Rintatolimod (Ampligen®): An Investigational Immunomodulatory Agent Targeted at Cancers of High-Unmet Need

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Marie Sklodowska-Curie Symposium on Cancer Research and Care
September 8th-10th, 2022

Lead Program Ampligen® (rintatolimod)

Significant Opportunity Across Multiple Disease Areas

Generally well-tolerated with over 100,000 IV doses in humans

Clinically tested in oncology as a single-agent therapeutic and in combination with other agents

Potential in oncology to enhance efficacy of PD-1 and PD-L1 checkpoint inhibitors[1]

Phase 3 in ME/CFS completed in U.S. – NDA filing pending confirmatory Phase 3 following complete response letter; Approved for the treatment of severe CFS in Argentina

Immuno-Oncology

Virology

Immune System Disorders

1: Animal experiments support expectations of human responses

Ampligen® Induces a Wide Range of Immunologic and Anti-tumor Activities

Immuno-modulator that selectively activates TLR3 pathway

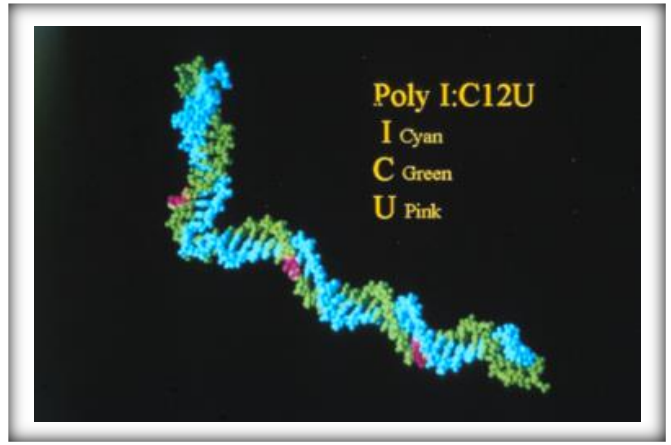
Exclusively activates TRIF adaptor and avoids MyD88 inflammatory pathway used by all other TLRs[1]

Promotes selective attraction of CTLs (Teff) with concomitant increase in Teff/Treg ratio in the TME[2]

Only known TLR3 agonist to avoid helicase activation of NF-κB[3]

Demonstrates positive increase of ratio of CXCL10 (CTL-attractant) to CCL22 (Treg-attractant) and increased ratio of CTL/Treg markers[4,5]

Induces epitope spreading and cross-reactive IgA antibody formation[6]



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1: Mitchell. (2016); 2: Theodoraki, et al. (2018); 3: Theodoraki, et al. (2017); 4: Kalinski, et al. (2016); 5. Kalinski Unpub. Data; 6: Overton, et al. (2014)

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Immuno-Therapy Targeting Multiple Cancers with High-Unmet Need

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The Critical Unmet Need in Oncology

Current Therapies are Effective but Only in a Subset of Patients, Leaving Many in Need of Better Options

United States Statistics

Ovarian Cancer[1]

21,410 New Cases Annually

13,770 Deaths Annually

80% recurrence rate following chemotherapy[2]

Pancreatic Cancer[1]

60,430 New Cases Annually

48,220 Deaths Annually

Breast Cancer[1]

281,550 New Cases Annually

43,600 Deaths Annually

12-20% of cases are triple-negative[3]

Colorectal Cancer[1]

149,500 New Cases Annually

52,980 Deaths Annually

Melanoma[1]

106,110 New Cases Annually

7,180 Deaths Annually

1: National Cancer Institute: Surveillance, Epidemiology and End Results - Ovarian Cancer; Pancreatic Cancer; Breast Cancer; Melanoma; 2: NIH National Cancer Institute Surgery for Recurrent Ovarian Cancer Does Not Improve Survival, December 10, 2019, by NCI Staff; 3: Manjunath M, Choudhary B. Triple-negative breast cancer: A run-through of features, classification and current therapies. Oncol Lett. 2021;22(1):512. doi:10.3892/ol.2021.12773

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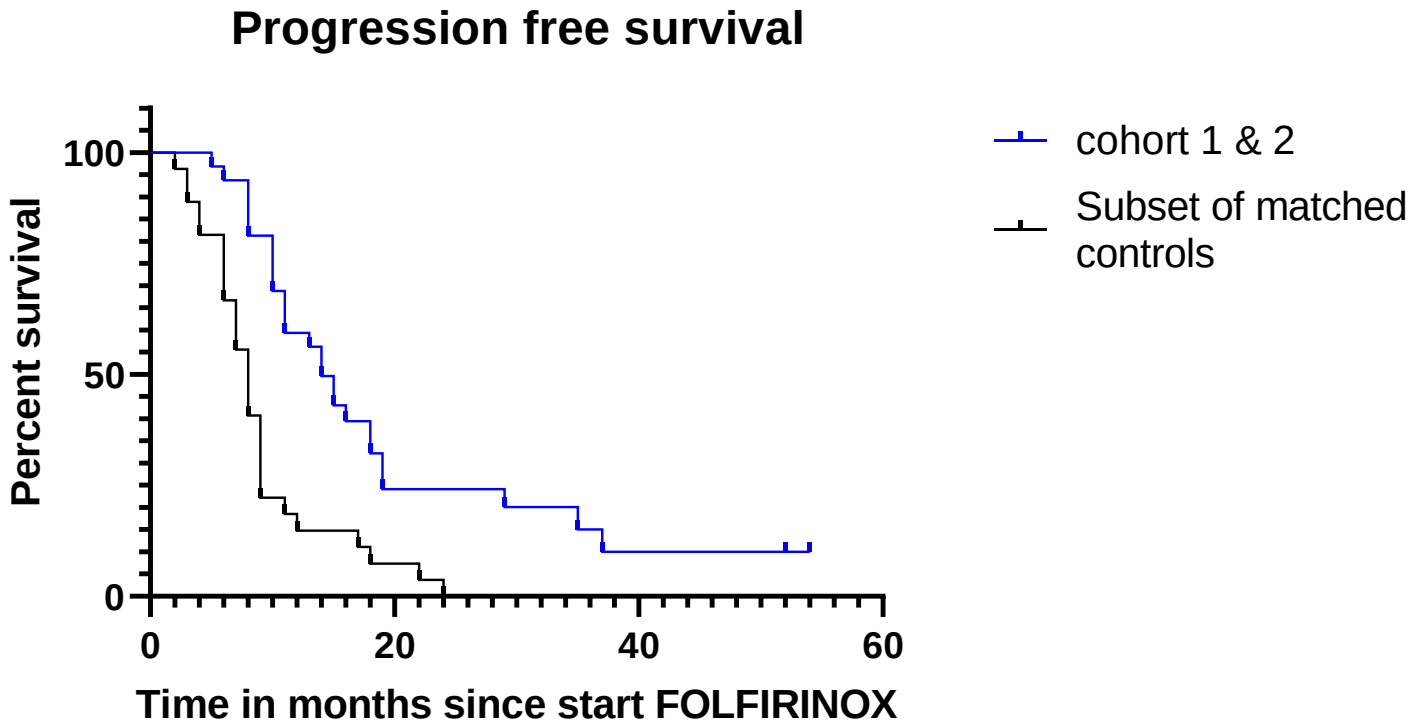
Broad Oncology Pipeline Across Multiple Unmet Needs

Indications	Approach	Partner	Preclinical	Phase 1	Phase 2	Phase 3	Approval
Ovarian Cancer (Advanced, Recurrent)	Chemokine Modulatory Regimen	UPMC LIFE CHANGING MEDICINE					
Colorectal Cancer (Metastatic)	Chemokine Modulatory Regimen	ROSWELL PARK COMPREHENSIVE CANCER CENTER					
Breast Cancer (Metastatic Triple-Negative)	Chemokine Modulatory Regimen / Pembrolizumab	ROSWELL PARK COMPREHENSIVE CANCER CENTER					
Ovarian Cancer (Advanced, Recurrent)	Combination: Pembrolizumab	UPMC LIFE CHANGING MEDICINE					
Prostate Cancer (Early-Stage)	Combination: Intron A	ROSWELL PARK COMPREHENSIVE CANCER CENTER					
Pancreatic Cancer	Single Agent	Erasmus MC University Medical Center Rotterdam	Early Access Program				
Pancreatic Cancer (Locally Advanced)	Ampligen following FOLFIRINOX	AIM ImmunoTech					
Breast Cancer (Early-Stage Triple- Negative)	Chemokine Modulatory Plus Neoadjuvant Chemo	ROSWELL PARK COMPREHENSIVE CANCER CENTER					
Pancreatic Cancer	Ampligen Plus Checkpoint Inhibitor	University of Nebraska Medical Center BREAKTHROUGHS FOR LIFE					
Melanoma	Single Agent	AIM ImmunoTech					
Melanoma (Refractory)	Combination Tumor-Selective Chemokine Modulation	ROSWELL PARK COMPREHENSIVE CANCER CENTER					

Rintatolimod (Ampligen®) Maintenance Therapy after FOLFIRINOX

Erasmus MC



Number at risk:				
Cohort 1&2	32	8	3	0
Controls	27	0	0	0

Study population:

Patients with metastatic or locally advanced non operable pancreatic cancer after FOLFIRINOX

Stable disease after min. 8 cycles, SIII at baseline <900, CA19.9 <1000

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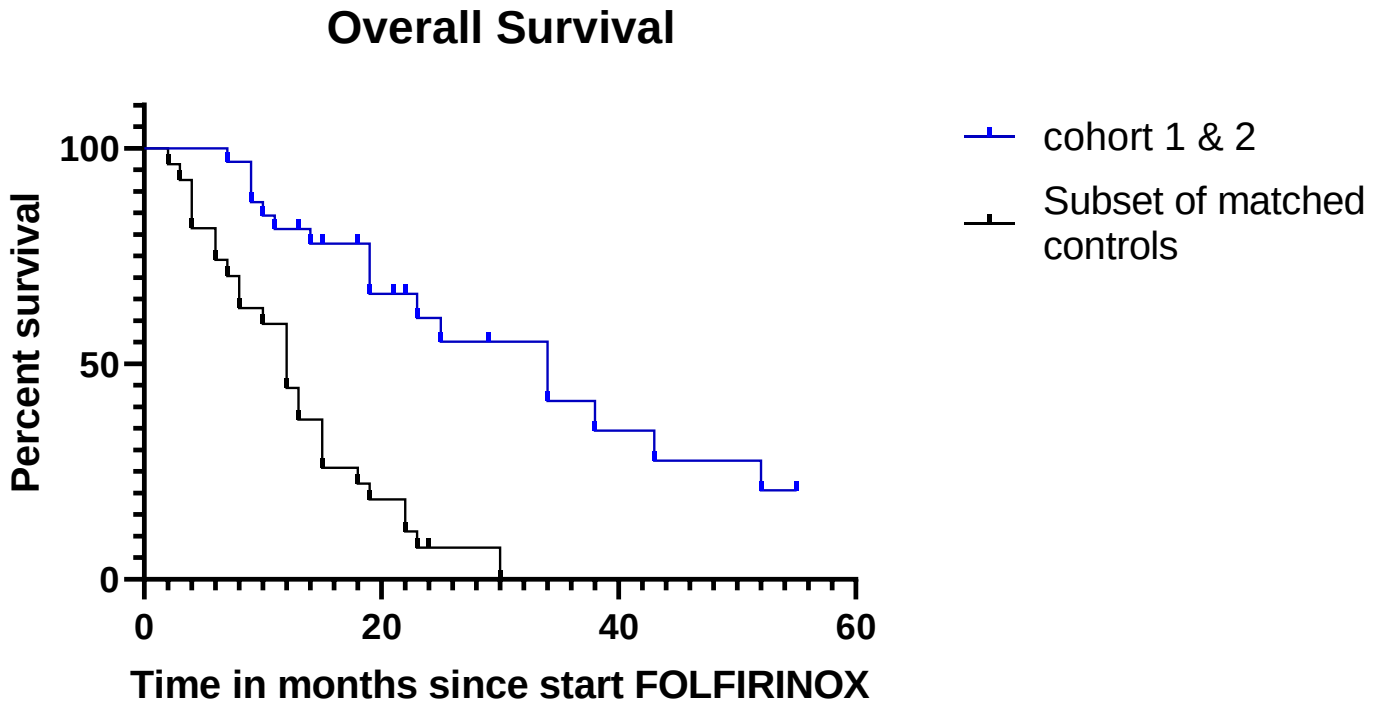
Rintatolimod (Ampligen®) Maintenance Therapy after FOLFIRINOX

Erasmus MC



Number at risk:				
Cohort 1&2	32	20	6	0
Controls	27	6	0	0

Study population:

Patients with metastatic or locally advanced non operable pancreatic cancer after FOLFIRINOX

Stable disease after min. 8 cycles, SIII at baseline <900, CA19.9 <1000

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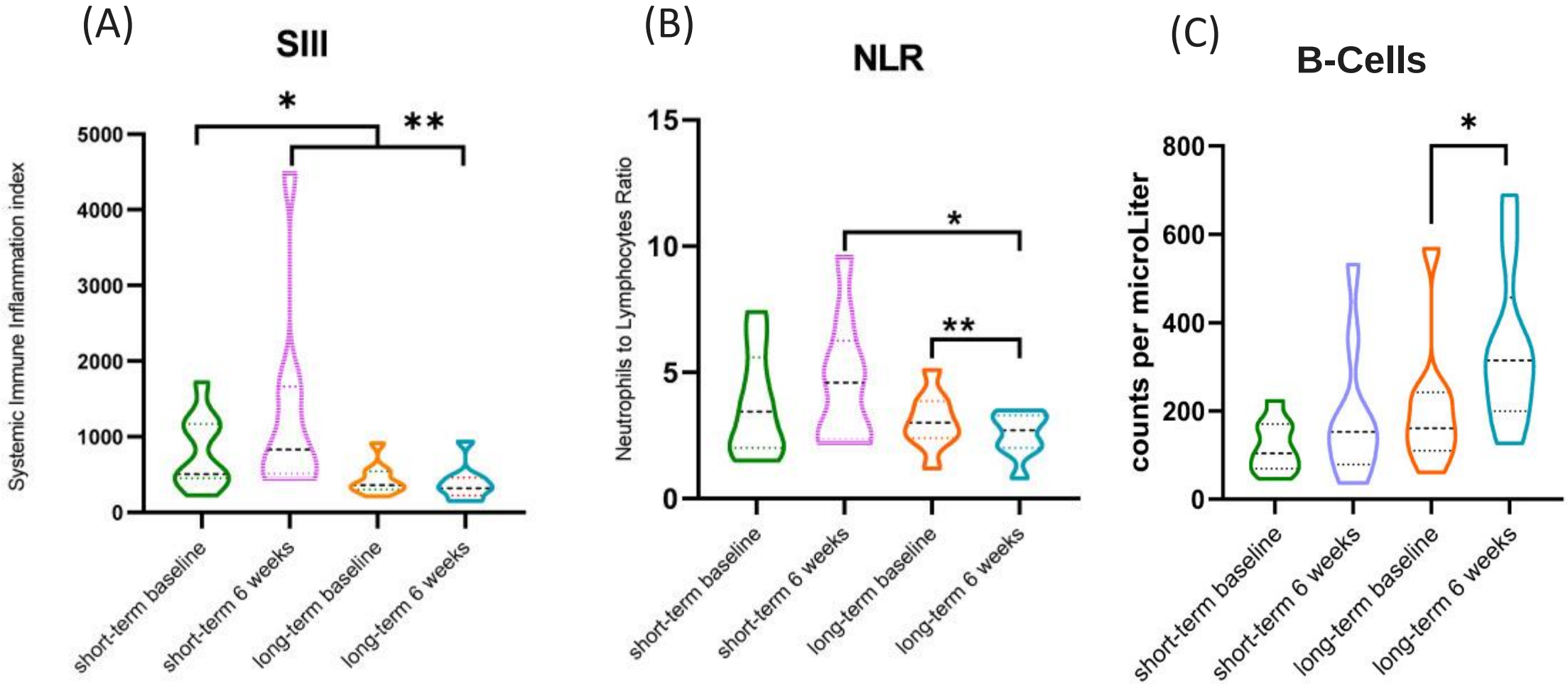
Long-term Survivors Exhibit Decreased SIII and NLR as well as Increased B-Cell Counts



(A) Systemic immune inflammation Index (SIII) in short-term survivors (n=9) and long-term survivors (n=9). * p=0.010, ** p=0.005 (Mann-Whitney U test).
(B) Neutrophil to lymphocyte ratio (NLR) in short-term and long-term survivors * p=0.006, ** p=0.014 (Mann-Whitney U test).
(C) B cells in circulating blood of short-term and long-term survivors * p=0.002 (Mann-Whitney U test).

el Haddaoui *Cancers* **2022**, *14*, 1377. https://doi.org/10.3390/cancers14061377

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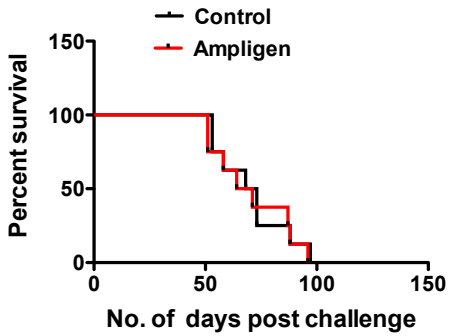
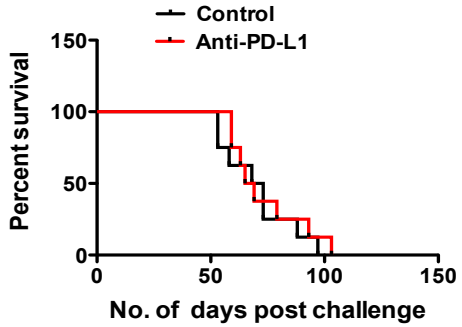
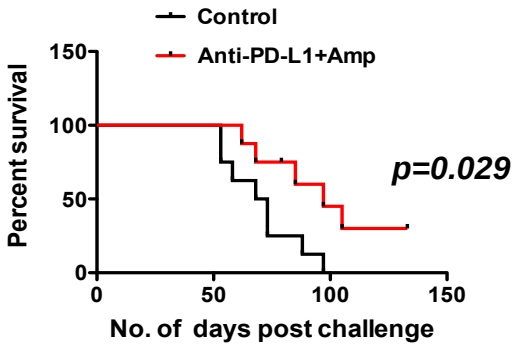
Synergistic Effects in Combination with Checkpoint Inhibitor, Anti-PD-L1

Pancreatic Cancer Mouse Model

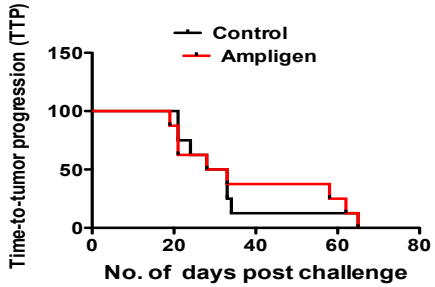
Synergistic Increase in Median Survival

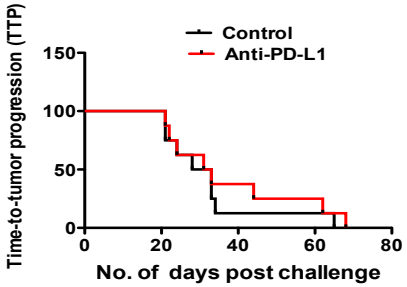


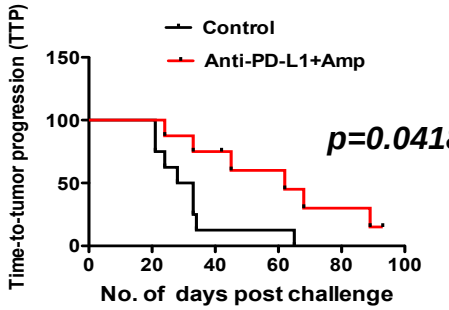




Synergistic Increase in Time to Progression



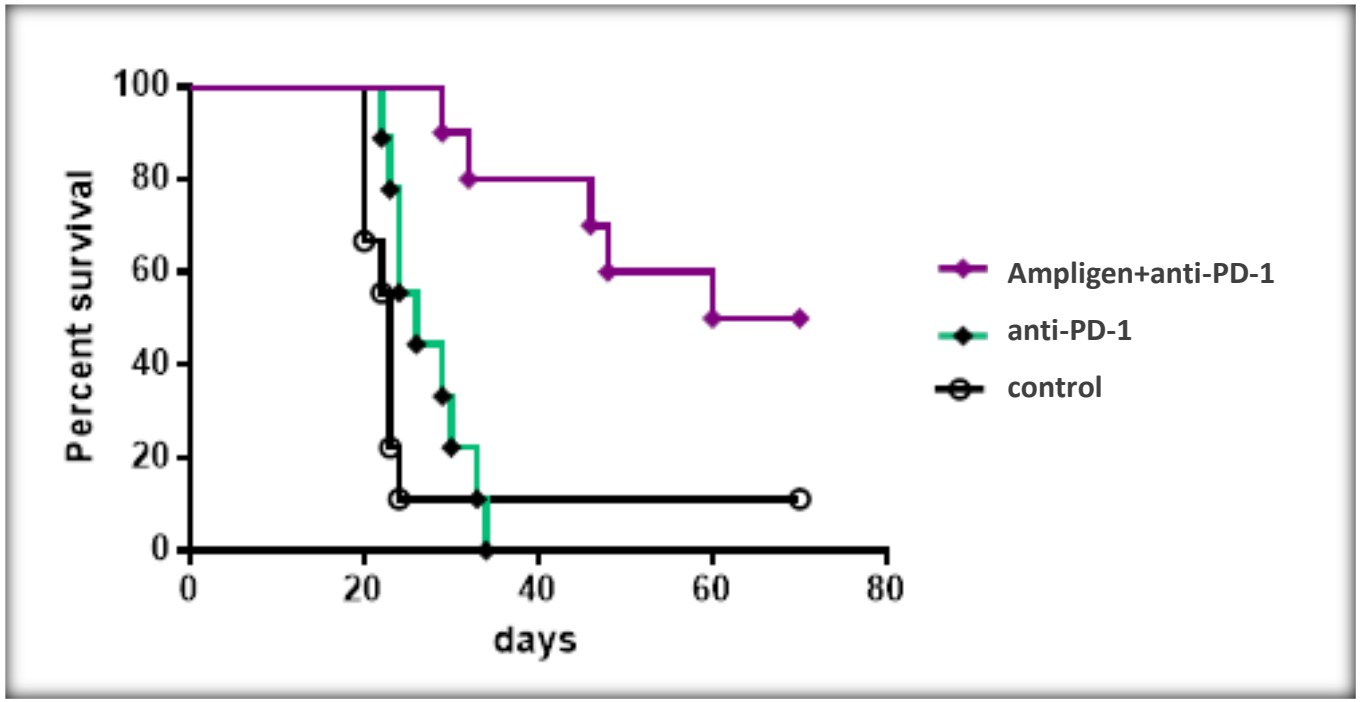




Source: University of Nebraska, PI Hollingsworth (unpublished data)

Increase in Median Survival Combining Ampligen® with Anti-PD-1

Colorectal Carcinoma Mouse Model



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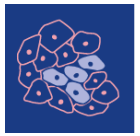
UPMC
LIFE CHANGING MEDICINE

Summary of Recent Ampligen Data Publications

AACR American Association for Cancer Research ANNUAL MEETING 2022 New Orleans

- Negative impact of paclitaxel on human breast tumor microenvironment and its reversal by the combination of interferon-α with TLR3 agonist rintatolimod
- Initial results of a phase II study evaluating a chemokine-modulatory (CKM) regimen in patients with colorectal cancer metastatic to the liver
- Systemic Rintatolimod and Interferon-α2b selectively reprogram local tumor microenvironment in patients with metastatic triple negative breast cancer for enhanced influx of cytotoxic T-lymphocytes but not regulatory T-cells
- Combined loco-regional and systemic, triple agent chemoimmunotherapy increases biomarkers of T cell chemotaxis in ovarian cancer



cancers

- Rintatolimod (Ampligen®) Enhances Numbers of Peripheral B Cells and Is Associated with Longer Survival in Patients with Locally Advanced and Metastasized Pancreatic Cancer Pre-Treated with FOLFIRINOX: A Single-Center Named Patient Program
- Rintatolimod Induces Antiviral Activities in Human Pancreatic Cancer Cells: Opening for an Anti-COVID-19 Opportunity in Cancer Patients?

Annals of SURGICAL ONCOLOGY
An Oncology Journal for Surgeons

- Phase II Trial of Adjuvant Dendritic Cell Vaccine in Combination with Celecoxib, Interferon-α, and Rintatolimod in Patients Undergoing Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Peritoneal Metastases

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SARS-CoV-2 (COVID-19)

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Chronic Illness Following COVID-19

Chronic illness following recovery is prevalent

Fatigue	Brain Fog	Sleep Disorder	Joint Pain

COVID-Induced Chronic Fatigue shares similarities to ME/CFS

COVID-Induced Chronic Fatigue (Long COVID or 'Long Haulers')

Amended ongoing open-label AMP-511 study in ME/CFS to include up to 20 long COVID subjects

Currently treating long COVID subjects

Post-COVID Conditions

Planned Phase 2 two-arm, randomized, double-blind, placebo-controlled, multicenter study to evaluate efficacy and safety

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AMP-511 Preliminary Data: Post-COVID Condition of Fatigue Over Time

AMP-511 Preliminary Data: Post-COVID Condition of Fatigue Over Time												
	Patient 1			Patient 2			Patient 3			Patient 4		
	BSL	Wk 6	Wk 12	BSL	Wk 6	Wk 12	BSL	Wk 6	Wk 12	BSL	Wk 6	Wk 12
Inability to exercise or be active	10.0	10.0	7.0	8.0	5.0	4.0	10.0	8.0	7.0	9.0	7.0	8.0
Fatigue	9.5	8.0	6.0	6.0	3.0	3.0	9.0	8.0	7.0	8.0	7.0	7.0
Post exertional malaise (tiredness the day after exercise)	7.5	ND	2.0	6.0	ND	1.0	8.0	ND	5.0	8.0	ND	9.0

Wilcoxon matched-pairs signed rank test measuring changes in total improvement (combining exercise ability, fatigue, and post-exertional malaise) at week 12 compared to baseline: p=0.002

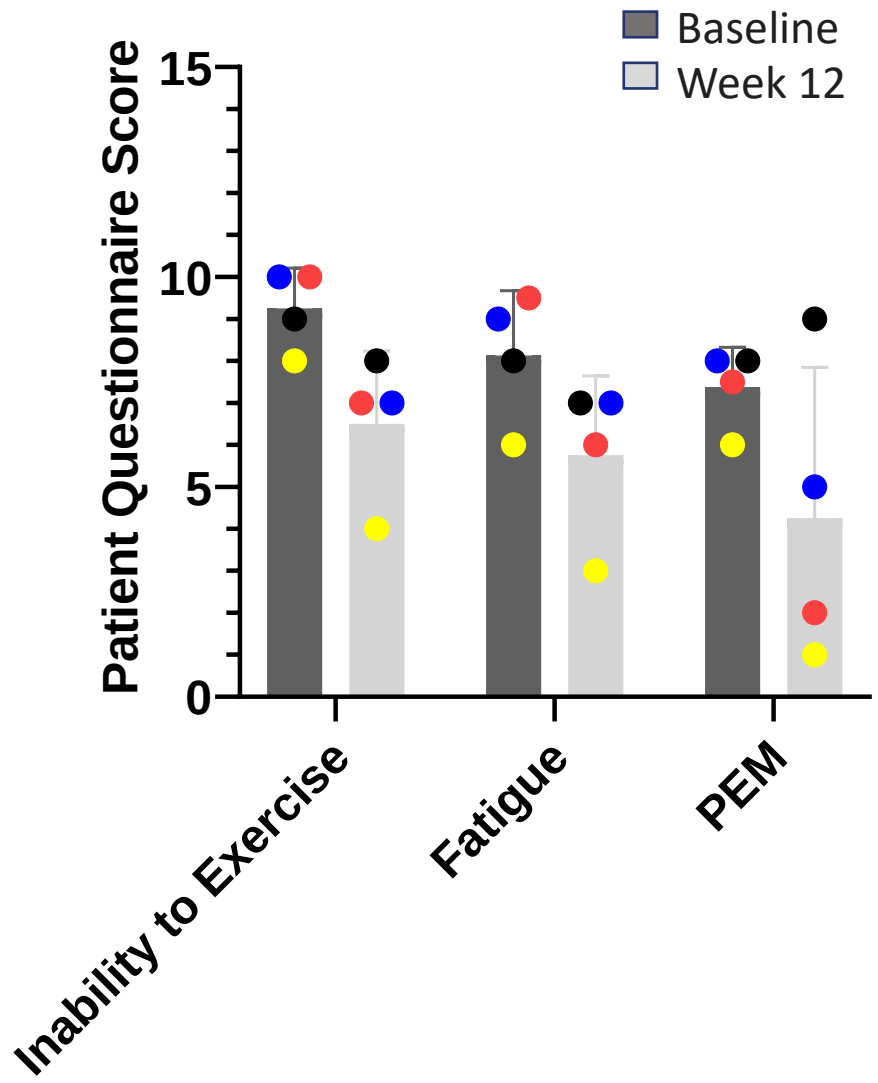
BSL = baseline; Baseline is mean of 2 baseline values

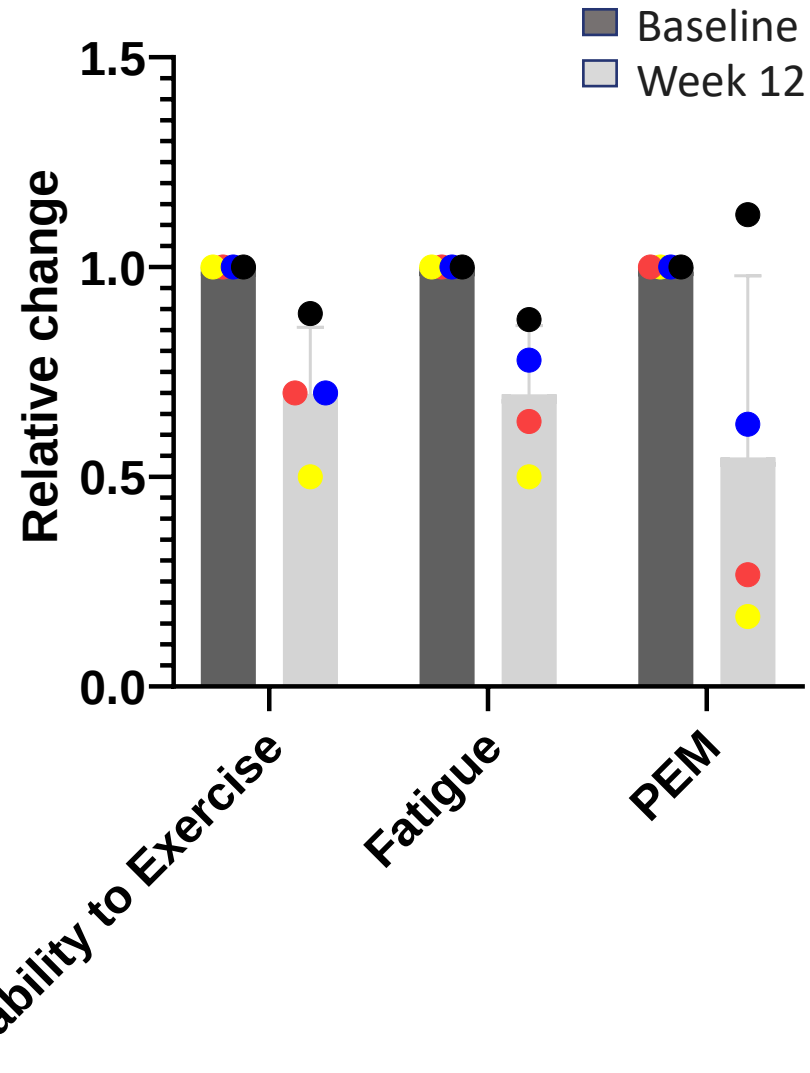
ND=Not done; Post exertional malaise was not collected at week 6

Severity Scores: 1-3= Mild, 4-6= Moderate, 7-8= Severe, 9-10= Very Severe

Source: Preliminary unpublished data from Hunter Hopkins Center. PI: Dr. Lapp

AMP-511 Preliminary Data: Post-COVID Condition of Fatigue





Source: Preliminary unpublished data from Hunter Hopkins Center. PI: Dr. Lapp

Antiviral Activity of Ampligen

Virus Genome (Virus)	Model
Double-Stranded DNA	
1. Herpes Simplex Type 2	Guinea pig, in vivo protection
2. Herpes Simplex Type 2	Mouse, in vivo protection
3. Herpes Simplex Type 2	Mouse, in vivo Protection
4. Hepatitis B	Duck, in vivo protection
5. Cytomegalovirus, strain AD 169	Human fibroblast, in vitro protection
6. Human Herpes Virus Type 6 (HHV-6)	HHV-6 infected cells in vitro
7. Human Herpes Virus Type 6 (HHV-6)	HHV-6 infected patient blood cells
8. Vaccinia Virus	Mouse, in vivo protection
Single-Stranded (+) RNA	
9. Banzi Virus	Mouse, in vivo protection
10. Venezuelan Equine Encephalitis Virus	Mouse, in vivo protection
11. Western Equine Encephalitis	Hamster, in vivo protection
12. Western Equine Encephalitis	Mouse, in vivo protection
13. Semliki Forest Virus	Mouse, in vivo protection
14. Banzi Virus	Mouse, in vivo protection
15. Mouse Hepatitis Virus Type 3	Mouse, in vivo protection
16. Encephalomyocarditis Virus	Mouse, in vivo protection
17. SARS-CoV-1 (coronavirus)	Mouse, in vivo and in vitro
18. SARS-CoV-1 (coronavirus)	Mouse, in vivo, decrease in virus
19. SARS-CoV-2 (coronavirus)	Human tracheal/bronchial epithelial cells, in vitro
20. Flavivirus (Modoc) Encephalitis	Mouse, in vivo protection
21. Enterovirus (coxsackie B3) Myocarditis	Mouse, in vivo protection
22. West Nile Virus	Mouse, in vivo protection

Virus Genome (Virus)	Model
Single-Stranded (-) RNA	
23. Influenza, Avian H5N1	Cynomolgus macaque; in vivo protection vaccine adjuvant
24. Influenza, Avian H5N1	A/Duck/H5N1 infected MDCK cells; in vitro protection
25. Influenza, Avian H5N1	Mouse, in vivo protection, vaccine adjuvant
26. Influenza, Avian H5N1	Mouse, in vivo protection
27. Punta Toro Bunyavirus	Mouse, in vivo protection
28. Phlebovirus	Mouse and Hamster, in vivo protection
29. Caraparu Bunyavirus	Mouse, in vivo protection
30. Vesicular Stomatitis Virus	Human fibroblasts, in vitro protection
31. Nipah Virus	Hamster, in vivo and in vitro protection
32. Ebola Virus (Zaire)	Hela cells, EC50=4 µg/ml
33. Ebola Virus (mouse adapted)	Mouse, in vivo protection, 100% survival at 6 mg/kg
Retroviruses	
34. HIV IIIB	T cell clones and PBMC, in vitro protection
35. HIV IIIB, LAV	T lymphoblastoid cell lines (CEM/MT2), in vitro protection
36. HIV, genomic strains	T (H9,MT-2) and monocyte/macroΦ cell (U937), in vitro
37. HIV IIIB	T cell (H9), in vitro protection/synergy with HAART
38. HIV	HIV infected patient blood cells
39. HIV	Randomized clinical trial of HIV infected patients,
40. Baboon Type C/endogenous	Human AV3-M7 cells, chronically infected
Production of Antiviral Molecules	
41. Antiviral Molecules	Mouse brain, parenteral injection protection

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Summary

- Ampligen has shown promise as an immunomodulatory adjuvant in multiple cancers (Colorectal, Ovarian, TNBC) and as a solely administered therapy in melanoma as well as following FOLFIRINOX in pancreatic cancer (metastatic and LAPC)
  - Over 750 patients treated, and 100,000 IV doses indicate a generally well tolerated safety profile with no increased serious adverse events when compared to placebo.
    - Preliminary data suggests a possible positive effect of Ampligen on post-covid conditions.
      - AIM ImmunoTech is open to collaborations and new therapeutic avenues

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