IMPRIME 1: An open label, multicenter Ph 2 study combining Imprime PGG with pembrolizumab (pembro) in previously-treated, metastatic Triple Negative Breast Cancer (mTNBC)

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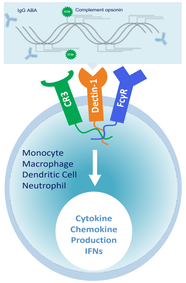
Imprime PGG: a Novel Innate Immune Activator



1. **Imprime PGG forms an immune complex**
   - Anti-β glucan antibodies (ABA)
     - patient selection biomarker, identifies ~50% of patients
   - Complement fragment (iC3b)
2. **Immune Complex binds Dectin-1 and Co-Receptors**
   - This immune complex is the "active" drug
3. **Innate Immune Cell Activation**
   - Alleviates immunosuppression
     - Promotes shift from immunosuppressive "M2" state
     - Drives infiltration of PD-L1+, CD80+ immune cells (M1)
   - Activates antigen presenting cells
     - Dendritic Cells, M1 APCs
     - Increases expression of co-stimulatory CD80, CD86 markers
   - Increases tumor specific T Cell activation and infiltration

Imprime PGG is a novel, IV administered Dectin-1 Receptor agonist that triggers an *integrated* anti-cancer immune response involving both innate and adaptive immunity to potentiate the efficacy of checkpoint inhibitor therapy

- **Checkpoint inhibitor (CPI) monotherapy trials have shown limited clinical benefit in previously treated mTNBC patients (Table 1).**
- **Imprime PGG is a novel, systemically administered DECTIN receptor agonist**
- **Imprime PGG-mediated innate activation requires Anti-Beta Glucan Antibody (ABA)**
- **Imprime PGG reprograms the immunosuppressive tumor microenvironment**
- **Imprime PGG activates antigen presenting cells**
- **Imprime PGG elicits increased anti-cancer T cell responses**
- **In preclinical tumor models, Imprime PGG enhances the efficacy of CPI monotherapy**

IMPRIME 1 (NCT02981303) Study Design

Patients (n=44)
- Histologically or cytologically confirmed diagnosis of metastatic/ stage IV TNBC
- ≥ 1 prior line of chemotherapy after the diagnosis of metastatic TNBC (mTNBC)
- No prior checkpoint inhibitor therapy (CPI-naïve)
- ECOG status 0-1
- Irrespective of PD-L1 status
- Baseline anti-beta glucan antibody (ABA) levels ≥ 20mcg/ml

Single arm, Combination study
- Imprime PGG administered by IV infusion 4mg/kg, weekly
- Pembrolizumab administered by IV infusion 200mg, q3W

Clinical Endpoints:
- 1° endpoint - ORR by RECIST v1.1 and safety.
- CT scans starting 6 weeks on therapy and every 6 weeks thereafter
- 2°/ exploratory endpoints included OS, PFS and DCR

Translational Endpoints- Immune Activation
- Tumor biopsies- preTx and 6 weeks on Tx (immunofluorescence)
- Peripheral Blood Samples (cycle 1, cycle 2, cycle 6)

**** Data presented in this poster are primary data. IMPRIME1 is ongoing.***

***** This trial also included a cohort of metastatic melanoma patients post-CPI therapy***

IMPRIME 1 Efficacy Data

Table 1. mTNBC CPI Monotherapy Trials and IMPRIME 1

Clinical Measure	Bavencio[a] % (N=58)	Tecentriq[b] % (N=94)	Keytruda[c] % (N=170)	IMPRIME 1 % (N=44#)
Overall Response Rate (ORR)	5.2	6.4	5.3	15.9
Stable Disease (SD)	26.0	13.0	18	38.6
Progressive Disease (PD)	65.0	64.0	60.6	40.9
Disease Control Rate (DCR)				
- CR+PR+SD any time	31.2	19.4	23.3	54.5
- CR+PR+SD ≥ 24 weeks	NR	10.0	7.6	25.0
Median Overall Survival (mos)	9.2	7.3	9.0	13.7*
Overall Survival Rate (%)				
- 6 month	NR	60.0	69.7	79.0
- 9 month	~50.0**	44.0	50.0	71.5
- 12 month	37.1	37.0	39.8	64.2

CR = Confirmed Complete Responder, PR = Confirmed Partial Responder, NR = Not Reported, #- ITT population, n = 44 patients, 2 not evaluable for response. IMPRIME 1 data from May 2, 2019. * Median follow up time 12.7 months
** Estimated from reported median OS, [a]Javelin Dirix et al., 2018- Pfizer, [b] PCD4989g Emens et al., 2019- Genentech, [c]Keynote-086 Adams et al., 2018- Merck

Table 2. Patient Populations and ORR

		Keynote-086 (Cohort A)			IMPRIME 1		
Parameter	Subgroup	# of patients	% of patients	ORR (%)	# of patients	% of patients	ORR (%)
Age	<50 years	65	38.2	6.2	21	47.7	14.3
	>50 years	**105**	**61.8**	**4.8**	**23**	**52.3**	**17.4**
Menopausal Status	Premenopausal	30	17.6	6.7	17	38.6	17.6
	Postmenopausal	**140**	**82.4**	**5.0**	**27**	**61.4**	**14.8**
ECOG Performance	0	90	52.9	5.6	21	47.7	4.8
	1	**80**	**47.1**	**5.0**	**23**	**52.3**	**26.1**
# Prior lines of Tx after Recurrent/ Metastatic Dx	<3	96	56.5	6.3	29	65.9	10.3
	≥3	**74**	**43.5**	**4.1**	**15**	**34.1**	**26.7**
Initial Tumor Burden (mm)	<100	129	75.9	~5.5%	35	79.5	11.4
	≥100	**41**	**24.1**	**~3.0%**	**9**	**20.5**	**33.3**
No. of Metastatic sites	<3	114	67.1	7.0	25	56.8	20.0
	>3	**56**	**32.9**	**1.8**	**19**	**43.2**	**10.5**
Visceral Disease	No	45	26.5	13.3	14	31.8	14.3
	Yes	**125**	**73.5**	**2.4**	**30**	**68.2**	**16.7**
Liver Metastases	No	124	72.9	7.3	32	72.7	18.8
	Yes	**46**	**27.1**	**0.0**	**12**	**27.3**	**8.3**
Lymph Node Metastases Only	Yes	18	10.6	27.8	4	9.1	25.0
	No	**152**	**89.4**	**2.6**	**40**	**90.9**	**15.0**
LDH Concentration*	<ULN	82	48.5	8.5	25	58.1	20.0
	>ULN	**87**	**51.5**	**2.3**	**18**	**41.9**	**11.1**

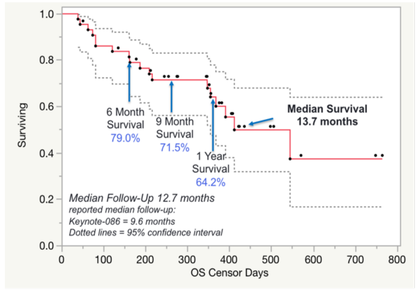
IMPRIME 1 data- only confirmed responses (ITT population; N=44 for IMPRIME 1 trial). Data updated May 2, 2019. LDH data available only from 43 patients. NOTE: ORRs in poor prognosis subgroups

Table 3. mTNBC Patients with Prior Hormone Therapy

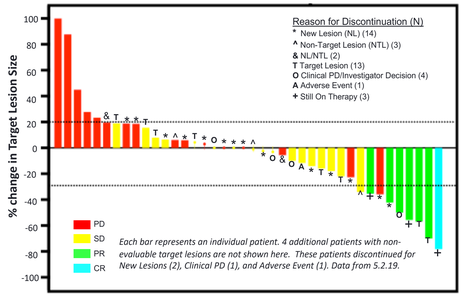
Patient	Best Response	Alive/ Deceased	PFS (Days)	OS (Days)	Prior Therapies Received			ASCO/CAP TNBC Criteria*
					Aromatase Inhibitor	Tamoxifen	CDK4/6 Inhibitor	
109128	PR	Alive	501	505+	Yes	Yes	Yes	Yes
103102	PR	Alive	267	764+	Yes	Yes	No	Yes
116106	PR	Alive	240	351+	Yes	No	No	No^
116110	PR	Alive	274+	274+	Yes	Yes	Yes	Yes
114105	PR	Alive	176	381+	No	Yes	No	Yes
105123	PR	Alive	211+	211+	No	Yes	No	Yes
124101	SD	Alive	164	276+	No	Yes	No	Yes
115117	SD	Alive	154	245+	Yes	No	No	Yes
110130	SD	Deceased	119	347	Yes	No	No	Yes
109139	SD	Alive	108	134+	Yes	Yes	No	Yes
120105	PD	Alive	41	346+	Yes	Yes	Yes	Yes

* TNBC documented as ER< 1%/ PR< 1%/ HER2- as per ASCO/CAP guidelines.
^ Disease documented as ER 5% (weakly positive)/ PR <1%/ HER2-

IMPRIME 1 Kaplan-Meier Overall Survival Plot



Best Overall Response and Reason for Discontinuation



IMPRIME 1 Study Summary

1. Imprime PGG in combination with pembrolizumab shows promising clinical benefit in previously-treated, metastatic TNBC patients
   - Across multiple clinical efficacy measures
     - Overall Survival, Overall Response and Disease Control Rates
2. Clinical response is evident as early as 6 weeks on treatment
3. Clinical benefit is particularly pronounced in mTNBC "converters"
   - ER/PR+ patients treated with tamoxifen and/ or aromatase ± CDK4/6 inhibitors
4. IMPRIME 1 demonstrates that the combination of Imprime PGG and pembrolizumab is well tolerated.
5. Tumor Biopsy and Peripheral Blood analyses show immune activation at the tumor site and in the periphery of IMPRIME 1 patients

These data support the continued development of Imprime PGG with pembrolizumab for previously-treated mTNBC patients

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IMPRIME 1 Safety Data

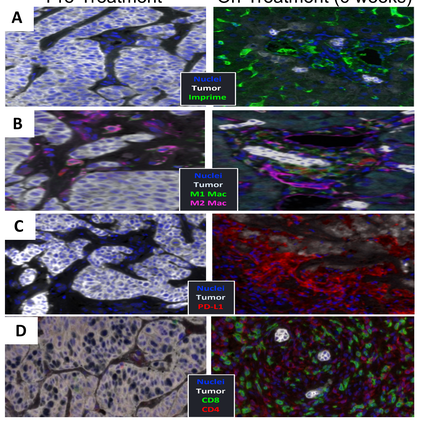
Adverse Events in ≥ 20% of IMPRIME 1 mTNBC Patients	All Events (N=43)	Gr III/IV Events (N=43)	Related Events* (N=43)
Any AE	41 (95.3%)	13 (30.2%)	35 (81.4%)
General disorders and administration site disorders			
Chills	13 (30.2%)	0	12 (27.9%)
Fatigue	11 (25.6%)	0	-
Pyrexia	9 (20.9%)	0	-
Gastrointestinal disorders			
Nausea	17 (39.5%)	0	15 (34.9%)
Diarrhea	10 (23.3%)	0	9 (20.9%)
Constipation	9 (20.9%)	0	-
Musculoskeletal and connective tissue disorders			
Arthralgia	12 (27.9%)	0	-
Back Pain	11 (25.6%)	0	-
Nervous system disorders			
Headache	10 (23.3%)	0	-

Rates of overall and serious AEs (i.e. life-threatening or requiring hospitalization) were similar to previous Imprime PGG studies. Immune-mediated adverse reactions (e.g. endocrinopathies) reported with checkpoint inhibitors were not observed with co-administration of Imprime PGG. AEs mostly reflect known toxicities associated with pembrolizumab or were complications of underlying disease. Most AEs deemed related to Imprime PGG were potentially associated with infusion related reactions (Grade I/II) and frequently mitigated with administration of premedication (H1 antagonist, 5-HT_3 antagonist, antipyretic and anti-inflammatory). Dyspnea was the only serious adverse event that occurred at a rate ≥ 5%. * Events related to Imprime PGG or pembrolizumab.

Adverse Events of Specific Interest in the IMPRIME 1 mTNBC Population	AE (N=43)	Gr III/IV SAE (N=43)
Immune-Mediated Events Potentially Associated w/ CPIs		
Hypothyroidism	2 (4.7)	0
Pancreatitis	2 (4.7)	1 (2.3)
Hyperthyroidism	1 (2.3)	0
Myocarditis	1 (2.3)	1 (2.3)
Pneumonitis	1 (2.3)	0
Events Potentially Associated with Infusion-Related Reactions		
Chills	7 (15.9)	0
Pyrexia	5 (11.4)	0
Back pain	4 (9.1)	0
Nausea	4 (9.1)	0
Cough	3 (6.8)	0
Dyspnea	3 (6.8)	0
Fatigue	3 (6.8)	0
Infusion-related Reactions	3 (6.8)	0
Pruritus	3 (6.8)	0

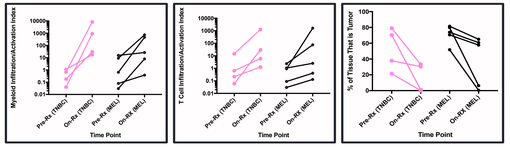
IMPRIME 1 Translational Research

IMPRIME 1 Tumor Biopsy Analyses: Liver Metastasis



Tumor biopsies were taken from patients pre-treatment and again 6 weeks on treatment. Tumor samples were assessed by immunofluorescence using the Perkin Elmer Vectra 3.0 system for the markers shown in the insets. These images were taken from the same liver metastasis. **A**- Staining for Imprime+ Myeloid cells. **B**- Staining for M2 (pink, CD206) and M1 (green, CD80) markers. **C**- Staining for PD-L1 (red) in the tumor bed. **D**- Activated CD8 (green) and CD4 (red) T cells in the tumor bed after IMPRIME 1 therapy. Note: on treatment, tumor is evident as small tumor cell clusters vs the large tumor sheets pre-treatment. **This patient started therapy with 3 liver metastases, 2 breast metastases and bone metastases. She remained on therapy > 500 days and is now without evidence for any liver metastases**..

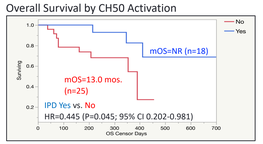
Myeloid Activation Index | **T Cell Activation Index** | **Tumor Cell Content**



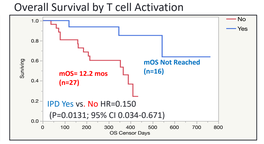
Breast Patients shown in Pink, Melanoma Patients shown in Black. Myeloid and T cell activation indices reflect cell infiltration and activation (CD80/CD206 for myeloid activation-M1 state, CD3+/Ki67/GranzymeB for T cell activation) as a composite measure. Each bar represents a single patient pre- and on-treatment (6 weeks). All quantitation performed using the Perkin Elmer Vectra 3.0 imaging system. These data represent the total number of tumor biopsy pairs (pre and on-Tx) collected.

IMPRIME 1 Peripheral Blood Analyses

Overall Survival by CH50 Activation



Overall Survival by T cell Activation



Peripheral blood from patients on IMPRIME 1 was taken at pre-cycle 2 (week 3) and pre-cycle 6 (week 15). ***Left panel***: As previously shown (Bose et al., *JI* 2019), acute decreases in CH50 reflect complement activation and consumption, an immediate response to Imprime PGG treatment. With weekly dosing, increased CH50 reflects a persistent activation of the innate immune system, a consequence of the continued action of Imprime PGG. Longitudinal blood samples from patients were analyzed for CH50 activation over baseline. Data shown represent a 1.3X or greater increase in CH50 vs baseline pre-treatment- an Immunopharmacodynamic (IPD) response. Overall survival was evaluated by Kaplan-Meier for those showing increased CH50 (IPD) at either pre-cycle 2 or 6.
Right Panel: CD8 T cell activation is associated with benefit from pembrolizumab. Activated CD8 T cells (PD1+/HLA-DR+/KI67+) were assessed on treatment by flow cytometry. Data shown represent ≥ 2X increase in CD8 T cells vs baseline pre-treatment. Sample not available from 1 patient. Note: N = 16 for those with increased activated T cells. Baseline samples showed very limited evidence for activated T cells in these mTNBC patients.