Phase 2 study of neoadjuvant treatment with cellular redox modulator NOV-002 in combination with doxorubicin and cyclophosphamide followed by docetaxel (AC→T) in patients with stage II-III HER-2(-) breast cancer

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Abstract

Body: Background: NOV-002 (a formulation of disodium glutathione disulfide) modulates signaling pathways involved in tumor cell proliferation and metastasis and enhances anti-tumor immune responsiveness in tumor models. The addition of NOV-002 to a range of cytotoxic chemotherapeutic regimens has been shown to increase their anti-tumor efficacy in some early phase oncology trials and in animal models. Pathological complete response (pCR) has been demonstrated to be associated with favorable overall survival in primary breast cancer, and neoadjuvant treatment of early breast cancer aims at achieving high rates of pCR. In patients with HER-2(-) breast cancer pCR rates with anthracycline and taxane combinations have been reported to be approximately 10-20% depending on hormone receptor status. We conducted a clinical trial in HER-2 negative patients (pts) combining daily NOV-002 with AC →T.

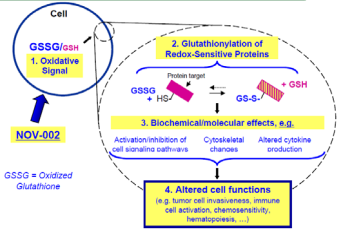
Methods: Women with newly diagnosed stages II-III HER-2 (-) breast cancer received AC x 4 [60/600 mg/m²] followed by T [100 mg/m²] x 4 every 3 weeks in conjunction with daily NOV-002 [60mg IV day 1 and subcutaneously days 2-21 of each cycle]. The primary endpoint is pCR, defined as: (i) ypN0, and (ii) ypT0 or presence of invasive tumor <10mm. Sample size was calculated using a Simon 2-stage optimal design assuming a doubling of the historical pCR rate with the addition of NOV-002 to AC T from a p0 of 0.16 to a p1 of 0.32. If a total of 12 or more patients experience a pCR by the end of the trial, then the treatment regimen will be declared active. The calculation assumes an alpha of 0.05 and 80% power.

Results: A total of 41 pts have been enrolled to date across three study sites, with 38 patients having completed chemotherapy and undergone surgery. One patient dropped out during cycle 1 and was not assessable for response; 2 are currently receiving chemotherapy. A total of 292 chemotherapy cycles have been administered, with 92% of all patients being able to complete all 8 cycles of planned chemotherapy. Of the 38 evaluable patients, 15 achieved a pCR (39%), meeting the primary endpoint of the trial. In the 8 patients (18%) with residual invasive primary breast tumor ≤10mm and ypN0 mean residual tumor size was 7.1 mm. Interestingly, of the 19 patients with biopsy-proven axillary involvement, 7 (35%) had no residual invasive tumor in axillary nodes at time of surgery. In the 33 patients with estrogen positive breast cancer, which is least sensitive to chemotherapy, 11 (33.3%) achieved a pCR. The most common toxicities with a frequency of >30% included: anemia, constipation, nausea, emesis, fatigue, leukopenia, neutropenia, hyperglycemia, and alopecia.

Conclusions: The addition of NOV-002 has to date resulted in a doubling of previously published pCR rates with AC→T in HER-2 (-) breast cancer patients. Subsequent investigation of NOV-002 in conjunction with neoadjuvant chemotherapy in breast cancer is warranted.

Background

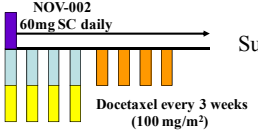
- The active ingredient in NOV-002 is **oxidized glutathione**
- Changes in the ratio of oxidized: reduced glutathione controls cellular redox state and can regulate protein function by the reversible formation of mixed disulfides between protein cysteines and glutathione, i.e. glutathionylation
- Protein glutathionylation by NOV-002 results in pleiotropic effects on cell functions including immune stimulation and increased chemosensitivity of tumor cells.



Methods

Newly Diagnosed Invasive Breast Cancer Clinical Stages II-III HER-2 –

Primary Endpoint: Pathologic + near pathologic complete response



N=46 pts; Type I error rate: .05; Power:.80

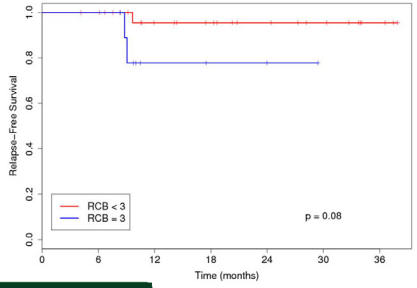


Figure 1. Low residual cancer burden after neo-adjuvant chemotherapy is associated with better relapse-free survival (RFS). Residual cancer burden (RCB)-0 (pCR), RCB-1 (npCR, minimal residual disease) or RCB-2 (moderate residual disease) vs. RCB-3 (extensive residual disease) in surgically evaluable patients [n=38]. RCB was calculated as a continuous index combining pathologic measurements of primary tumor (size and cellularity) and nodal metastases (number and size). Although this study was not powered for RFS, after a relatively short median follow up of 14.3 months, a trend is emerging with patients with RCB 0-2 having a better RFS rate than pts with extensive residual disease (RCB 3).

http://www.mdanderson.org/breastcancer_RCB

Results

Baseline Characteristics	Number (%)
Total Patients Enrolled	N = 41*
Age	
Mean (median)	53 (53)
18-49	16 (39)
50-64	18 (44)
≥ 65	7 (17)
Race/Ethnicity	
White-Non-Hispanic	16 (39)
Hispanic	10 (24.3)
African-American	13 (31.7)
Asian	2 (4.8)
Menopausal Status	
Pre-menopausal	17 (41.5)
Post-menopausal	22 (53.6)
Unknown	2 (4.8)
Clinical Tumor Size*	
T2	25 (58)
T3	15 (35)
T4	3 (7)
Clinical Node Status*	
N0	24 (55.8)
N1	17 (39.5)
N2	2 (4.7)
Tumor Grade*	
1	9 (21)
2	12 (28)
3	20 (46.5)
Not reported	2 (4.5)
Tumor Hormone Receptor Status*	
ER+ and/or PR+	36 (84)
ER - & PR -	7 (16)

*Two patients with bilateral breast cancer

Efficacy Data / Pathologic Complete Responses (pCR)	
Surgically Evaluable Pts	N = 38* (%)
pCR§	15/40 (37.5)
ER or PR+	11/33 (33.3)
ER, PR -	4/7 (57)
Pts with invasive tumor <1.0cm	8 (18)
Maximum residual invasive carcinoma [cm]	
Mean	.71
Median	.48
Residual Breast Cancer Burden (RCB)	
0	7 (17.5)
1	7 (17.5)
2	15(37.5)
3	11(27.5)
Axillary Conversion Rate (19 pts with biopsy proven involvement) (+) → (-)**	7 (35)

§pCR defined as: the absence of any histological evidence of *invasive* breast cancer in axillary nodes, and either (i) no invasive cancer in the tissue specimen removed from the breast, or (ii) the presence of invasive tumor ≤ 1cm after preoperative treatment determined at definitive breast surgery.
* Two patients with bilateral breast cancer, one ER+ and one ER/PR-.
**One pt with biopsy proven bilateral axillary involvement.

Treatment Emergent Serious Adverse Events by MedDRA* Preferred Term (N = 41)	Patients (%)	Number of Events
Febrile neutropenia	4 (9.8%)	4
Cellulitis	1 (2.4%)	1
Neutropenia	1 (2.4%)	1
Muscular weakness	1 (2.4%)	1
Deep vein thrombosis	1 (2.4%)	1
Femoral artery occlusion	1 (2.4%)	1
Constipation	1 (2.4%)	1
Nausea	1 (2.4%)	1
Palmar-plantar erythrodysaesthesia syndrome	1 (2.4%)	1
Pulmonary embolism	1 (2.4%)	1
*MedDRA coding is based on Version 10.1.		

Conclusions

❖**The addition of NOV-002 has to date resulted in a doubling of previously published pCR rates with AC T in HER-2 (-) breast cancer patients.**

❖**Subsequent investigation of NOV-002 in conjunction with neoadjuvant chemotherapy in breast cancer is warranted.**