Advances in Novel Formulations of Taxanes

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Outline

- Challenges with conventional taxanes
- NanoAqualip technology: a solution?
- NanoAqualip formulations in breast cancer
- Data beyond breast cancer

Polysorbate 80 hypersensitivity reactions: a renewed call to action

LeAnn B. Norris, PharmD, BCPS, BCOP,[1] Zaina P. Qureshi, PhD, MPH,[1] P. Brandon Bookstaver, PharmD, BCPS (AQ-ID), AAHIVE,[1] Dennis W. Raisch, PhD, MS, RPh,[2] Oliver Sartor, MD,[3] Hao Chen, MS,[4] Fei Chen, PhD,[4] and Charles L. Bennett, MD, PhD, MPP[1,5]

In the past decade, reports of hypersensitivity reactions with docetaxel use have been inc ure 2). The reported rate of hypersensitivity reactions with docetaxel is estimated at 30% in patients who do not receive premedications.[3] (8 mg) twice daily for 3 days (1 day prior to chemotherapy and continuing on days 2 and 3). With premedications, reported rates of docetaxel hypersensitivity range from 8% to 13%.

Norris LB et al. Commun Oncol 2010;7:425–428

Support Care Cancer
DOI 10.1007/s00520-014-2547-y

ORIGINAL ARTICLE

Awareness of the adverse effects associated with prophylactic corticosteroid use during docetaxel therapy

Ka-Eun Yoo · Rae Young Kang · Ju-Yeun Lee · Yu Jeung Lee · Sung Yun Suh · Kwi Suk Kim · Hyang Sook Kim · Se-Hoon Lee · Byung Koo Lee

Received: 15 July 2014 / Accepted: 30 November 2014

Results The incidences of hyperglycemia in overall patients and in patients without previous diabetes mellitus were 13.7 and 10.9 %, respectively. Infectious episodes greater than grade 2 and grade 3 developed in 29.6 and 19.9 % of patients, respectively. Multivariable logistic regression analysis

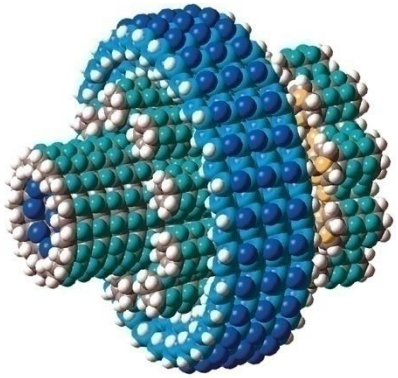
In conclusion, this study suggests that adverse effects associated with prophylactic steroid use should be better recognized. Optimal management of steroid-induced hyperglycemia is recommended to reduce infection risk during docetaxel therapy. Further studies are required to find the optimal pro-

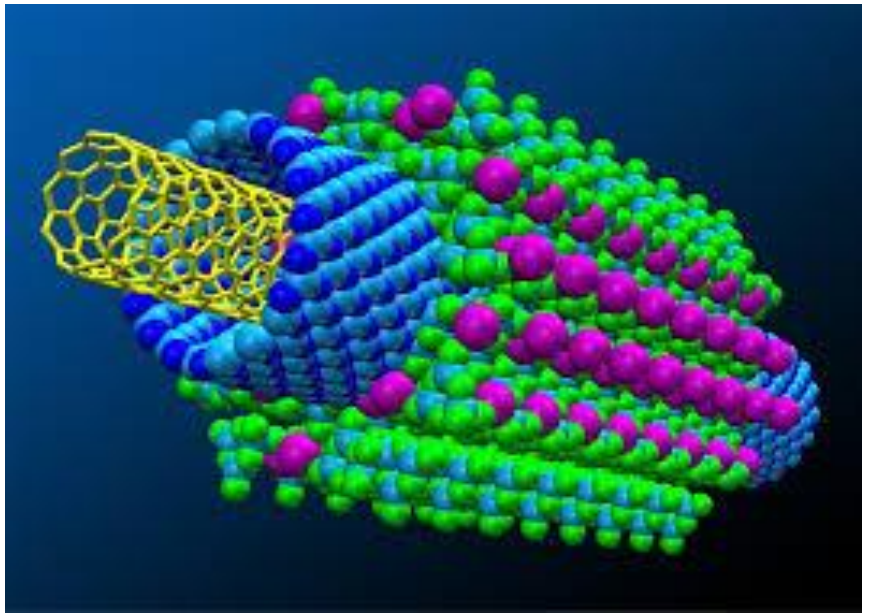
Yoo KE *et al.* Support Care Cancer. 2015 Jul;23(7):1969-77.

Recommendations of the SEC (Oncology & Haematology) made in its 126th meeting held on 26.05.2022 at CDSCO (HQ), New Delhi:

S.No	File Name & Drug Name, Strength	Firm Name	Recommendations
New Drugs Division			
1.	12-01/19-DC (Pt-337) Docetaxel	NCC-PvPI, IPC, Ghaziabad	The SRP recommendation received from PvPI was discussed by the committee. After detailed deliberation, the committee recommended that CDSCO should request the State Drugs Controllers to direct the manufacturers to include Docetaxel associated Candidiasis as an adverse event in the corresponding prescribing information leaflet.

NANOTECHNOLOGY





NanoAqualip technology

NANOAQUALIP™ TECHNOLOGY

Lipid-based Platform Technology for difficult to formulate poorly water soluble drugs

Advantages

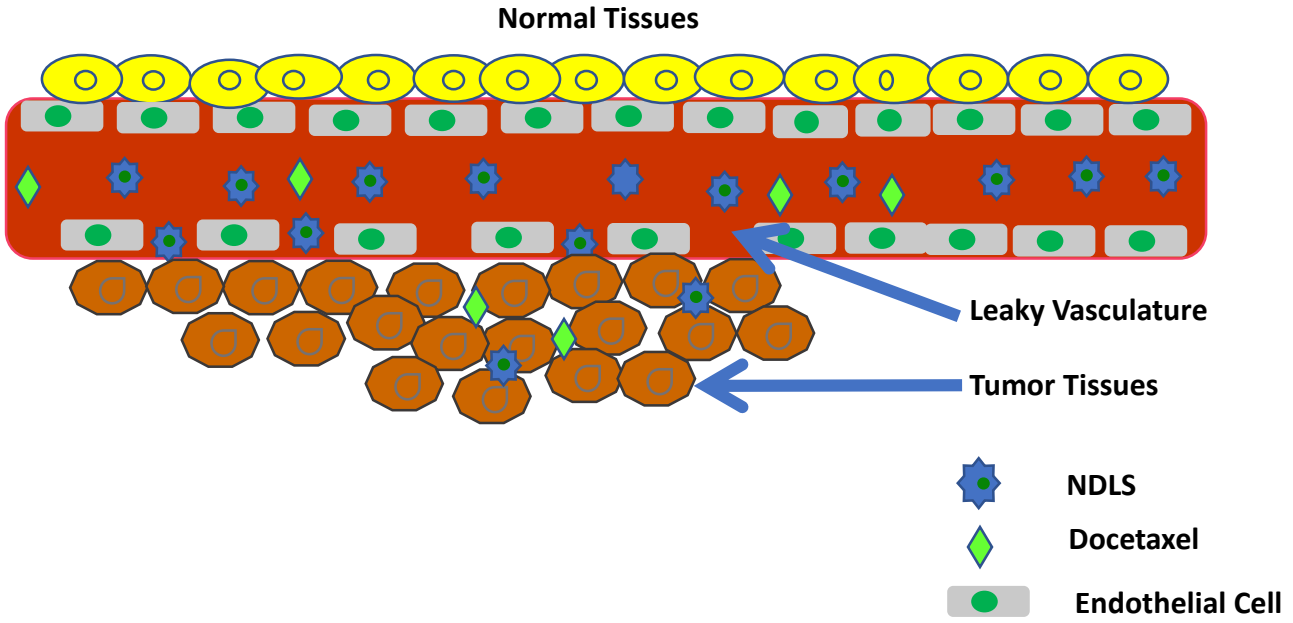
- Complete Aqueous based system
- Free of Hazardous organic solvents
- Particles are nanosize (100 nm)
- All excipients used are naturally occurring lipids

Differences between Conventional & NanoAqualip formulations

No	Concerns	Conventional Taxane formulations	NanoAqualip formulations
1	Organic solvents like Polysorbate-80, Cremophor used for solubilization	Yes	Complete Aqueous based system
2	Leaching of plasticizers from PVC bags, IV sets	Yes	Not a concern
3	Hypersensitivity reactions	Yes	Grade 3 and 4 HSRs not a major concern
4	Adverse effects due to steroids premedications	Yes	No
5	Safety concerns e.g. Neurotoxicity	Yes	Initial data suggests a lesser incidence

OPTIMUM Molecular Size

- Leaky vasculature enables **100 nm** NDLS to penetrate into tumor tissues

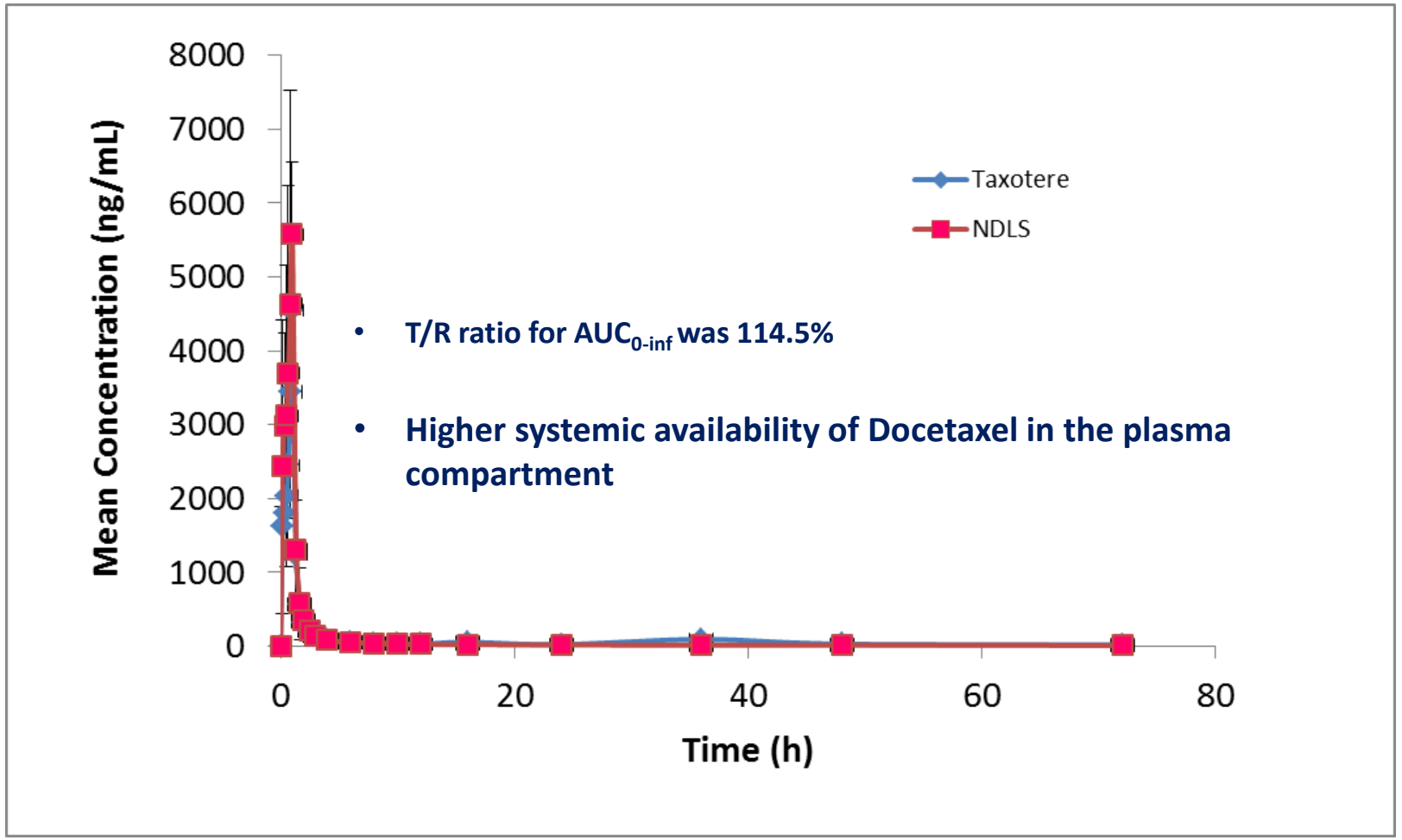


NDLS – PK comparison

Mean ± SD	Taxotere®	NDLS
T_{max} (h)	1.000	1.000
C_{max} (ng/ml)	5033 ± 2467	7029 ± 2302
AUC_{0-t} (ng.h/ml)	5724 ± 4502	6012 ± 2649
$AUC_{0-\infty}$ (ng.h/ml)	6126 ± 4561	6404 ± 2776
$t_{1/2}$ (h)	21 ± 26	21 ± 18

Ahmad et al., J Nanomed Nanotechnol 2015, 6:3

NDLS – PK profile



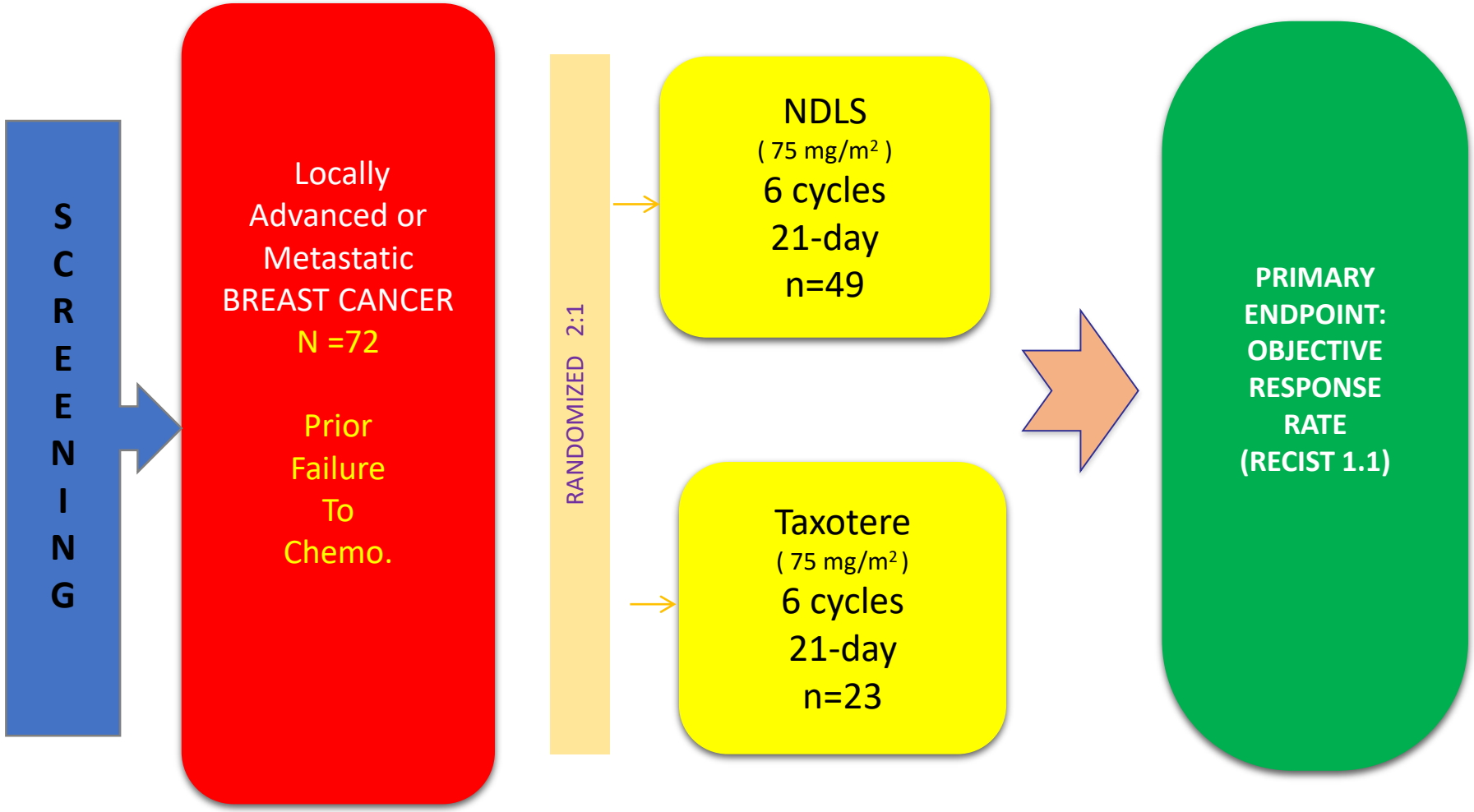
Ahmad et al., J Nanomed Nanotechnol 2015, 6:3

Open label, randomized, multiple dose Clinical Study

Nanosomal Docetaxel Lipid Suspension (NDLS)

Ahmad et.al . Therapeutic efficacy of a novel Nanosomal Docetaxel Lipid Suspension compared to Taxotere in locally advanced or metastatic breast cancer patients. ***Clinical Breast Cancer.*** **2014 Jun;14(3):177-81.**

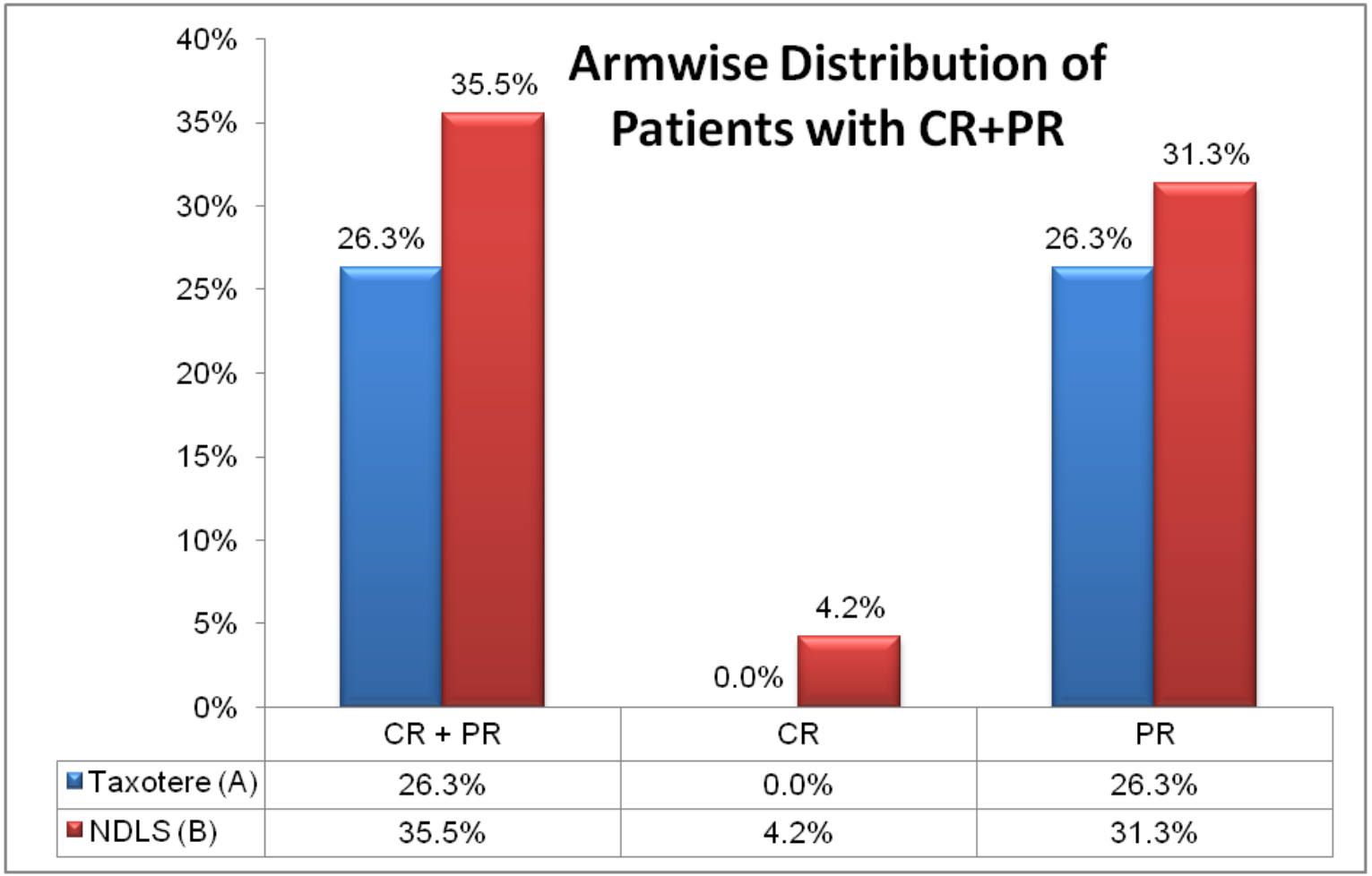
NDLS Efficacy – Study Design



No steroid pre-medications in the NDLS arm

Ahmad A et al. Clin Breast Cancer. 2014 Jun;14(3):177-81.

NDLS - Overall Response Rate



	CR + PR	CR	PR
Taxotere (A)	26.3%	0.0%	26.3%
NDLS (B)	35.5%	4.2%	31.3%

Ahmad A et al. Clin Breast Cancer. 2014 Jun;14(3):177-81.

Adverse Events Profile- NDLS Vs. Conventional Docetaxel®

	NDLS 75 mg/m² %	Conventional Docetaxel® 75 mg/m² %
Adverse Events (all grades)	18	26
Vomiting	10	22
Nausea	14	13
Alopecia	35	26
Diarrhea	29	22
Neutropenia	71	57
Febrile Neutropenia	6	4

Ahmad A et al. Clin Breast Cancer. 2014 Jun;14(3):177-81.

Adverse Events Profile- NDLS Vs. Taxotere®

- **Serious allergic reactions like bronchospasm or swelling of face were not observed with NDLS inspite of no premedication.**
- **Whereas with conventional docetaxel, 2 cases (8.7%) of bronchospasm and 3 cases (13%) of swelling of face were observed**
- No clinically significant changes were observed in Haematology & Biochemistry of NDLS compared to Taxotere®
- Neutropenia was consistent with those reported for Taxotere®

Ahmad A et al. Clin Breast Cancer. 2014 Jun;14(3):177-81.

NDLS based (neo)adjuvant chemotherapy in patients with breast cancer

- Prospective, observational study.

- Patients with stage IIb-III breast cancer received neo/adjuvant doxorubicin and cyclophosphamide (AC) followed by
  - conventional docetaxel (arm A) or
  - NDLS (Doceaqualip; arm B)
  - at a dose 75 mg/m IV every 3-weekly for 4 cycles as neo/adjuvant therapy.

Revathi B et al. J Clin Oncol 40, 2022 (suppl 16; abstr e12591)

Baseline Demographics		
Parameters	**Arm A (Docetaxel)** **(N=30)**	**Arm B (NDLS)** **(N=30)**
Age in years, mean (SD)	48.9 (7.07)	49.2 (5.52)
BSA, kg/m^2, mean (SD)	1.73 (0.29)	1.81 (0.29)
Menopausal status, n (%)		
Pre-menopausal	13 (43.3%)	10 (33.3%)
Post-menopausal	17 (56.67%)	20 (66.67%)
Cancer stage, n (%)		
IIb	14 (46.67%)	11 (36.67%)
IIIa	8 (26.67%)	10 (33.33%)
IIIb	6 (20%)	6 (20%)
IIIc	2 (6.67%)	3 (10%)
ECOG score, n (%)		
0	4 (13.33%)	5 (16.67%)
1	19 (66.33%)	17 (56.67%)

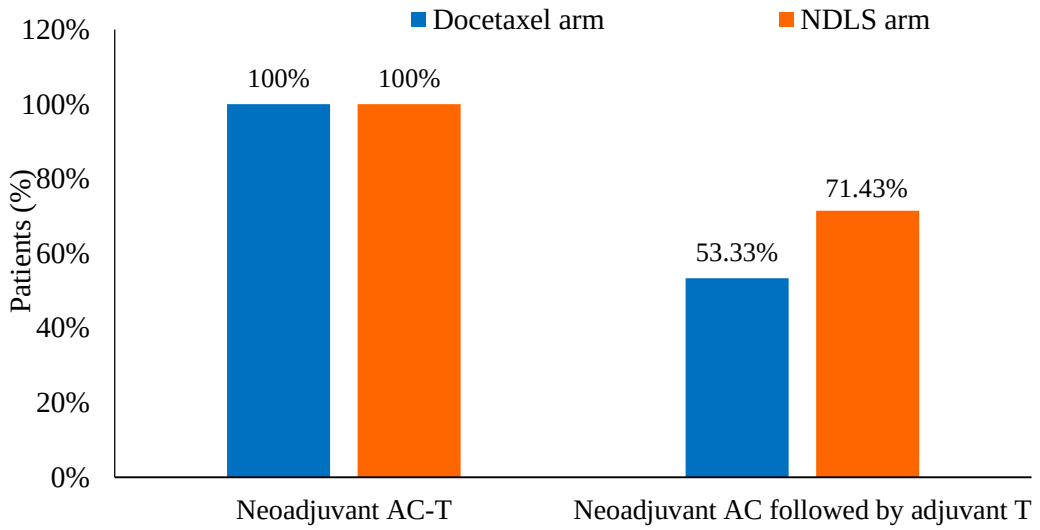
Revathi B et al. J Clin Oncol 40, 2022 (suppl 16; abstr e12594)

Baseline Demographics		
Parameters	**Arm A (Docetaxel)** **(N=30)**	**Arm B (NDLS)** **(N=30)**
Hormone receptor status, n (%)		
ER+/HER2−	2 (6.67%)	2 (6.67%)
ER+/HER2+	23 (76.67%)	20 (66.67%)
Triple positive	20 (66.67%)	20 (66.67%)
TNBC	5 (16.67%)	8 (26.67%)
Ki-67 status, n (%)		
Low	8 (26.67%)	8 (26.67%)
Intermediate	19 (63.33%)	17 (56.67%)
High	3 (10%)	5 (16.67%)

2022 ASCO ANNUAL MEETING

Revathi B et al. J Clin Oncol 40, 2022 (suppl 16; abstr e12591)

Pathologic complete response rates



- Grade 3/4 infusion-related reactions, hyperglycemia and neuropathy were noted in 5, 8 and 3 patients, respectively, in the conventional docetaxel arm while it was not reported in any patient in the NDLS arm.
- NDLS based neo/adjuvant chemotherapy was efficacious in the treatment of breast cancer and showed comparable pCR, CR and OS rates versus conventional docetaxel.

Revathi B et al. J Clin Oncol 40, 2022 (suppl 16; abstr e12591)

Results

Response rates		Arm A (N=30)*		Arm B (N=30)*	
		Neoadjuvant AC-T (n=10)	Neoadjuvant AC-Adjuvant T (n=15)	Neoadjuvant AC-NDLS (n=9)	Neoadjuvant AC-Adjuvant NDLS (n=14)
Pathological response	pCR	10/10 (100%)	8/15 (53.33%)	9/9 (100%)	10/14 (71.43%)
pCR by receptor status	ER+/HER2−	1/1 (100%)	0/0	0/0	0/0
	ER+/HER2+	8/8 (100%)	5/11 (45.45%)	4/4 (100%)	7/11 (63.64%)
	ER−/HER2−	1/1 (100%)	3/4 (75%)	5/5 (100%)	3/3 (100%)
Clinical response	CR	10/10 (100%)	13/15 (86.67%)	8/9 (88.89%)	14/14 (100%)
	PD	0/0	2/15 (13.33%)	1/9 (11.11%)	0/0

AC, doxorubicin and cyclophosphamide; CR, complete response; NDLS, nanosomal docetaxel lipid suspension; pCR, pathologic complete response; PD, progressive disease; T, docetaxel.

P=not significant for all comparisons.

*In arm A, 5 patients received adjuvant AC followed by docetaxel; in arm B, 7 patients received adjuvant AC followed by NDLS.

Revathi B et al. J Clin Oncol 40, 2022 (suppl 16; abstr e12591)

NDLS in patients with advanced NSCLC previously treated with platinum-based chemotherapy

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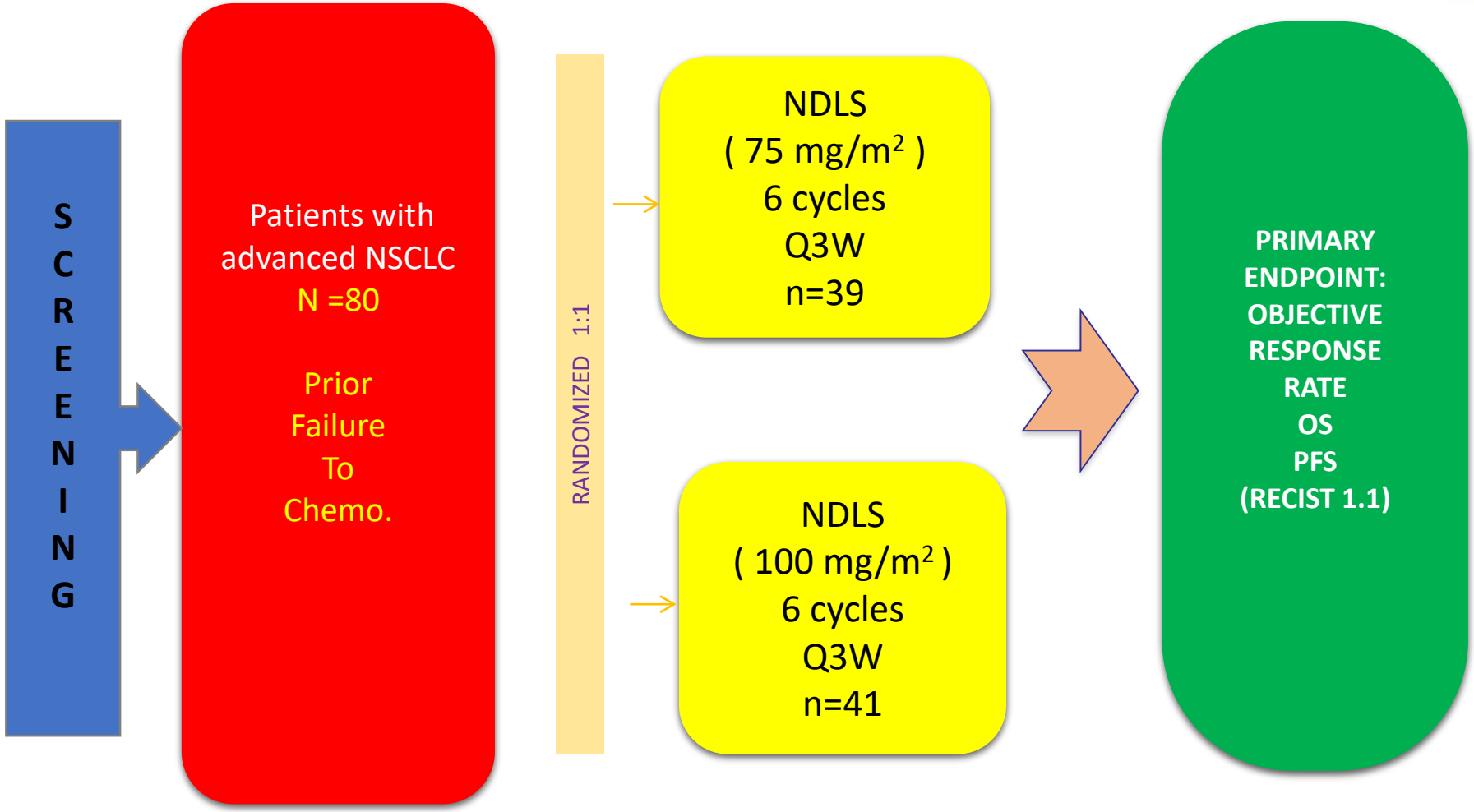
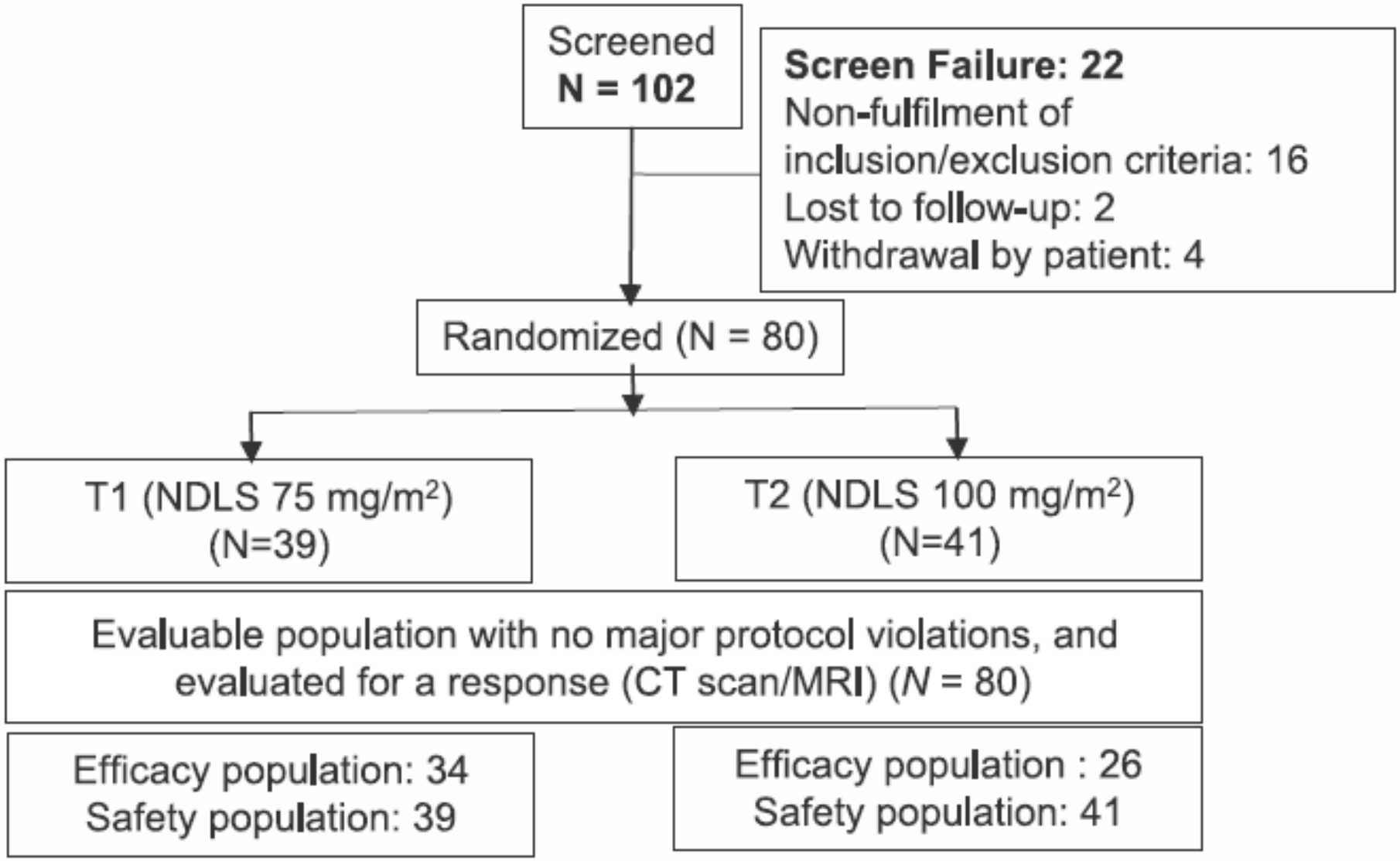


No steroid premedications administered

Deshmukh C et al. ESMO 2022. Poster No. 1038P

Patient disposition



Deshmukh C et al. ESMO 2022. Poster No. 1038P

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Baseline demographics

Parameter (Units)	Safety Set (N=80)		
	NDLS 75 mg/m ^{2} Q3W T1 arm (N=39)	NDLS 100 mg/m ^{2} Q3W T2 arm (N=41)	Total (N=80)
Age (years), mean ± SD	54 ± 7.5	54 ± 5.8	54 ± 6.6
Height (cm) , mean ± SD	163.5 ± 8.6	161.4 ± 7.8	162.4 ± 8.2
Weight (kg) , mean ± SD	58.3 ±12.5	53.6 ± 11.2	55.9 ± 12
BSA (m^2) , mean ± SD	1.62 ± 0.2	1.55 ± 0.2	1.58 ± 0.2
Gender, n (%)			
Male	32 (82)	28 (68)	60 (75)
Female	7 (18)	13 (32)	20 (25)

Deshmukh C et al. ESMO 2022. Poster No. 1038P

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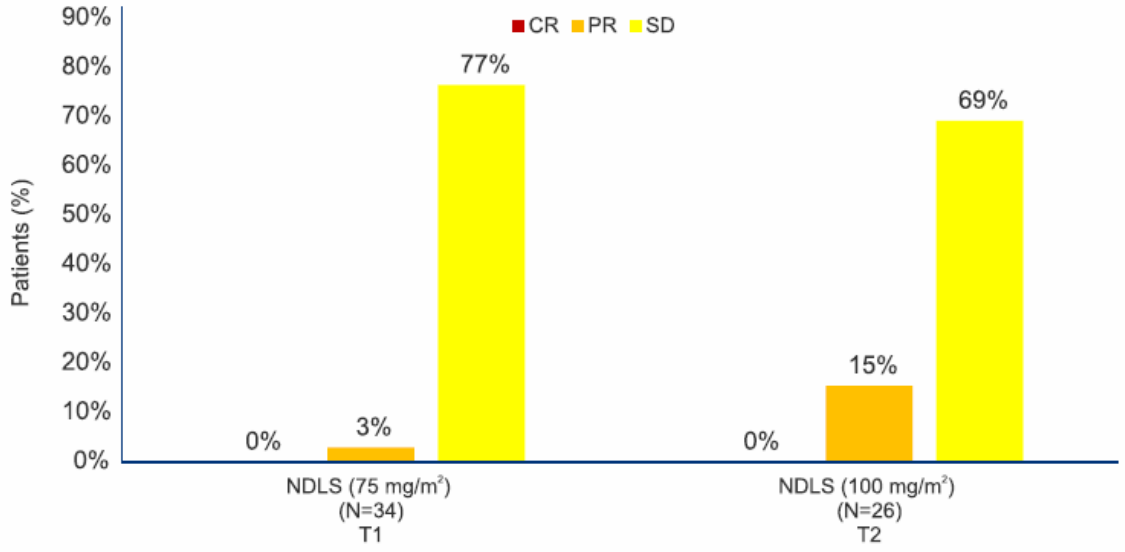
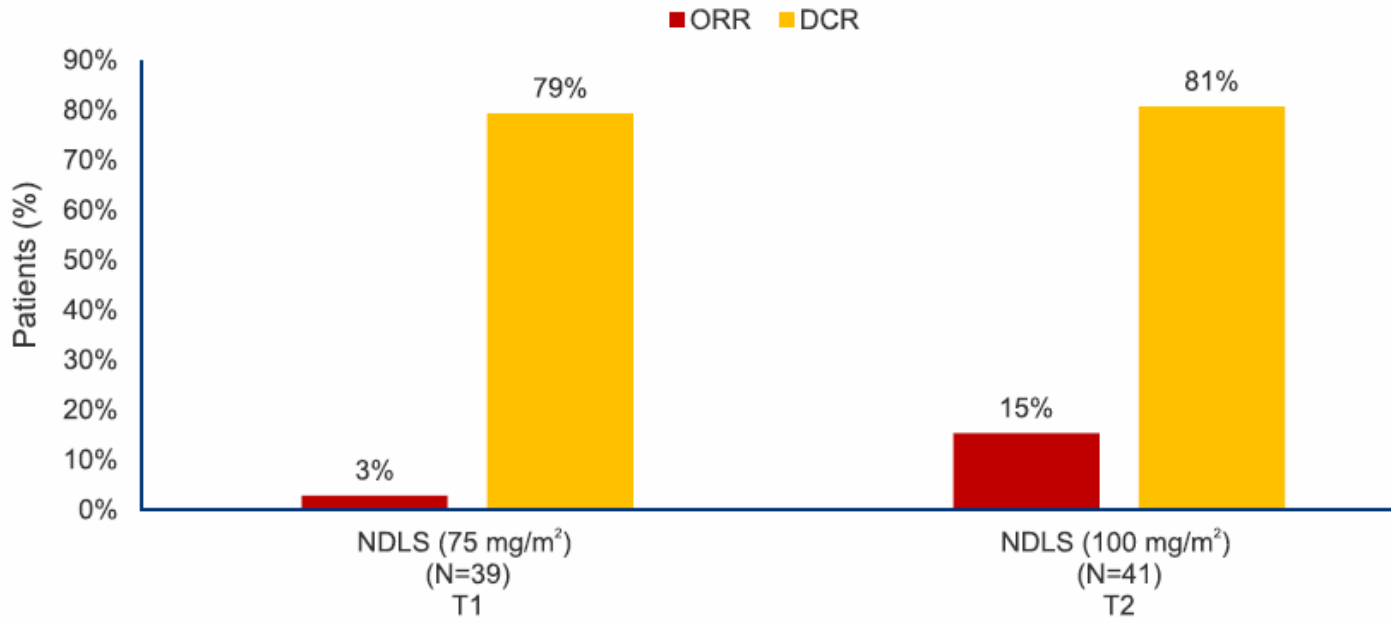
Response rates

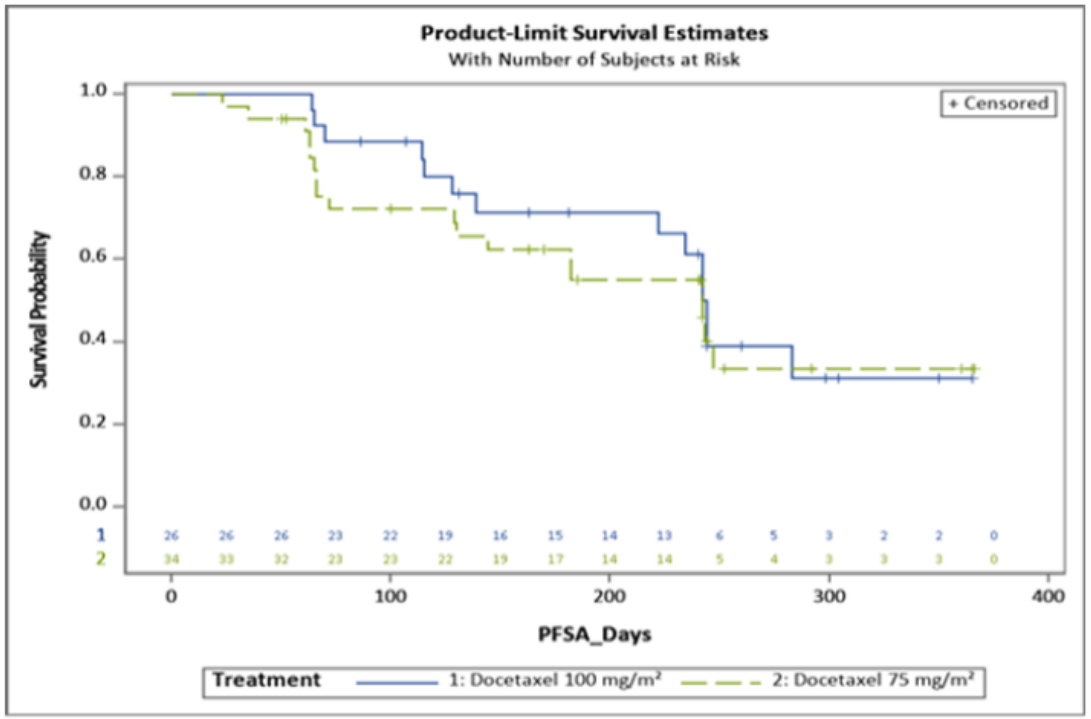


ORR & DCR rates



Deshmukh C et al. ESMO 2022. Poster No. 1038P

PFS at 12 months



Safety

Adverse events	Docetaxel 75 mg/m² (N=39) n (%)		Docetaxel 100 mg/m² (N=41) n (%)	
	Grade 1-2	Grade ≥ 3	Grade 1-2	Grade ≥ 3
Anemia	4 (10.3)	1 (2.6)	7 (17.1)	2 (4.9)
Leukopenia	5 (12.8)	1 (2.6)	5 (12.2)	2 (4.9)
Abdominal pain	4 (10.3)	0	2 (4.9)	0
Diarrhea	4 (10.3)	0	9 (22)	1 (2.4)
Vomiting	9 (23.1)	0	9 (22)	0
Asthenia	9 (23.1)	2 (5.1)	11 (26.8)	1 (2.4)
Pain	3 (7.7)	0	5 (12.2)	0
Pyrexia	6 (15.4)	0	8 (19.5)	0
Decreased appetite	7 (17.9)	0	5 (12.2)	0
Dyspnea	2 (5.1)	1 (2.6)	6 (14.6)	1 (2.4)
Alopecia	3 (7.7)	0	5 (12.2)	0

- At 1-year follow-up, median PFS in NDLS 75 and NDLS 100 mg/m2 arms was 8.07 and 8.13 months, respectively.
- The OS and PFS for both arms were 98.3% and 31.5%, respectively, at 1-year.
- The median OS was not reached for both arms.
- Most patients did not require steroid premedication.
- Anemia, leukopenia, abdominal pain, diarrhea, vomiting, asthenia, pyrexia, and anorexia were commonly reported (≥10% patients) adverse events.
- Only 2 events of grade 3 neutropenia (1 in each arm) were observed.

Hindawi
Prostate Cancer
Volume 2020, Article ID 4242989, 7 pages
https://doi.org/10.1155/2020/4242989

Research Article

A Multicentric, Retrospective Efficacy and Safety Study of Nanosomal Docetaxel Lipid Suspension in Metastatic Castration-Resistant Prostate Cancer

Aseem Samar,[1] Srikant Tiwari,[2] Sundaram Subramanian,[3] Nisarg Joshi,[4] Jaykumar Sejpal,[4] Mujtaba A. Khan,[4] and Imran Ahmad [5]

Results

- Data of 24 patients with mCRPC were analyzed in this study.

- NDLS was administered as a 2-weekly regimen in 37.5% (9/24; all first-line) patients and as a 3-weekly regimen in 62.5% patients (15/24)

Samar A et al. Prostate Cancer. 2020 Nov 24;2020:4242989.

Treatment delivery

Treatment	2-weekly NDLS ($N=9$)	3-weekly NDLS ($N=15$)
Cumulative dose (mg), median (range)	650 (240–1660)	500 (300–750)
No. of cycles, median (range)	14 (6–40)	10 (6–11)
Actual dose intensity (mg/m^2/week), median (range)	21.04 (20–37.50)	18.75 (16.67–25)
Relative dose intensity* (%), median (range)	84 (80–150)	75 (67–100)

*Calculated at a planned dose intensity of 25 mg/m^2/week.

Samar A et al. Prostate Cancer. 2020 Nov 24;2020:4242989.

Efficacy evaluation

Parameter		2-weekly NDLS ($n=9$) (%)	3-weekly NDLS ($n=15$) (%)
PSA decline	PSA decline >50%	77.8%	60%
	PSA decline >90%	55.6%	40%
Median %PSA decline		96.31%	83.29%
Median TTF (days)		200	195
Therapy after NDLS treatment*	Abiraterone ($n=4$)	1	3
	Biculatamide** ($n=5$)	0	5
	Cabazitaxel ($n=1$)	1	0
	Cyclophosphamide ($n=1$)	0	1
	Enzalutamide ($n=2$)	1	1
	Mitoxantrone ($n=1$)	0	1

Samar A et al. Prostate Cancer. 2020 Nov 24;2020:4242989.

Safety profile

AEs	2-weekly group ($N=9$)		3-weekly group ($N=15$)
	Grade I/II, *n* (%)	Grade III, *n* (%)	All grade I/II, *n* (%)
Hematological AEs			
Anemia	8 (88.89)	–	13 (86.67)
Lymphopenia	6 (66.67)	–	5 (33.33)
Nausea	1 (11.11)	–	4 (26.67)
Vomiting	1 (11.11)	–	6 (40)
Weakness	3 (33.33)	–	9 (60)
Hyperglycemia	1 (11.11)	–	–
Anorexia	–	–	1 (6.67)
Diarrhea	–	2 (22.22)	4 (26.67)
Alteration in LFT	–		1 (6.67)
Mouth ulcer	1 (11.11)	–	–
Constipation	2 (22.22)	–	6 (40)

Nanosomal docetaxel lipid suspension (NDLS) as 2-weekly and 3-weekly regimens was effective and well tolerated in managing patients with mCRPC

Samar A et al. Prostate Cancer. 2020 Nov 24;2020:4242989.

Conclusions

- Serious adverse effects like HSRs are common with docetaxel and paclitaxel, and to avoid them we need to use corticosteroids as a premedication.
- Steroids can worsen hyperglycemia and increase risk of infections.
- NDLS is free from solvents and can be administered without steroid premedication.
- No grade 3/4 hypersensitivity reactions were observed despite no steroid premedication.


THANK YOU