Supplementary Online Content

Matsuda N, Wang X, Lim B, et al. Safety and efficacy of panitumumab plus neoadjuvant chemotherapy in patients with primary HER2-negative inflammatory breast cancer. *JAMA Oncol*. Published online June 7, 2018. doi:10.1001/jamaoncol.2018.1436

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Dermatology/Skin/Nail Assessment (from NCI Common Toxicity Criteria for Adverse Events, version 3.0, with modifications)

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Nail changes	Discoloration; ridging (koilonychias; pitting), paronychia: intervention not indicated	Partial or complete loss of nail(s); pain in nailbed(s), paronychia: intervention indicated	Interfering with activities of daily living (ADL)	___
Erythema	Painless erythema	Painful erythema	Erythema with desquamation*	Life-threatening; disabling
Pruritus/itching	Mild or localized	Intense or widespread	Intense or widespread and interfering with ADL	___
Rash: acne/acneiform	Intervention not indicated	Intervention indicated	Associated with pain requiring narcotic analgesics, ulceration, or desquamation*	___
Rash/desquamation* (Use for non-acneiform rash or non-folliculitis rash)	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation* or other lesions covering <50% of body surface area (BSA)	Severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation* covering ≥50% of BSA	Generalized exfoliative, ulcerative, or bullous dermatitis
Ulceration	___	Superficial ulceration <2 cm; local wound care; medical intervention indicated	Ulceration ≥ 2cm; operative debridement, primary closure or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., complete resection, tissue reconstruction, flap, or grafting)

*Desquamation is defined as sloughing of skin and does not apply to dry flaking skin.

eTable 2. Expression of Candidate Proteins at Baseline and Week 2 and Change in Expression of Candidate Proteins between Baseline and Week 2 by Patient pCR Status [a]

	No pCR (N=26)		pCR (N=11)		
Variable	N	Median (range)	N	Median (range)	*P* Value
EGFR					
Baseline	18	0 (0-300)	5	120 (0-300)	.14
Week 2	3	285 (20-300)	4	105 (10-285)	.48
Change	3	0 (0-265)	2	7.5 (-15-30)	.77
pEGFR					
Baseline	7	60 (20-300)	4	160 (160-300)	**.05**
Week 2	6	225 (30-300)	4	110 (0-240)	.28
Change	6	185 (-30-280)	4	-50 (-300-80)	**.09**
E-cadherin					
Baseline	12	170 (0-300)	7	5 (0-300)	.49
Week 2	6	300 (300-300)	4	300 (180-300)	.31
Change	6	90 (0-300)	4	89.5 (0-300)	1.00
Vimentin					
Baseline	9	0 (0-210)	7	30 (0-60)	.31
Week 2	5	15 (0-270)	4	40 (5-270)	.38
Change	4	9.5 (0-110)	4	25 (-25-210)	.66
COX-2					
Baseline	12	115 (0-300)	7	240 (150-300)	**.05**
Week 2	6	200 (80-300)	4	160 (80-300)	.66
Change	6	15 (-140-240)	4	-85 (-160-140)	.59
Nodal					
Baseline	11	240 (70-300)	7	285 (80-300)	.58
Week 2	6	250 (0-300)	4	180 (160-300)	.91
Change	5	0 (-100-120)	4	0 (-100-80)	1.00

[A] Gene expression in patient samples was measured by immunohistochemical staining before (baseline) and after (week 2) the first dose of panitumumab.

eTable 3. Genes Significantly Changed in Patient Samples between Before and After Panitumumab Treatment.

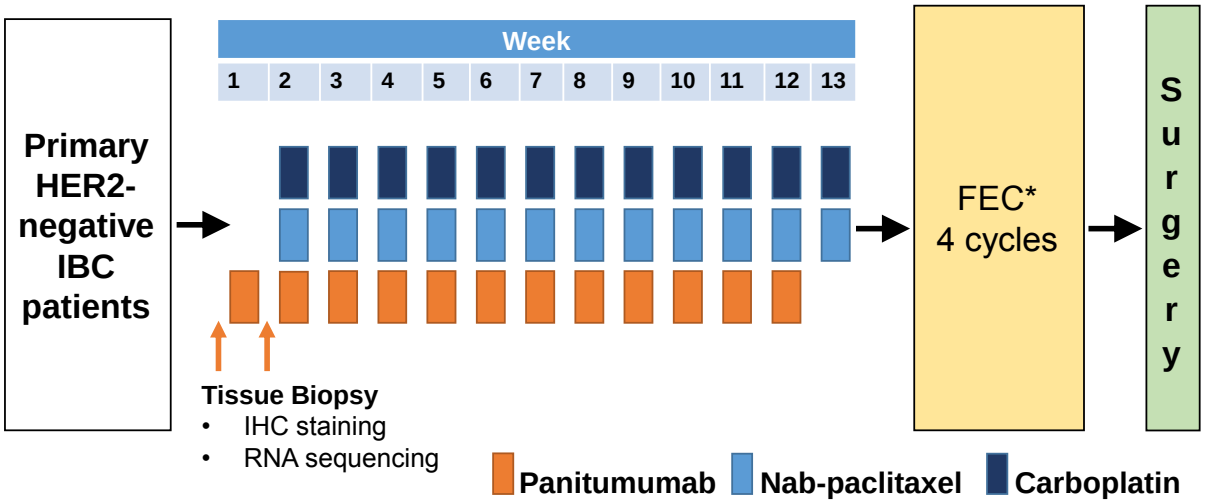
Gene	Gene Name	Log (Fold Change)*	*P* Value	Biological Functions
TN-IBC				
POU3F3	POU class 3 homeobox 3	-2.57	.03	Regulation of cell proliferation, apoptotic process, and transcription from RNA polymerase II promoter; regulation of nervous system development.
EGR1	Early growth response 1	-0.85	.05	Regulation of transcription from RNA polymerase II promoter; regulation of BMP and canonical Wnt receptor signaling pathway; regulation of smooth muscle cell migration and proliferation; regulation of apoptotic process, T cell differentiation, and wound healing.
BBOX1	Gamma-butyrobetaine hydroxylase 1	1.95	.002	Carnitine biosynthetic process and oxidation-reduction process.
GLYATL2	Glycine-N-acyltransferase-like 2	1.56	.03	Mitochondrial acyltransferase that transfers the acyl group to the N-terminus of glycine.
MUCL1	Mucin-like 1	2.31	.03	O-glycan processing.
LCN2	Lipocalin 2	2.18	.03	Apoptotic process; immune system process; innate immune response; and cellular response to interleukin-1.
HR+/HER2-				
FAM196A	Family with sequence similarity 196 member A	-2.72	.04	Unknown.
SHISA2	Shisa family member 2	-2.31	.001	Regulation of fibroblast growth factor receptor and Wnt receptor signaling pathways.
MMP13	Matrix metallopeptidase 13	-2.05	.001	Extracellular matrix disassembly and metastasis.
GJB2	Gap junction protein beta 2	-2.03	.00	Cell-cell signaling; cell communication; and gap junction assembly.
SLC24A2	Solute carrier family 24 member 2	-1.58	.007	Calcium and other ions transmembrane transport and cellular calcium ion homeostasis.
IL1RL1	Interleukin 1 receptor-like 1	-1.58	.006	Cytokine-mediated signaling pathway; regulation of T-helper 1 type immune response, inflammatory response, and macrophage activation; and signal transduction.
MMP11	Matrix metallopeptidase 11	-1.47	.02	Extracellular matrix disassembly and metastasis.
SERPINA11	Serpin family A member 11	-1.44	.05	Negative regulation of endopeptidase or peptidase activity.

HDC	Histidine decarboxylase	-1.39	.02	Histamine biosynthetic process and histamine metabolic process.
GRIA2	Glutamate ionotropic receptor AMPA type subunit 2	-1.24	.01	Ion transmembrane transport; regulation of receptor recycling; and signal transduction.
ADAMTS16	ADAM metallopeptidase with thrombospondin type 1 motif 16	-1.21	.03	Metallopeptidase activity and proteolysis.
IGFBP5	Insulin-like growth factor binding protein 5	-1.11	.001	Regulation of cell growth and migration; regulation of insulin-like growth factor receptor signaling pathway; cellular protein metabolic process; and signal transduction.
GJA1	Gap junction protein alpha 1	-1.01	1.35E-08	Component of gap junctions and regulates cell death, proliferation, and differentiation.
SNORA24	Small nucleolar RNA, H/ACA box 24	-0.96	.006	Unknown.
DACH1	Dachshund family transcription factor 1	-0.93	.01	Cell proliferation; negative regulation of cell migration; and negative regulation of fibroblast proliferation.
KIAA1549L	KIAA1549-like	-0.75	.007	Positive regulation of defense response to virus by host.
SULF1	Sulfatase 1	-0.73	.01	Apoptotic process; cell adhesion; negative regulation of cell migration.
RORC	RAR related orphan receptor C	-0.66	.03	Adipose tissue development; alpha-beta T cell differentiation; and cell differentiation.
KCNMA1	Potassium calcium-activated channel subfamily M alpha 1	-0.52	.04	Cellular potassium ion homeostasis; ion transport; and regulation of apoptotic process.
PLIN1	Perilipin 1	3.26	.05	Lipid catabolic process; lipid metabolic process; triglyceride catabolic process.
ADH1B	Alcohol dehydrogenase 1B (class I), beta polypeptide	3.20	4.17E-05	Metabolism of ethanol, retinol, other aliphatic alcohols, hydroxysteroids, and lipid peroxidation products.
G0S2	G0/G1 switch 2	2.74	.01	Apoptotic process; regulation of extrinsic apoptotic signaling pathway.
PI16	Peptidase inhibitor 16	2.26	.004	Regulation of cell growth involved in cardiac muscle cell development and regulation of peptidase activity.
CHRDL1	Chordin-like 1	2.08	.008	Encodes an antagonist of bone morphogenetic protein 4; regulation of retinal angiogenesis in response to hypoxia.
CFD	Complement factor D	1.86	.001	Complement activation and innate immune response.

LILRB5	Leukocyte immunoglobulin-like receptor B5	1.55	.01	Adaptive immune response.
ABCA8	ATP binding cassette subfamily A member 8	1.33	.04	Transport of molecules across extra- and intracellular membranes.
ABCA6	ATP binding cassette subfamily A member 6	0.87	.05	Transport of molecules across extra- and intracellular membranes.
PLTP	Phospholipid transfer protein	0.69	.05	Lipid binding and transport.

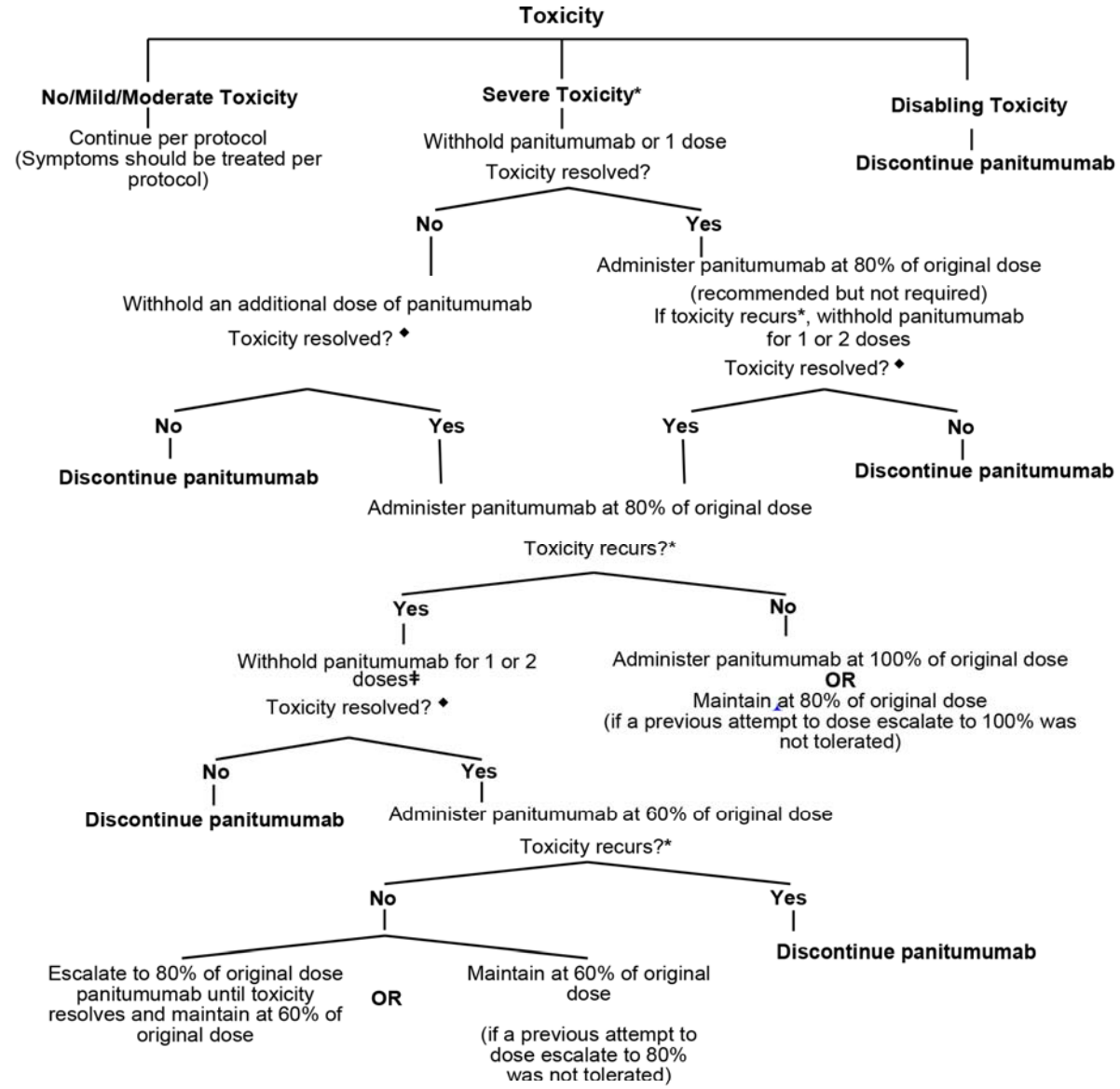
*Fold change: gene expression at week 2/gene expression at baseline.

eFigure 1. Trial Design.



*FEC: 5-fluorouracil (500 mg/m^2), epirubicin (100 mg/m^2), cyclophosphamide (500 mg/m^2), every 3 weeks for the first 17 patients. Because 3 of the 17 patients developed grade 3 or higher thrombocytopenia and 1 required platelet transfusion, the PNC treatment cycle for the remaining 23 patients was revised to 3 weeks of weekly treatment followed by 1 week off to allow bone marrow recovery.

eFigure 2. Panitumumab Dose Modification Algorithm for Toxicity.

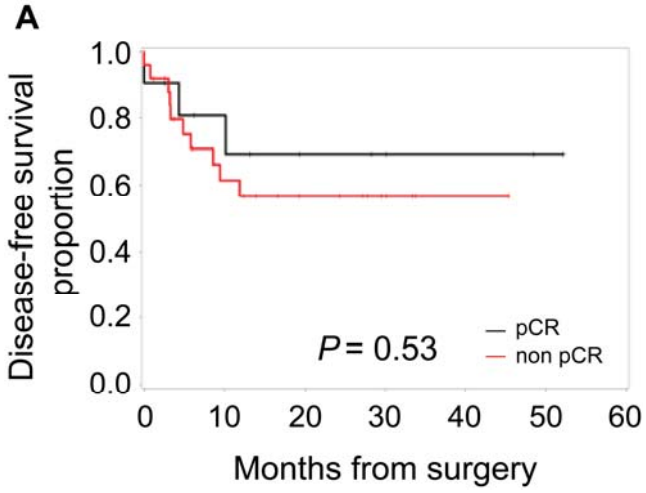


* Assess toxicity before each dose. Toxicity recurs = meets the criteria for withholding a dose of panitumumab at any time during the study.

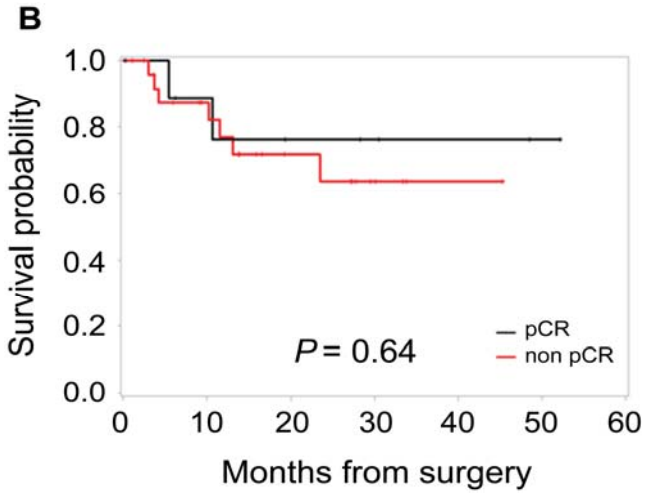
◆ Assess toxicity before each dose. Toxicity resolved = meets the criteria for restarting panitumumab. Subjects from whom > 2 subsequent cycles of panitumumab are required to be withheld should not be re-treated with panitumumab.

‡ Up to 2 subsequent doses of panitumumab may be withheld but panitumumab may not be withheld longer than 6 weeks from the previous dose. The second dose should only be withheld if the toxicity has not resolved by the time that the subsequent cycle of chemotherapy is due.

eFigure 3. Disease-free Survival (A) and Overall Survival (B) Estimates for 37 Evaluable Patients

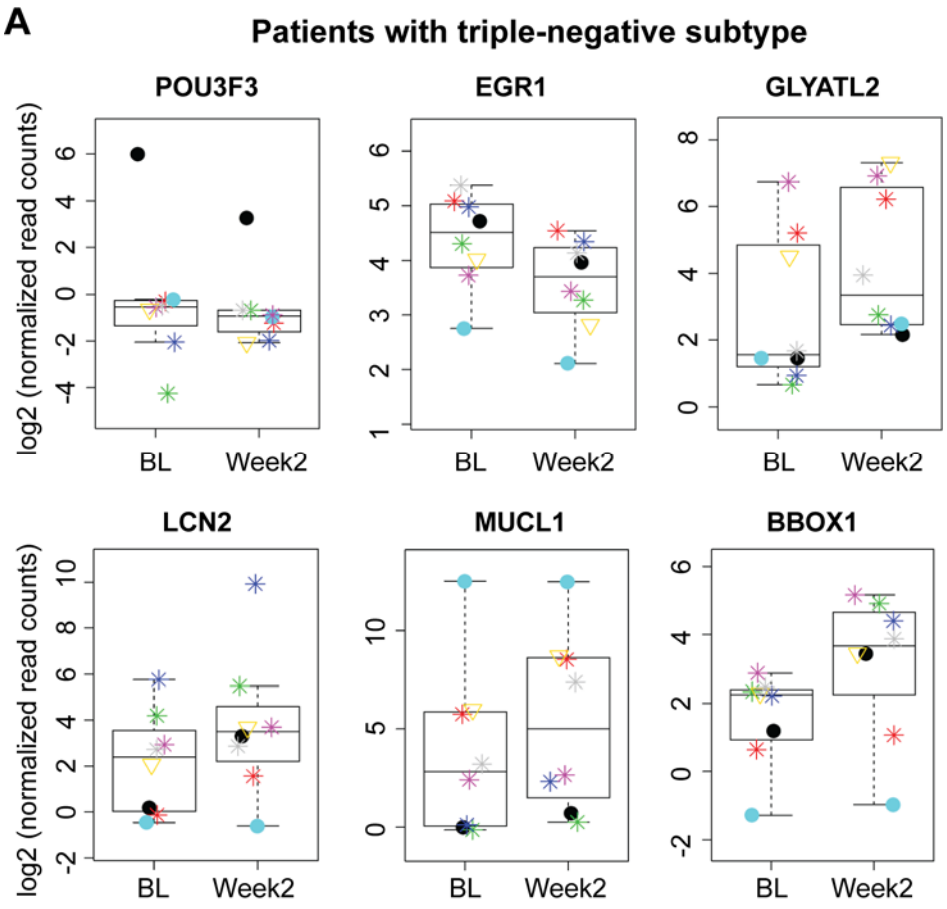


No. at risk	0 months	10 months	20 months	30 months	40 months	50 months
No pCR	26	13	8	4	1	0
pCR	11	7	4	3	2	1

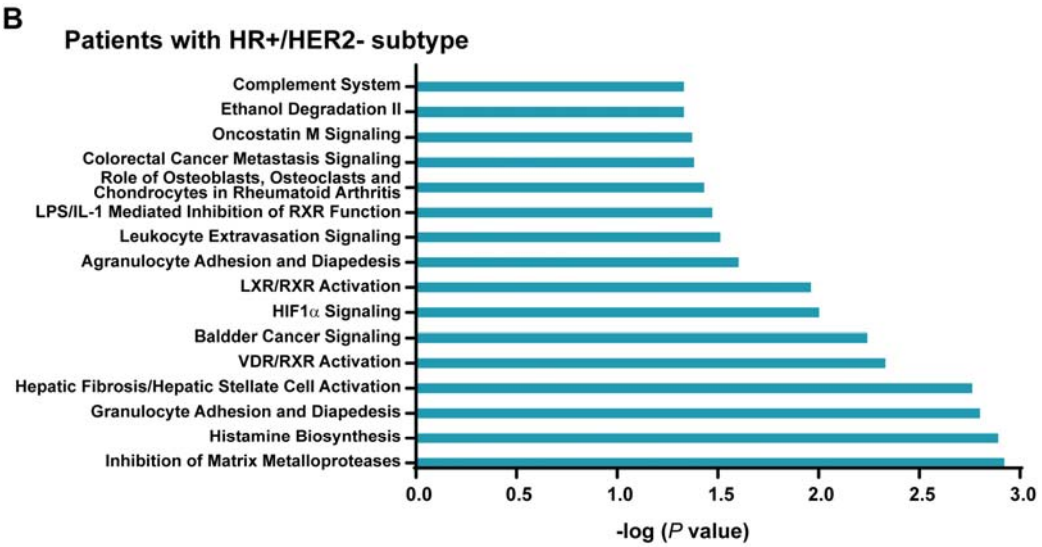


No. at risk	0 months	10 months	20 months	30 months	40 months	50 months
No pCR	26	17	9	4	1	0
pCR	11	7	4	3	2	1

eFigure 4. Differentially Expressed Genes Regulated by Panitumumab. (A) Genes differentially expressed after panitumumab treatment in patients with TN-IBC. Each symbol represents an individual patient. * pCR; • Non-pCR; ∆ unknown. (B) Ingenuity Pathway Analysis showing the canonical pathways of differentially regulated genes (top panel) and related biological processes (bottom panel) in patients with HR-positive/HER2-negative IBC.



B



Biological Processes	Involved Pathways
Metastasis	Matrix metalloproteases
	Colorectal cancer metastasis signaling
Cellular immune response	Granulocyte adhesion and diapedesis
	Agranulocyte adhesion and diapedesis
	Leukocyte extravasation signaling
	Complement system pathways
Inflammation	Oncostatin M
	Granulocyte adhesion and diapedesis
	Agranulocyte adhesion and diapedesis
	Leukocyte extravasation signaling
Retinoid signaling regulated biological function	VDR/RXR activation
	LXR/RXR activation
	LPS/IL-1 mediated inhibition of RXR function