A randomized phase III clinical trial evaluating the non-inferiority of reduced dose chemotherapeutic regimens based on CARG risk scores compared to standard doses in older patients with advanced esophageal, esophagogastric, gastric, and biliary tract cancers (CARGO) – results of ethics mandated analysis

Nov 2023
Valencia, Spain

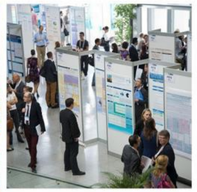
Dr Anita Kumar,
Fellow, Geriatric Oncology (on behalf of the Geriatric Oncology Group, TMH)
Dept. of Medical Oncology
TMH, Mumbai

SIOG
INTERNATIONAL SOCIETY OF GERIATRIC ONCOLOGY

Conflict of Interest Disclosure

I declare the following conflict(s) of interest:

I do not have any relationships with companies to report. ·

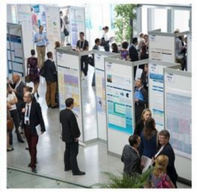


BACKGROUND & HYPOTHESIS

- Dosing schedules for older patients being treated for cancer with chemotherapy is based on extrapolation from clinical trials evaluating younger fitter patients
- Older patients are under-represented in seminal clinical trials
- CGA directed management has shown to reduce side-effects in older patients receiving chemotherapy
- Using lower doses of chemotherapy compared to ‘standard’ doses of chemotherapy has led to improved QOL and similar survivals in older patients with Advanced Gastroesophageal Cancer

JAMA. 2004 Jun 9;291(22):2720-6
Lancet.2021 Nov 20;398(10314):1894-1904.
JAMA Oncol. 2021 Jun 1;7(6):869-877





BACKGROUND & HYPOTHESIS

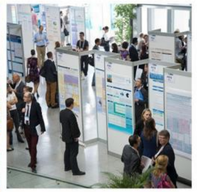
- There is no validated mechanism for choosing dosing schedules for chemotherapy in older patients with cancer
- The CARG score predicts for incidence of grade 3-5 toxicities in older patients with solid tumors receiving chemotherapy
- The CARG score has been validated in older Indian patients with cancer

Hypothesis

To evaluate whether chemotherapy at reduced doses based on CARG risk assessment is non-inferior to chemotherapy at standard doses in older patients with esophageal, gastric, and biliary tract cancers in terms of Overall Survival (OS)

J Clin Oncol. 2011 Sep 1;29(25):3457-65
BMJ Open. 2021; 11(6): e047376.
10.1200/JCO.2021.39.15_suppl.e24023 Journal of Clinical Oncology 39, no. 15_suppl





•. 2011 Sep 1;29(25):3457-65

MATERIALS & METHODS – CARG SCORE

Risk Factor	Score
Age ≥72 years	2
Cancer type GI or GU	2
Standard dose chemotherapy	2
Polychemotherapy	2
Hb (<11g/dL male<10g/dL female)	3
Creatinine clearance<34ml/min	3
Hearing – fair or worse	2
≥1 fall in last 6/12	3
Need help with medications	1
Limited walking 1 block	2
Decreased social activity because of physical/emotional health	1

GI cancers receiving doublet chemotherapy cannot be low risk – atleast intermediate/high risk

Risk stratification

- Low risk (0-5 points)
- Intermediate risk (6-9 points)
- High risk (10-19 points)

Approximately 100 metres

MATERIALS & METHODS

Inclusion criteria	• **Patients with advanced or metastatic disease of esophagus (SCC), stomach (adenocarcinoma), Biliary tract cancer (adenocarcinoma)** • **Age** >=65 years 60- 65 years with a G8 score of <=14 • **ECOG performance status 0-2** • Patients who can give informed consent for the study. • Patient does not have any contraindications to receive chemotherapy, • Adequate baseline blood tests • No major surgery within last 4 weeks, Written patient consent form
Exclusion criteria	• Clinically significant heart problems • Severe breathing problems • Baseline significant nerve problems

•. 2011 Sep 1;29(25):3457-65

MATERIALS & METHODS

Regimens allowed

- Paclitaxel plus Carboplatin q 3 weekly
- CAPOX q 3 weekly
- mFOLFOX q 2 weekly
- mFOLFIRI q 2 weekly
- Gemcitabine-Cisplatin q 3 weekly
- Gemcitabine-Oxaliplatin q 2 weekly

Interim analysis mandated by Ethics (Stopping rule)

An analysis of PFS after accrual of 10% of patients in the study, i.e., 42 patients (convenience sample size) will be conducted. A statistical analysis of the PFS in both arms of the study was conducted. If a statistical difference in median PFS between the 2 arms with superiority in either arm is seen with an alpha of <0.05, IEC will be informed

Patients with advanced/metastatic

1.SCC-esophagus/GE jxn
2.Adenocarcinoma - GE junction/stomach
3.BTC

PS 0-2

Age >=60 years

N=410

Arm A (Standard)

Palliative chemotherapy - 100% doses

CARG risk score-based treatment dosing of palliative chemotherapy

Low risk - 100%
Intermediate risk - 80%
High risk - 60%

Arm B (Experimental)

Primary Endpoint
Non inferior OS

Secondary endpoints

- PFS
- RR
- QOL
- OTU
- Adverse event rates

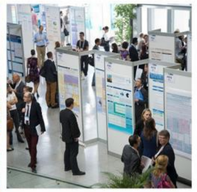
SIOG
INTERNATIONAL SOCIETY OF GERIATRIC ONCOLOGY

Sample size estimation

The estimated 12-month OS with standard chemotherapy in esophageal, GE junction, gastric, and BTC with treatment regimens, mentioned is approximately 33%. Assuming the CARG assessed dose modified cohort will not have a 12-month OS of less than 30%, a randomized study with a power of 80% and alpha of 0.05 with a non-inferiority margin of 15% will require a total of 372 patients. To further explain, if there is a true difference in favor of the standard treatment of 3% (33% vs 30%), then 372 patients are required to be 80% sure that the upper limit of a one-sided 95% confidence interval (or equivalently a 90% two-sided confidence interval) will exclude a difference in favor of the standard group of more than 15%. Assuming an attrition rate of 10% per arm, a total of 410 patients will be required for completion of the study.

2023
VALENCIA
SPAIN
9-11 NOV





•. 2011 Sep 1;29(25):3457-65

RESULTS

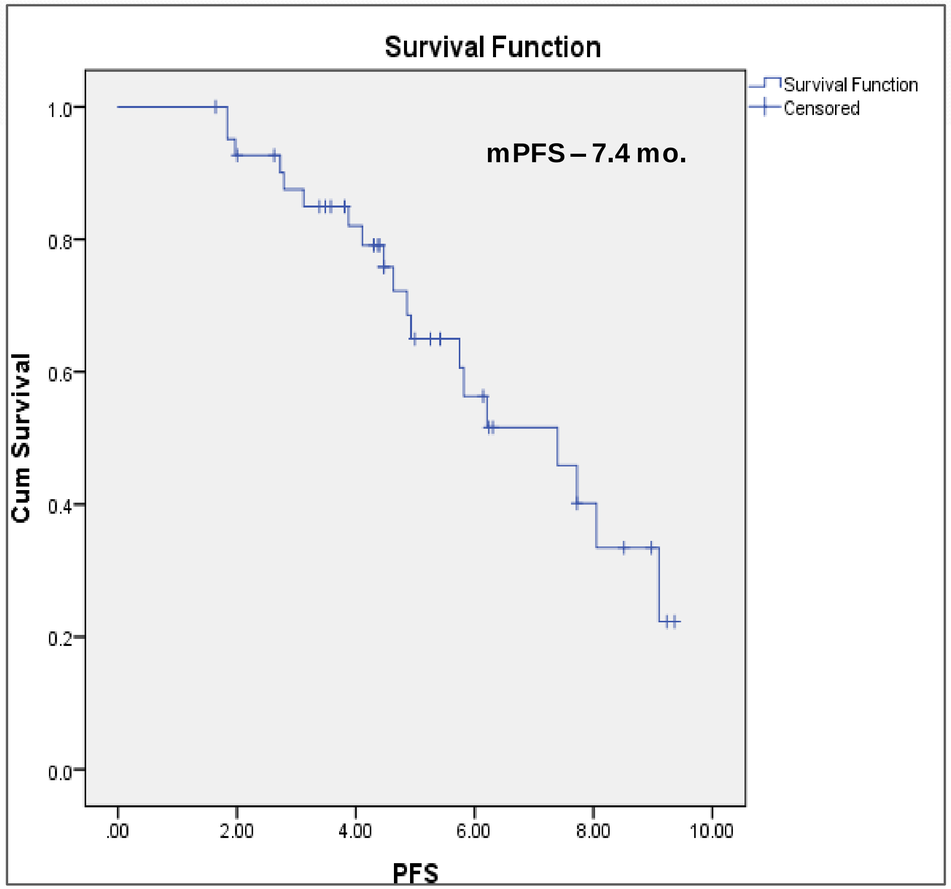
Characteristic	Standard (%) N=21	Experimental (%) N=21	Overall (%) N=42
Median age (yrs.)	66	69	68
ECOG PS			
• 0	0 (0)	0(0)	0(0)
• 1	15(71)	18(86)	33(79)
• 2	6(29)	3(14)	9(21)
Primary site			
• Biliary tract	16(76)	14(67)	30(71)
• G/GE junction	4(19)	5(24)	9 (21)
• Esophageal	1(5)	2(10)	3(7)
CARG Score			
• Intermediate Risk	15(71)	15(71)	30(71)
• High Risk	6(29)	6(29)	11(26)
Dosing			
• 100%	21 (100)	0	21 (50)
• 80%	0	11 (52)	11 (26)
• 60%	0	10 (48)	10 (24)

Characteristic	Standard (%) N=21	Experimental (%) N=21	Overall (%) N=21
Impaired MNA	14(67)	18(86)	32(76)
Psychological issues	9(43)	14(67)	23(55)
Impaired cognition	3(14)	2(10)	5(12)
Presence of falls	1(5)	0(0)	1(2)
Presence of deficits in function	19(90)	17(81)	36
CIRS – G >4	2(10)	8(38)	10(24)
Polypharmacy	4(19)	6(29)	10(24)

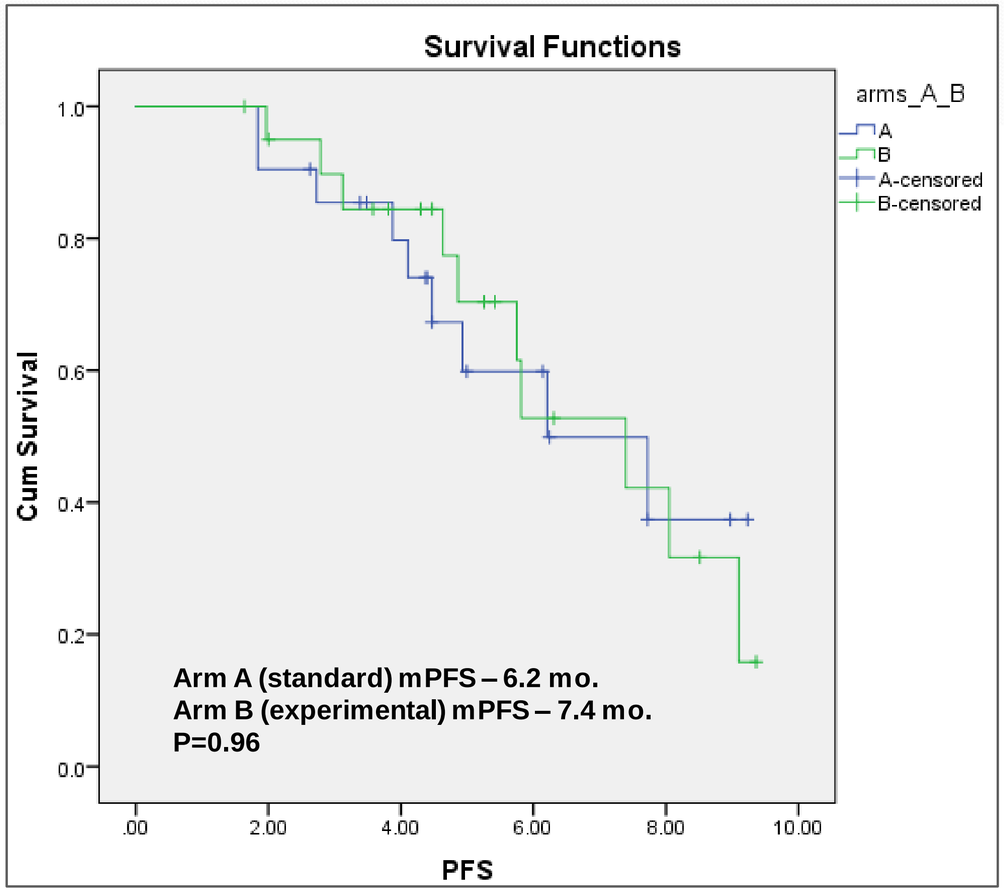
•. 2011 Sep 1;29(25):3457-65

RESULTS – Median Progression Free Survival (mPFS) & Toxicity

Whole cohort (N=42)



Standard vs Experimental arms



Grade 3 and grade 4 toxicities

Standard arm – 22%

Experimental arm – 14%

SIOG
INTERNATIONAL SOCIETY OF GERIATRIC ONCOLOGY

CONCLUSIONS

- The initial IEC mandated safety analysis suggests that there is no significant difference in mPFS between the standard and experimental arms in the study
- The incidence of grade 3 and grade 4 chemotherapy related side-effects is lesser in the experimental arm as expected
- The study proceeds to full enrolment of 410 patients as planned and enrolment is expected to be completed in around three years from now

ACKNOWLEDGEMENTS

To all the patients and their families who are and will be part of the trial

To all members of the Geriatric Oncology Clinic

To all members of the GI Medical Oncology Unit

Department of Medical Oncology, TMH, Mumbai

THANK YOU


2023
VALENCIA
SPAIN
9-11 NOV