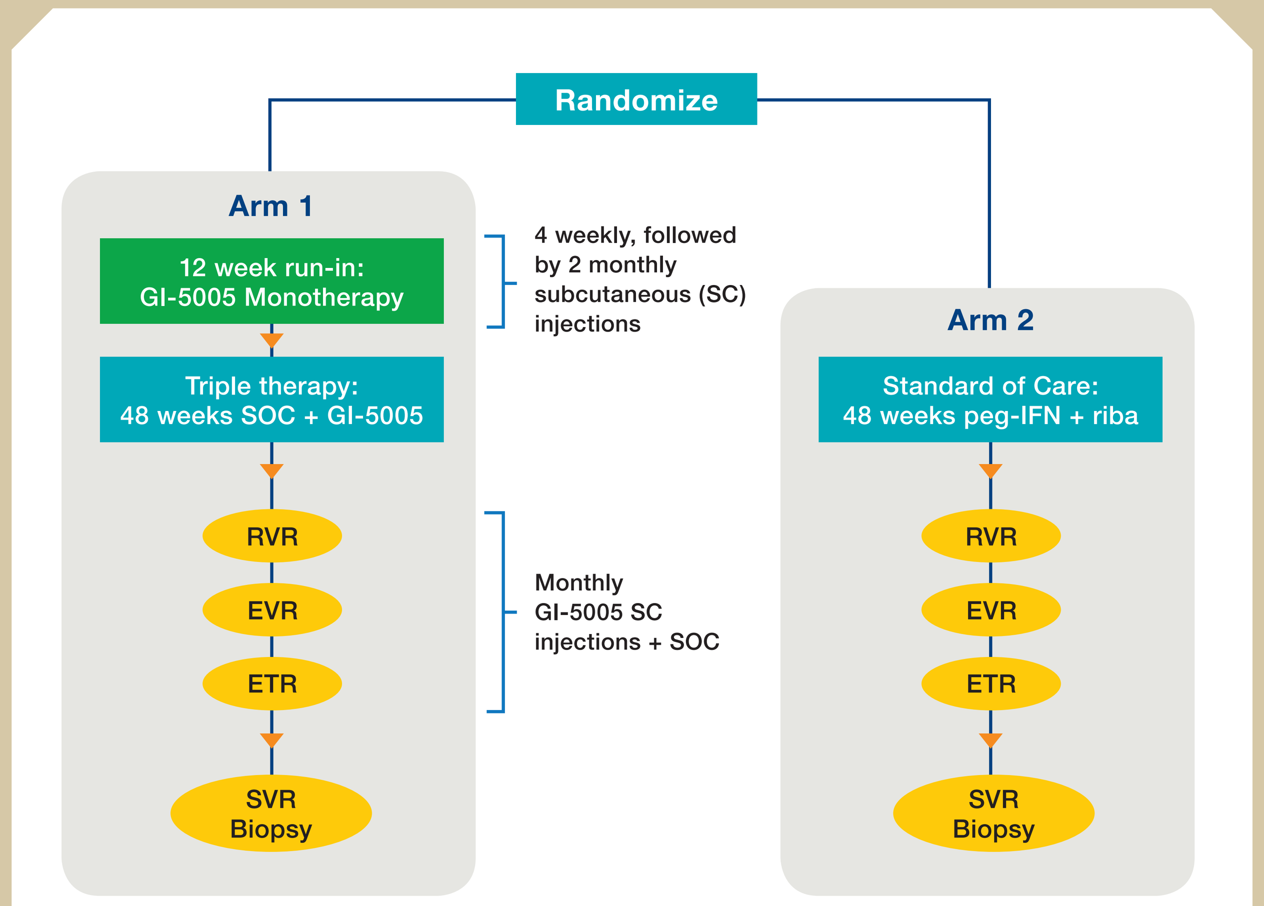
Introduction

Chronic hepatitis C virus (HCV) infection is a health problem that affects 4.8 million people in the US and approximately 180 million people worldwide. The majority of patients exposed to HCV develop chronic infection. However, approximately 20% are able to clear their infection during the acute phase without medical intervention. A strong HCV-specific T cell response has been associated with those spontaneously resolving infections (B. Rehermann 2005 Nat. Rev. Immuno.). The current standard of care (SOC) is pegylated interferon plus ribavirin, which works primarily through the inhibition of viral replication. Only ~40% of HCV genotype 1 patients receiving SOC achieve a sustained virologic response. Achievement of SVR depends on the patient's ability to clear infected cells from the liver and requires long periods of antiviral suppression by SOC to allow a weak host immune response sufficient time to completely eliminate HCV infected cells.

Substantial gains in the treatment of HCV could be attained through a combination approach that inhibits viral replication (SOC or small molecule antivirals) and enhances HCV-specific cellular immune responses (GI-5005). The GI-5005 Tarmogen® product consists of recombinant *S. cerevisiae* yeast expressing large conserved regions from HCV NS3 and Core. In a randomized, placebo-controlled, phase 1b trial, GI-5005 monotherapy was well tolerated, generated strong HCV-specific T cell responses, and favorably impacted ALT and HCV RNA levels. The GI-5005-02 phase 2 study, described herein, is the first clinical study evaluating GI-5005 in combination with SOC versus SOC alone. We have previously shown in this phase 2 study that GI-5005 plus SOC improved second phase viral kinetics, rapid virologic response (RVR), EVR rates, as well as ALT normalization and Fibrotest scores. Shown here are the 48 week complete virologic response and ALT normalization data.



Phase 2 design

GI-5005-02 is a randomized, open-label phase 2 trial evaluating the efficacy, immunogenicity, and safety of GI-5005 in combination with standard of care Pegasys and ribavirin therapy (triple therapy) vs. standard of care (SOC) alone in subjects with genotype 1 HCV. Treatment naïve subjects in Arm 1 receive monotherapy GI-5005 for 12 weeks (4 weekly doses plus 2 monthly doses), followed by 48 weeks of triple therapy (GI-5005 administered monthly with SOC). In Arm 1 prior treatment failures receive 12 week monotherapy run-in, followed by 72 weeks of triple therapy. Arm 2 patients receive Pegasys/ribavirin as per the product labels (72 week treatment duration for prior treatment failures). Randomization was stratified by response to prior therapy (interferon-naïve or non-responder). Efficacy endpoints for the trial include viral kinetics, RVR, EVR, ETR, SVR, Fibrotest, biochemical response by ALT reductions and normalization, and histologic improvement by liver biopsy assessment.

Demographics

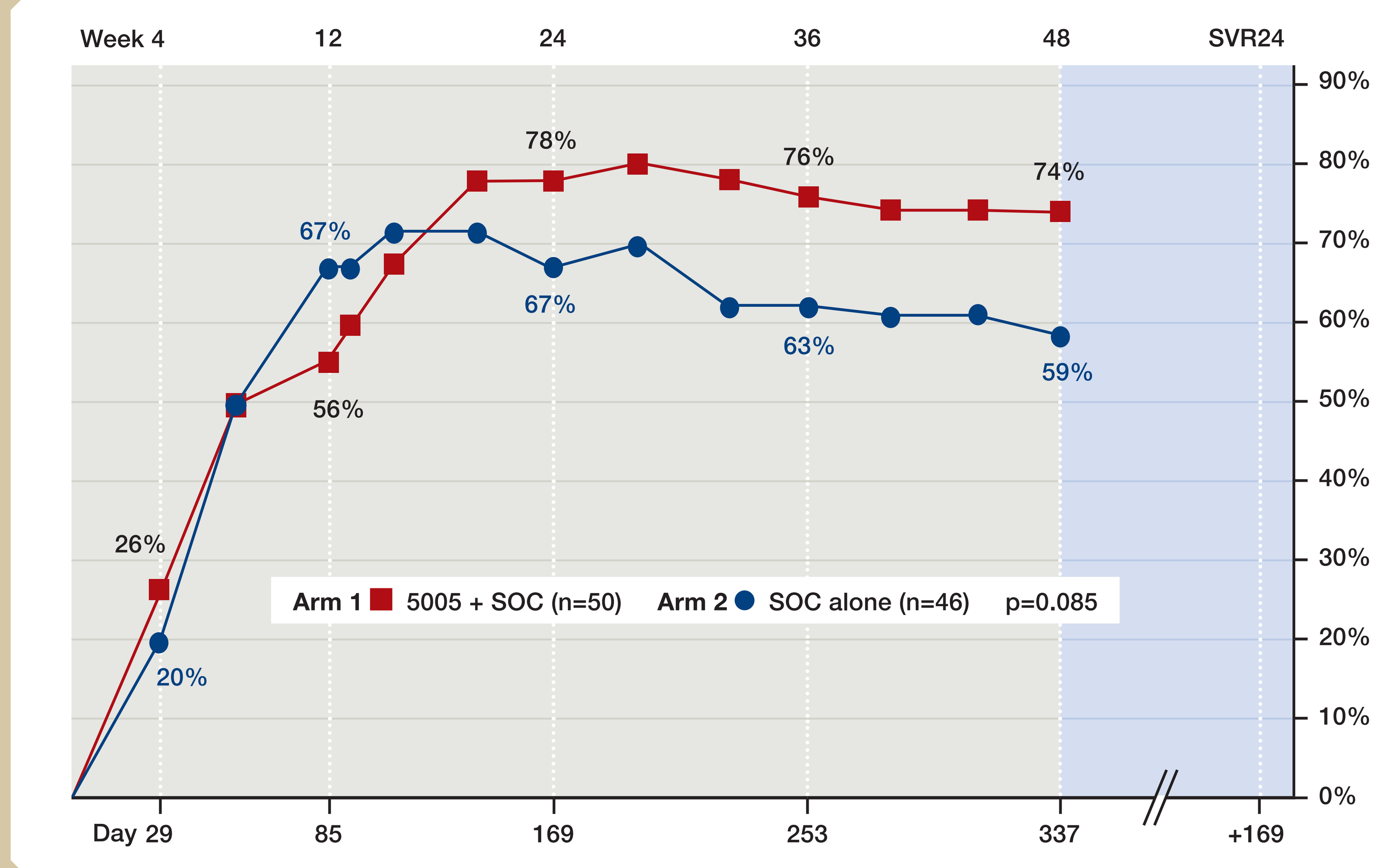
The triple therapy and SOC groups were well balanced for age, gender, race, HCV RNA at baseline (median 6.82 $\log_{10}$ IU/mL in triple vs. 6.86 $\log_{10}$ IU/mL in SOC), ALT at baseline (median 65.5 U/L in triple vs. 61.0 U/L in SOC), and prior response to SOC (73.6% naïve in triple vs. 72.1% naïve in SOC).

Variable	Treatment Group		Total (n=140)
	SOC + GI-5005 (n=72)	SOC Alone (n=68)	
HCV Genotype			
Type 1	7 (9.7)	11 (16.2)	18 (12.9)
Type 1a	39 (54.2)	37 (54.4)	76 (54.3)
Type 1b	26 (36.1)	20 (29.4)	46 (32.9)
Prior Treatment Status			
Naïve	53 (73.6)	49 (72.1)	102 (72.9)
Non-response to prior treatment	19 (26.4)	19 (27.9)	38 (27.1)

Variable	Treatment Group		Total (n=140)
	SOC + GI-5005 (n=72)	SOC Alone (n=68)	
Sex			
Male	42 (58.3)	45 (66.2)	87 (62.1)
Female	30 (41.7)	23 (33.8)	53 (37.9)
Race			
White	50 (69.4)	47 (69.1)	97 (69.3)
African American	7 (9.7)	11 (16.2)	18 (12.9)
Hispanic	6 (8.3)	6 (8.8)	12 (8.6)
Asian	6 (8.3)	4 (5.9)	10 (7.1)
Other	3 (4.2)	0 (0.0)	3 (2.1)
Age			
18 to <25 years	3 (4.2)	3 (4.4)	6 (4.3)
25 to <45	20 (27.8)	14 (20.6)	34 (24.3)
45 to <65	47 (65.3)	47 (69.1)	94 (67.1)
65 to <75	2 (2.8)	4 (5.9)	6 (4.3)
Median (years)	48.0	49.0	48.0
Range	20 to 74	20 to 68	20 to 74

Variable	Treatment Group		Total (n=140)
	SOC + GI-5005 (n=72)	SOC Alone (n=68)	
ALT (U/L)[1]			
Mean (SD)	74.4 (41.2)	65.1 (47.3)	70.0 (44.3)
Median	63.0	53.5	57.0
Range	17 to 266	14 to 275	14 to 275
HCV RNA ($\log_{10}$ IU/mL)[2]			
Mean (SD)	6.58 (0.63)	6.64 (0.81)	6.61 (0.72)
Median	6.72	6.79	6.78
Range	4.64 to 7.48	3.01 to 7.72	3.01 to 7.72

[1] *ALT baseline values taken on Day1 of study therapy*
[2] *HCV baseline values taken on Day 1 of SOC*



Complete virologic response in naïve patients at end of treatment (week 48)

A sustained improvement of complete virologic response (HCV RNA < 25IU/mL by PCR assay) was observed favoring the triple therapy group beginning by week 20 and maintained for the remaining 28 weeks of therapy. At week 48 the complete virologic response was 74% triple vs 59% SOC (mITT; all patients receiving at least 1 dose of combination therapy). A consistent treatment effect was observed at 48 weeks using the ITT population (all randomized patients); 70% triple vs 55% SOC (p value = 0.092) . The treatment effect for complete virologic response favors triple therapy and is > 10% for all major subgroups including all patients (59.7 vs 48.5%), Naïve (69.8% vs 55.1%), Naïve&White (71.8% vs 60.6%), Naïve&Non-White (64.3% vs 43.8%), Naïve Hispanic or Black (60% vs 33%), and Naïve&non-Black (71.1% vs 60%). Blacks were not comparably represented in the naïve subgroups and a meaningful comparison could not be performed. The NR groups had similar response at 48 weeks (31.6% in both groups) and will receive an additional 24 weeks of therapy as per the protocol. Patients will be followed through sustained virologic response at 24 weeks post-treatment, at which time the data will be reported.

Safety

During the 12 week GI-5005 monotherapy period no patients discontinued therapy due to adverse events (AE). Comparable numbers of patients from the triple therapy group and SOC group discontinued therapy due to adverse events; 7/65 (10.8%) SOC group discontinued SOC (2 additional patients discontinued SOC during salvage therapy), 5/69 (7.7%) triple therapy group discontinued SOC, 6/69 (8.7%) triple therapy group discontinued GI-5005. During the treatment period 7/69 (10.1%) SAEs were observed in the triple therapy group (related only to SOC) compared to 4/65 (6.2%) in the SOC group. Several serious adverse events in the triple therapy group were clearly unrelated to therapy (1 cat bite, and 2 events of substance abuse).

Discontinuous due to adverse events

	SOC + GI-5005	SOC Alone
	n=69	n=65
Discontinued only SOC	1 (1.4%)	7 (10.8%)
Discontinued only GI-5005	2 (2.9%)	n/a
Discontinued both SOC and GI-5005	4 (5.8%)	n/a
Total discontinuations	7 (10.1%)	7 (10.8%)

**analysis of patients receiving at least 1 dose of any study drug*

Common non-serious adverse events

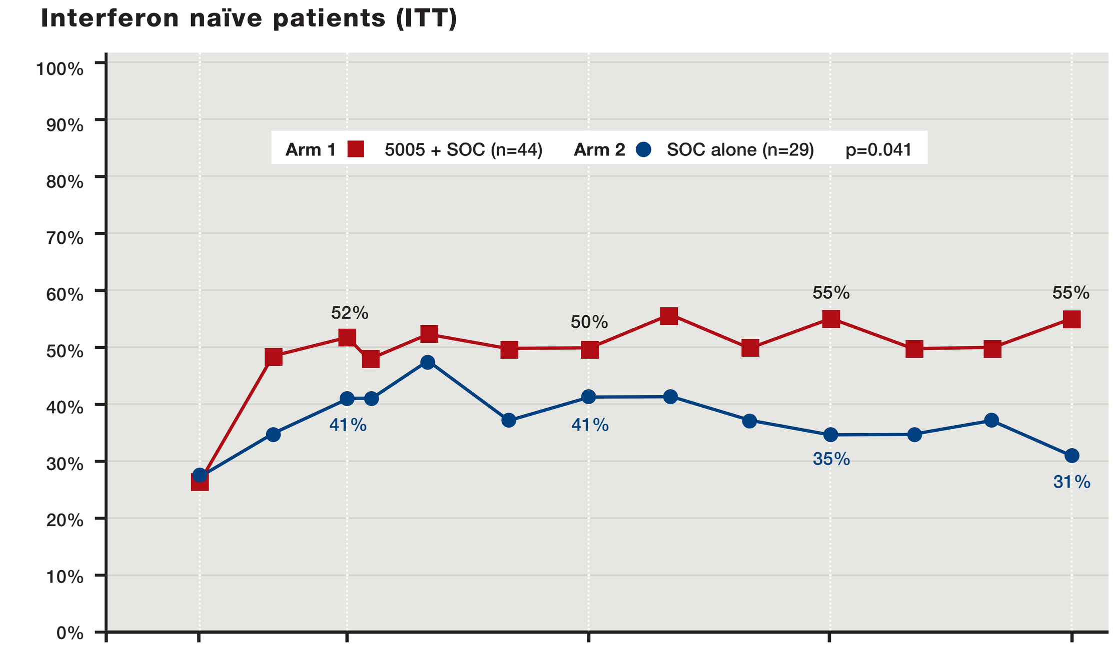
	SOC + GI-5005	SOC Alone
	n=69	n=65
Fatigue	35 (51%)	42 (65%)
Nausea	25 (36%)	25 (39%)
Headache	25 (36%)	26 (40%)
Anaemia	19 (28%)	13 (20%)
Pyrexia	19 (28%)	16 (25%)
Rash	18 (26%)	15 (23%)
Insomnia	17 (25%)	23 (35%)
Injection site reaction	16 (23%)	23 (35%)
Irritability	15 (22%)	17 (26%)
Depression	14 (20%)	21 (32%)
Cough	14 (20%)	13 (20%)
Chills	12 (17%)	15 (23%)
Diarrhoea	11 (16%)	14 (22%)
Myalgia	10 (15%)	15 (23%)
Pruritus	9 (13%)	13 (20%)
Dizziness	8 (12%)	14 (22%)
Back pain	5 (7%)	13 (20%)

**any adverse event preferred term with an incidence or >/= 20% in either group*
**analysis of patients receiving at least 1 dose of any study drug*

ALT Normalization

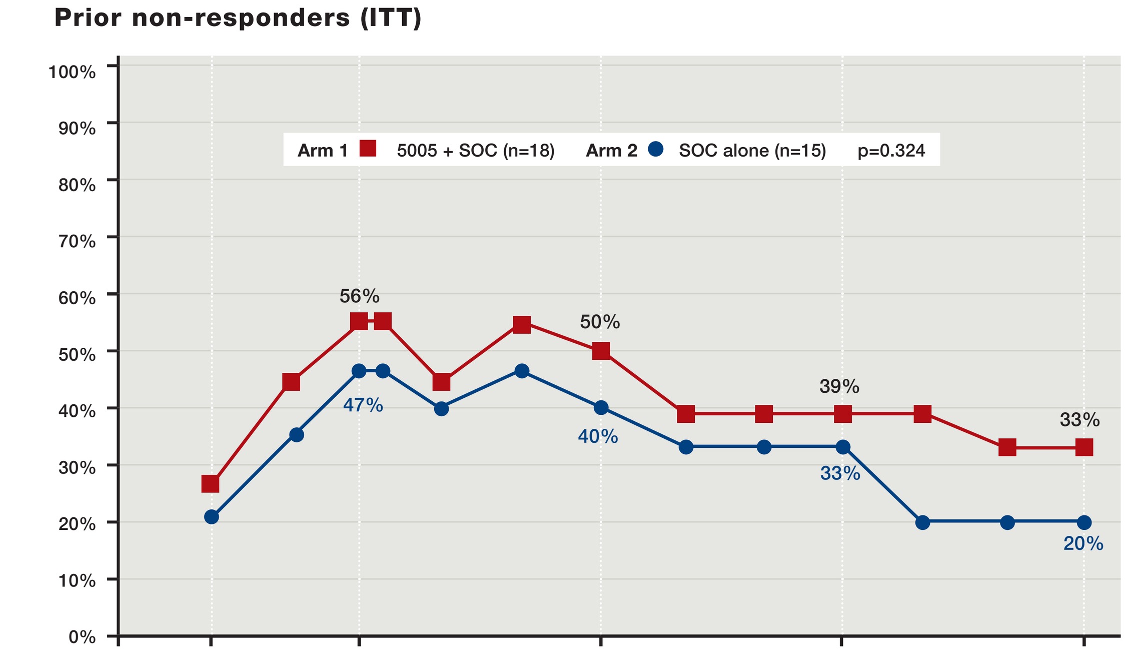
A higher proportion of patients treated with GI-5000 triple therapy normalized their ALT compared to patients receiving SOC alone. This treatment effect occurred early during therapy and was maintained for the entire treatment period in all patients, treatment naïve, and prior non-responders. At 48 weeks the ALT normalization was 48% triple vs 27% SOC in all patients, 55% triple vs 31% SOC in naïve patients, and 33% triple vs 20% SOC in NRs. ALT normalization is defined as >/= 2 consecutive ALT values < ULN.

Interferon naïve patients (ITT)



ALT normalization defined as >/= 2 consecutive visits at least 14 days apart.

Prior non-responders (ITT)



ALT normalization defined as >/= 2 consecutive visits at least 14 days apart.

Conclusions

- GI-5005 is well tolerated and showed comparable rates of serious adverse events and discontinuations due to adverse events compared to SOC
- GI-5005 plus SOC demonstrated a 15% improvement in complete virologic response at 48 weeks in naïve patients at end of treatment
- GI-5005 plus SOC demonstrated a nearly 2-fold improvement in the proportion of treatment naïve patients who normalize ALT during treatment
- GI-5005 plus SOC demonstrated a 13% improvement in the proportion of prior non-responders who normalize ALT during treatment
- GI-5005 in combination with SOC represents a novel triple therapy approach with no significant additional toxicities and a convenient monthly dosing regimen
- GI-5005 in combination with different inhibitors of viral replication, such as small molecule polymerase and protease inhibitors may result in the future ability to further improve response rates or to spare or eliminate components of the current standard of care (pegylated interferon/ribavirin)

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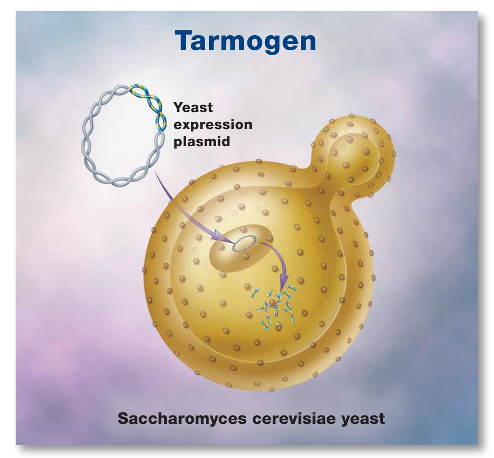
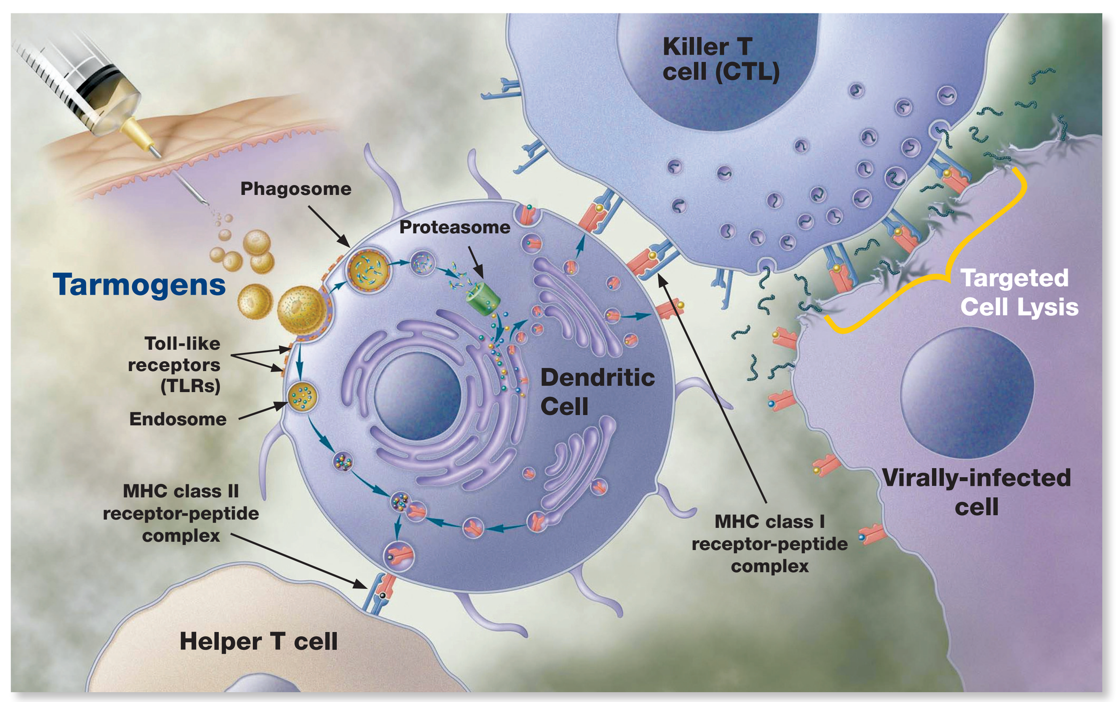
Active immunotherapy with yeast-based Tarmogens



Tarmogen® products are whole, heat-killed recombinant *Saccharomyces cerevisiae* yeast modified to express one or more protein targets that stimulate the immune system against diseased cells. The target antigens are markers of diseased cells and can be conserved viral proteins, mutated proteins unique to cancer cells, or proteins over-expressed in cancer. To create a new Tarmogen, DNA encoding target protein antigens is engineered into a yeast expression plasmid. The heat-inactivated yeast, with the target protein inside, is administered as the final Tarmogen product. Tarmogens stimulate the innate and antigen-specific immune system to produce a highly specific and potent T cell response against the diseased cell, with little or no impact on healthy cells.[1]



Tarmogens are administered subcutaneously and are avidly taken up by antigen presenting cells (APCs), such as dendritic cells and macrophages in a process mediated by Toll-like receptors (TLRs) found on the cell surface. Uptake of Tarmogens activates the APCs and results in their migration to lymph nodes and their production of immune-stimulating cytokines.[2]

Tarmogens are degraded inside APCs within hours and the target antigens are presented by MHC class I and II receptors on the APC surface. Tarmogens are initially digested in phagosomes, whereupon the antigens are delivered to the cytosol, and these proteins are cleaved by proteasomes into small peptides. These small peptides are loaded into newly folded MHC class I receptors in the secretory pathway of the APC. The peptide-MHC I receptor complex is shuttled to the surface of the APC, where the antigenic peptides are presented to CD8+ killer T cells (causing activation of these cells). Tarmogens are also digested in endosomes, and the product-associated peptides are loaded into MHC class II receptors for antigen presentation to CD4+ helper T cells (causing activation of these cells).[2]

Therapeutic benefit from the Tarmogen is driven by the targeted activation of the immune system. Tarmogens activate killer T cells capable of locating and destroying the target cancer or virally-infected cells. Repeated dosing with Tarmogens further increases the number of T cells available to eliminate diseased cells. In summary, Tarmogens couple the innate immune response to yeast with potent activation of antigen-specific cellular immune responses against cancer cells or virally infected cells.[3,4]

For more information, visit www.globeimmune.com.

[1] Munson et al. "Coupling Innate and Adaptive Immunity with Yeast-Based Cancer Immunotherapy" Chapter 9; Cancer Vaccines and Tumor Immunity. January 2008

[2] Bernstein et al. "Recombinant Saccharomyces cerevisiae (yeast-CEA) as a potent activator of murine dendritic cells." Vaccine (2008) 26, 509-521.

[3] Wansley et al. "Vaccination with a Recombinant Saccharomyces cerevisiae Expressing a Tumor Antigen Breaks Immune Tolerance and Elicits Therapeutic Antitumor Responses" Clinical Cancer Research. July 2008.

[4] Haller et al. "Whole recombinant yeast-based immunotherapy induces potent T cell responses targeting HCV NS3 and Core proteins" Vaccine (2007) 25, 1452-1463.

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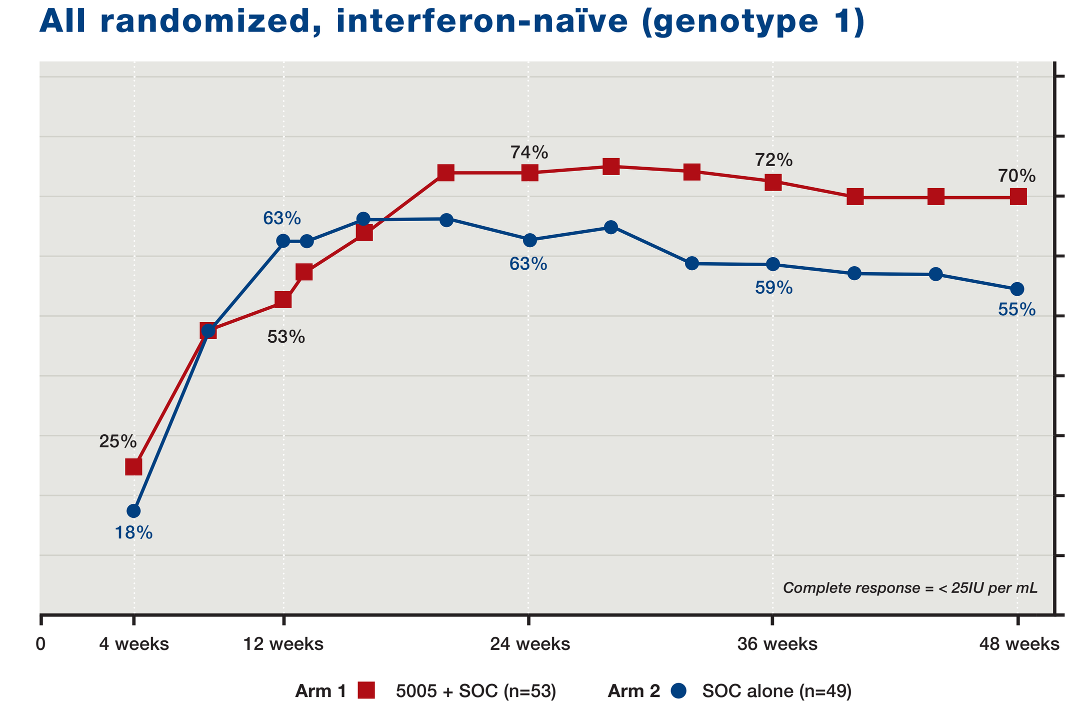
Background and aims: GI-5005 is a whole heat-killed *S. cerevisiae* therapeutic vaccine expressing HCV NS3 and Core antigens. GI-5005 elicits antigen-specific T-cell responses (Hepatology 2007; 46: 816A) with the goal of improving the rate of immune-mediated elimination of HCV-infected hepatic cells.

Methods: Naïve and non-responder (NR) chronic HCV genotype 1 patients were randomized 1:1, and stratified by prior treatment status in this open label trial; Arm 1- GI-5005 monotherapy run-in consisting of five weekly followed by 2 monthly subcutaneous (SC) doses of 40YU (1 YU = 10_7 yeast) GI-5005 over 12 weeks, followed by triple therapy consisting of monthly 40YU GI-5005 doses plus 48 weeks pegIFN a-2a/ribavirin (SOC), Arm 2- SOC alone. NRs will receive 72 weeks of triple therapy versus SOC.

All randomized, interferon-naïve (genotype 1)



Results: Triple therapy was well tolerated with no significant new toxicities observed and an equivalent number of SOC discontinuations due to adverse events in each group; Triple therapy - 5/68 (7.3%) and SOC 5/65 (7.7%). Improvement in end of treatment response (HCV RNA < 25IU/mL by PCR assay at 48 weeks) was observed in naïve genotype 1 patients in the triple therapy group compared to SOC alone (all randomized); Triple therapy - 37/53 (70%) vs SOC- 27/49 (55%), one-tailed Fisher's exact test p=0.09. Complete response (HCV RNA <25IU/mL) was assessed in NRs at week 48 (all randomized); Triple therapy - 6/19 (32%) vs SOC- 6/19 (32%). Race, baseline viral load, SOC compliance, and discontinuations did not reveal a significant influence on the observed treatment effect.

Conclusions: Triple therapy with GI-5005 plus pegIFN/ribavirin is well tolerated and improved week 48 ETR rates compared to SOC in genotype 1 naïve patients. Final sustained virologic response 24 weeks post-treatment will be reported after completion of the trial. These data support further investigation of GI-5005 triple therapy as well as novel combination strategies for GI-5005 with other HCV inhibitory agents.