Optimizing chemotherapy in the first line for frail older pts with advanced non-small cell lung cancer

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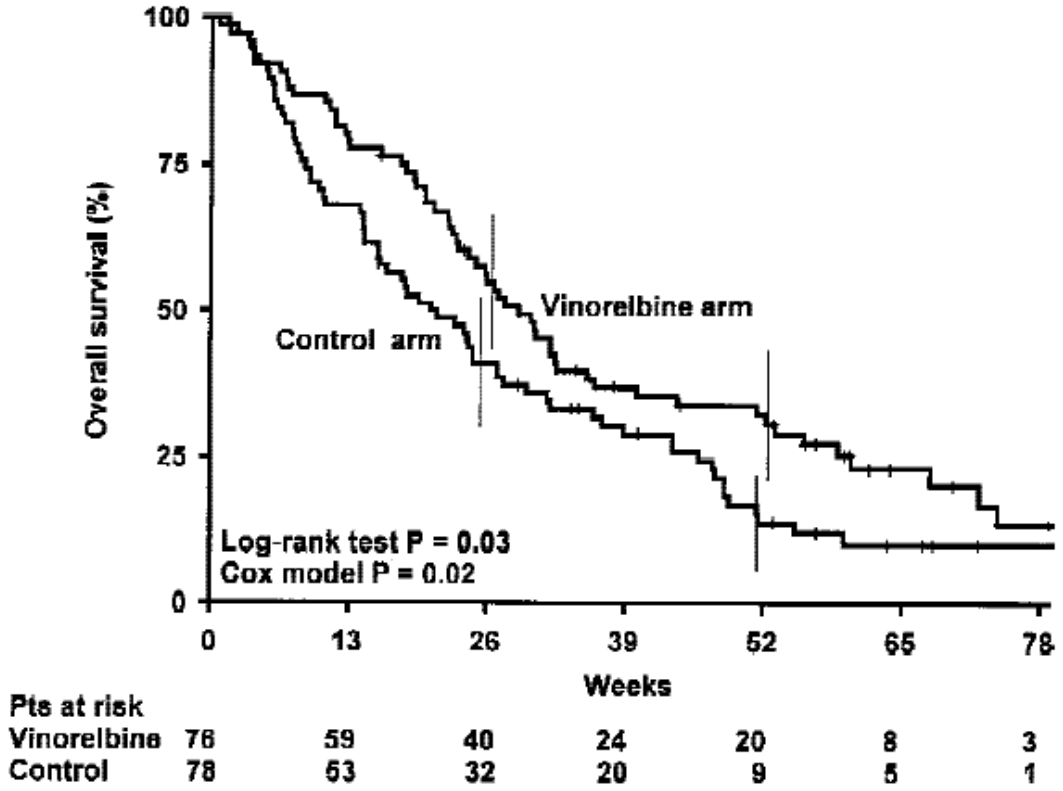
Background

- Incidence of lung cancer peaks at age 65 years, making lung CA mostly a disease of older persons
- Older persons have been excluded from most of the pivotal trials
- The management of older persons with cancer is complex and unfortunately, robust evidence is lacking

Background: ELVIS: Chemo vs BSC

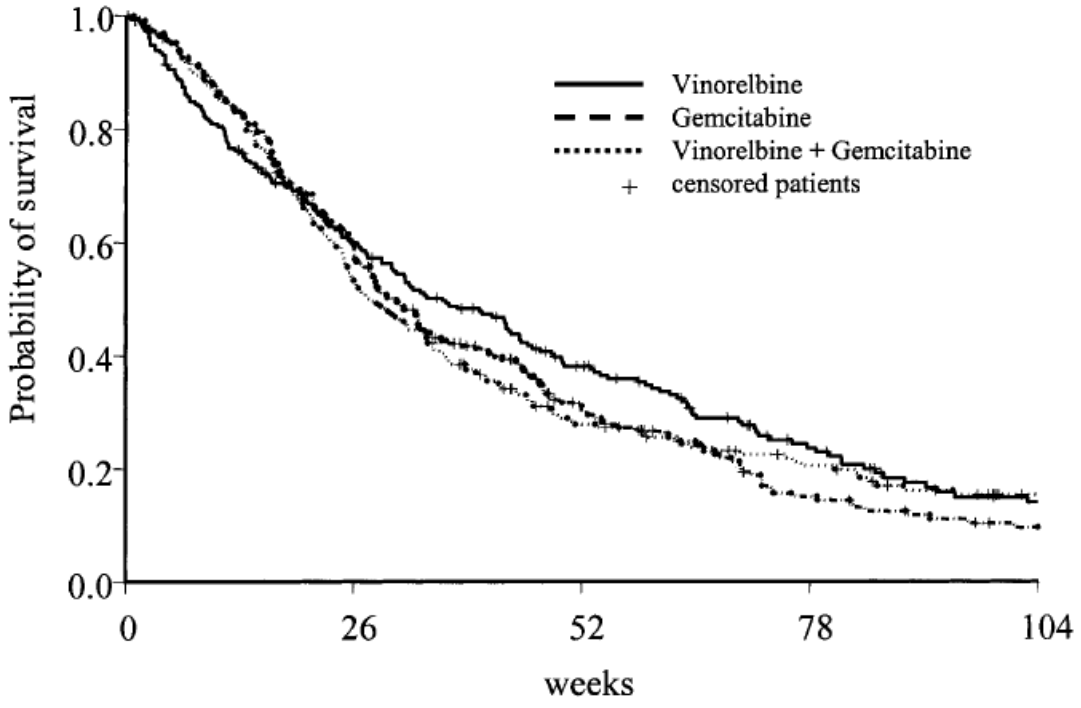
- **E**lderly **L**ung **C**ancer **V**inorelbine **I**talian **S**tudy
- Phase III RCT in 161 patients > 70 years
- Stage IIIB/IV NSCLC randomized to BSC vs Vinorelbine 30 mg/m^2 D1,8 Q 21d
- ORR: 19.7%
- Toxicities: gr 3/4 neutropenia-10%, gr 2/3 anemia-16%, constipation and fatigue
- OS improved: V-28 wks vs 21 wks-BSC; HR, 0.65 (95% CI, 0.45-0.93)
- 1-yr survival: V-32%, BSC-14%



Gridelli, et al. JNCI 1991

Background: MILES-Monochemo vs Non-platinum combo

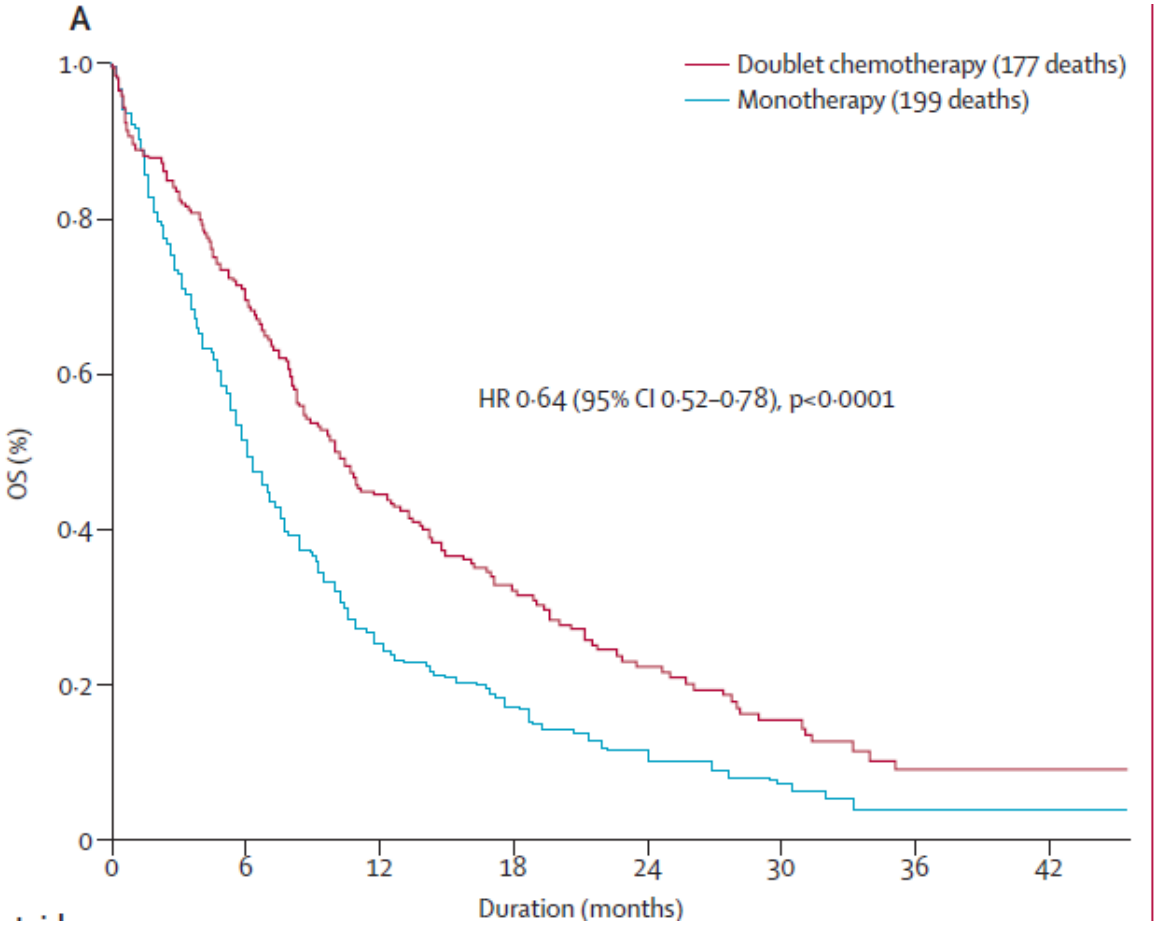
- **M**ulticenter **I**talian **L**ung **C**ancer in the **E**lderly **S**tudy
- Phase III RCT in 698 patients > 70 years old.
- RND to Vlb or Gem or Vlb + Gem
- No improvement in ORR: VG-21%, V-18%, G-16%; VG vs V: P=0.47; VG vs G: P=0.18
- No improvement in PFS: VG-19 weeks, V-18 weeks, G-17 weeks; VG vs V: P=0.32, HR-0.95 [95% CI, 0.76-1.15]; VG vs G: P=0.31, HR-0.95 [95% CI, 0.78-1.16])
- No improvement in OS:VG-30 weeks, V-36 weeks, G-28 weeks; VG vs V: P=0.93, HR-1.17 [95% CI, 0.95-1.44], VG vs G: P=0.69, HR-1.06 [95% CI, 0.86-1.29]).
- Combination was more toxic
- No difference in QoL



Gridelli, et al. JNCI 2003

Background: IFCT-0501: Monochemo vs Plat-comb

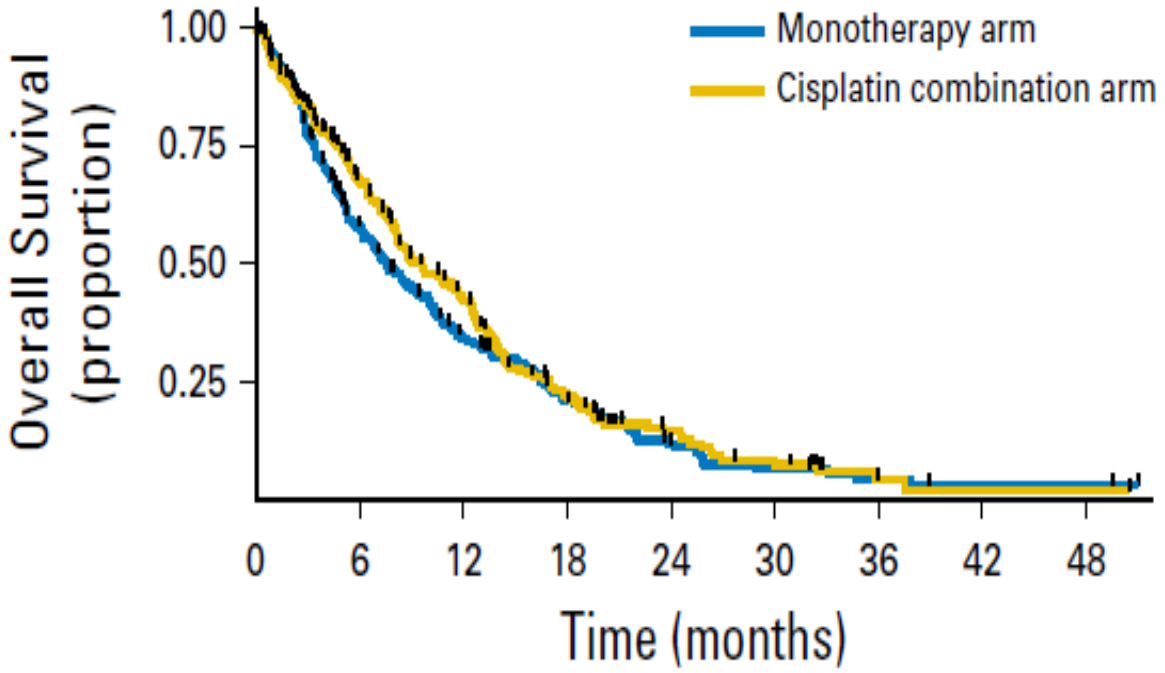
- Phase III RCT in 451 pts 70-89 yrs
- RND to Pacli/Carbo x 4 # or Vlb or Gem
- Toxicities increased:
  - Neutropenia (48.4% versus 12.4%),
  - Febrile neutropenia (9% versus 3%)
  - Asthenia (10.3% versus 5.8%)
  - Treatment-related deaths-4.4% in PC arm
- Median OS significantly improved: V or G-6.2m to PC-10.3m; HR, 0.64; 95% CI, 0.52-0.78; P<0.0001
- 1-yr survival: V or G-25.4%, PC-44.5%



Quoix, et al. Lancet 2011

Background: MILES-3 & MILES-4: Monochemo vs Cisplatin-comb

- Phase III RCT in 531 pts > 70 yrs
- RND to
  - Pemetrexed alone OR Gemcitabine alone
  - Cisplatin + Pemetrexed or Gemcitabine
- Toxicities significantly increased
- ORR improved:15.5% vs 8.5%, P=0.02
- PFS improved: 4.6 vs 3 months; HR, 0.76; 95% CI, 0.63-0.92; P=0.006
- OS not significant: 9.6 vs 7.5 months; HR, 0.86; 95% CI, 0.7-1.05; P=0.14



Gridelli, et al. JCO 2018

NCCN Guidelines Version 5.2021
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PD-L1 EXPRESSION POSITIVE (≥1%–49%)[ll]

FIRST-LINE THERAPY[oo]

PD-L1 expression positive (≥1%–49%) and negative for actionable molecular markers and no contraindications to PD-1 or PD-L1 inhibitors[kkk]

→ PS 0–2

→ Adenocarcinoma, large cell, NSCLC NOS

- **Preferred**
  (Carboplatin or cisplatin) + pemetrexed + pembrolizumab (category 1)
- **Other Recommended**
  Carboplatin + paclitaxel + bevacizumab[ss] + atezolizumab (category 1)
  or
  Carboplatin + albumin-bound paclitaxel + atezolizumab
  or
  Nivolumab + ipilimumab + pemetrexed + (carboplatin or cisplatin) (category 1)
- **Useful in Certain Circumstances**
  Nivolumab + ipilimumab (category 1)
  or
  Pembrolizumab (category 2B)[sss]

→ Response or stable disease → **Continuation maintenance[oo]**
- Pembrolizumab (category 1)[lll]
- Pembrolizumab + pemetrexed (category 1)[mmm]
- Atezolizumab and bevacizumab (category 1)[nnn]
- Atezolizumab[ooo]
- Nivolumab + ipilimumab (category 1)[ppp]

→ Progression → See Systemic Therapy[qqq] (NSCL-K 1 of 5) or Subsequent Therapy (NSCL-K 4 of 5)[qqq]

→ Squamous cell carcinoma

- **Preferred**
  Carboplatin + (paclitaxel or albumin-bound paclitaxel) + pembrolizumab (category 1)
- **Other Recommended**
  Nivolumab + ipilimumab + paclitaxel + carboplatin (category 1)
- **Useful in Certain Circumstances**
  Nivolumab + ipilimumab (category 1)
  or
  Pembrolizumab (category 2B)[sss]

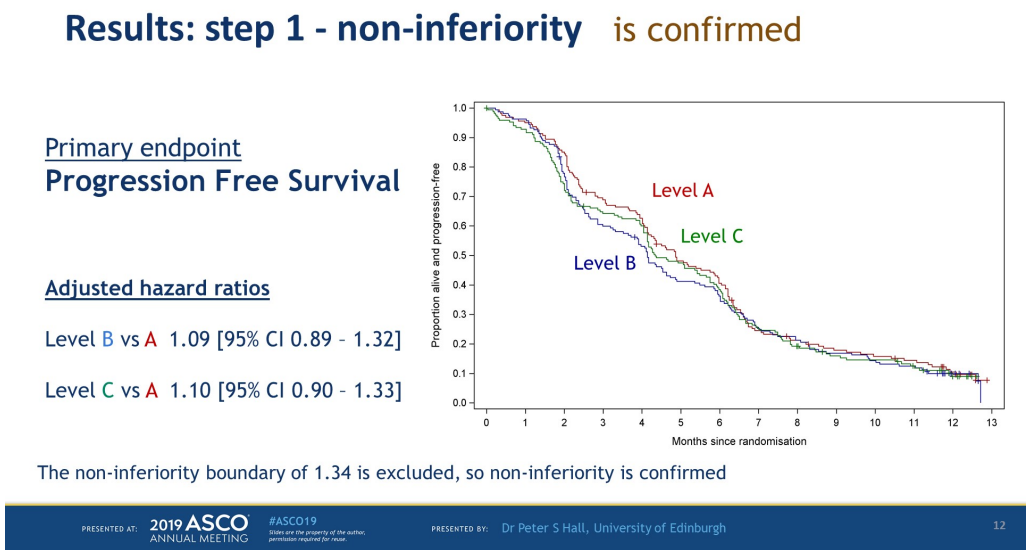
→ Response or stable disease → **Continuation maintenance[oo]**
- Pembrolizumab[lll,rrr]
- Nivolumab + ipilimumab (category 1)[ppp]

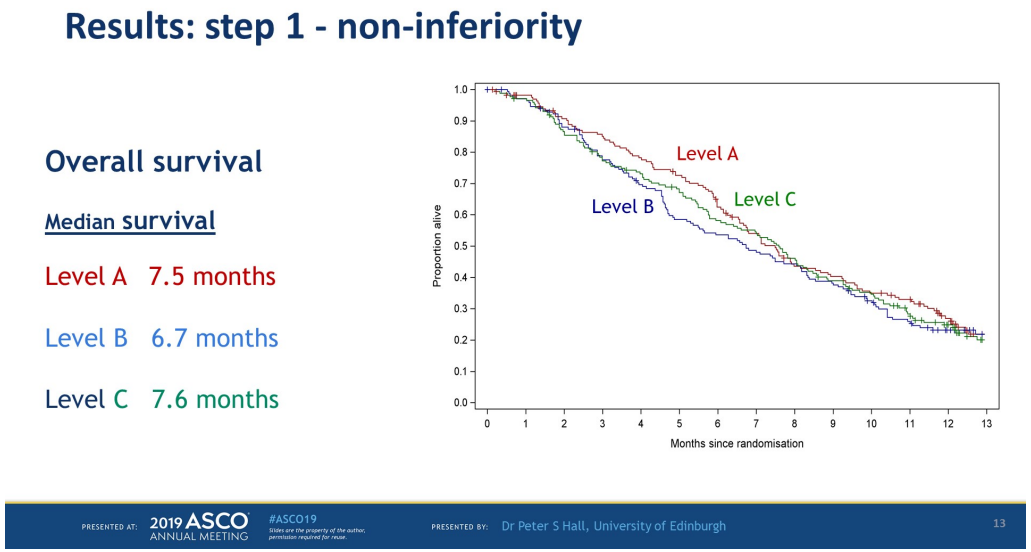
→ Progression → See Systemic Therapy[qqq] (NSCL-K 2 of 5) or Subsequent Therapy (NSCL-K 4 of 5)[qqq]

See PD-L1 expression positive (≥50%) NSCL-33

Background: GO2 trial (advanced gastroesophageal CA)

- Phase III non-inferiority RCT in 514 frail elderly pts
- RND to
  - Level A-Full dose Cape-Ox (n=170)
  - Level B-80% dose Cape-Ox (n=171)
  - Level C-60% dose Cape-Ox (n=173)
- Non-inferiority of PFS confirmed for
  - Level B vs Level A (HR, 1.09; 95% CI, 0.89-1.32)
  - Level C versus Level A (HR, 1.1; 95% CI, 0.9-1.33)
- Toxicities lowest for Level C
- No difference in OS
- OTU scores at 9 weeks best for Level C





Hall, et al. ASCO 2019

Background: GO2 trial-OTU

"Overall Treatment Utility" (OTU) scored after 9 weeks:

good OTU

all of:

- clinician score "benefit"*

and

- patient satisfied

and

- no major toxicity

and

- no drop in QL¶

intermediate OTU

either:

- clinician score "no benefit"
- (but patient satisfied and no major toxicity or QL drop)

or

- either patient dissatisfied or major toxicity or QL drop
- (but clinician scores benefit)

poor OTU

both:

- clinician score "no benefit"

and any of

- patient dissatisfied
- major toxicity
- QL deterioration

or

- patient has died

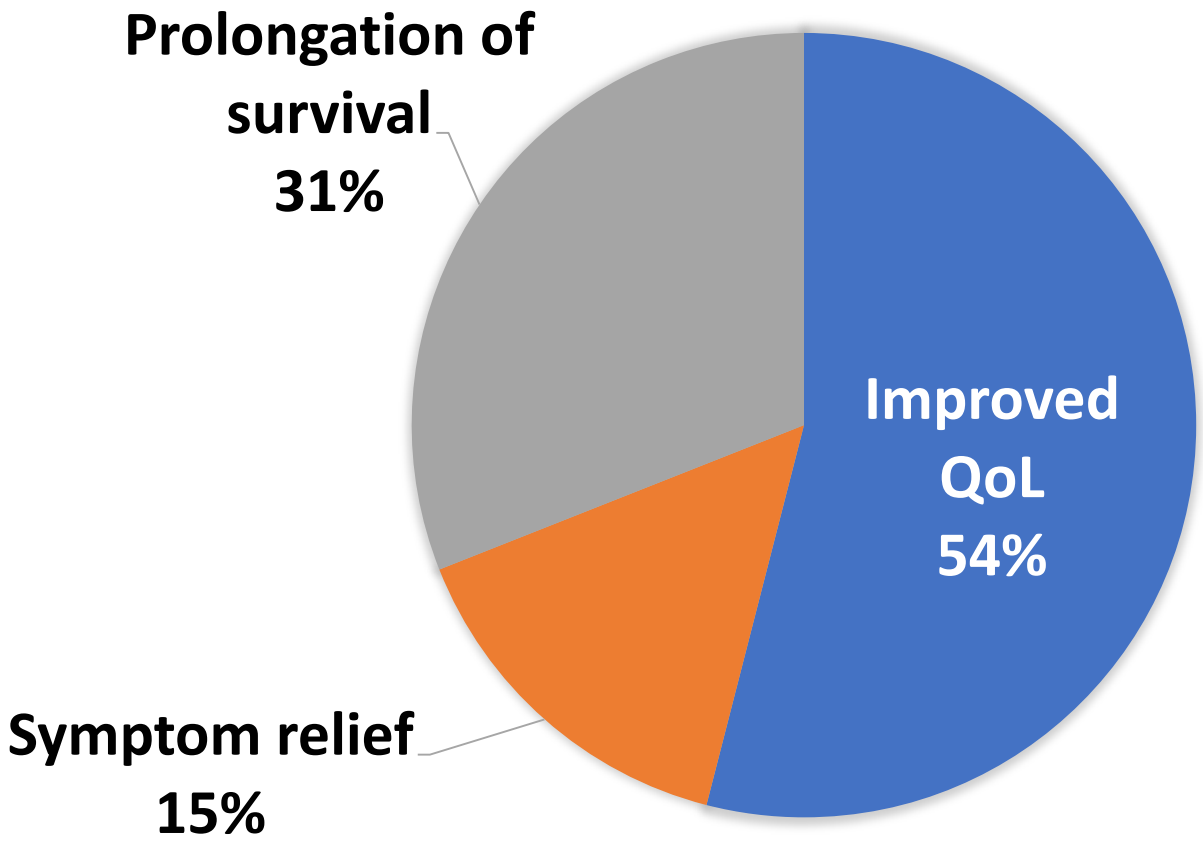
NB: decision rules to ensure OTU can be scored in 100% patients

*clinician score of "benefit": no clinical/radiological evidence of cancer progression and no general health deterioration

¶ drop in QL defined as ≥16% fall (≥2 on the 12-point EORTC global QL scale). Cocks, K et al., Eur J Cancer (2012) 48, 1713-21

First developed in FOCUS2 trial [Seymour, et al (2011) The Lancet 377(9779): 1749-1759]. For more info see www.blogs.ed.ac.uk/canceroutcomes

EXPECTATIONS FROM THERAPY IN PTS WITH ADVANCED NSCLC (N=94, DEC 2020 TO JULY 2021)



Unpublished data from the geriatric oncology clinic at Tata Memorial Hospital, Mumbai

Aim and Hypothesis

- Aim: To identify the optimal dose of platinum-based combination chemotherapy, balancing efficacy with toxicities, QoL and patient tolerability.

- Hypothesis: A lower dose of platinum-based combination chemotherapy in older patients with advanced NSCLC is non-inferior to the standard full dose platinum-based chemotherapy, with lower toxicity, maintenance of QoL and better OTU.

Endpoints

- Primary:
  - OS
- Secondary:
  - PFS
  - Toxicities
  - QoL
  - OTU
  - Response rate
  - Chemotherapy-induced cognitive impairment
  - PK/PD
  - Factors that affect OS, PFS and predict toxicity

Study Schema

ELIGIBILITY CRITERIA

- Age ≥ 60 yrs
- Histologic/cytologic NSCLC
- Stage IIIB not amenable to radical therapy or Stage IV
- First-line palliative intent
- No activating EGFR or ALK mutation
- ECOG PS 0 to 2
- Adequate organ function
- No hypersensitivity to pemetrexed, paclitaxel or carboplatin
- Score on the G8 ≤ 14

STRATIFY

- Age (=/< 70 vs > 70)
- ECOG PS (0/1 v.2)
- HPR (non-sq vs sq)
- Plan for IO (yes vs no)

Randomized
1:1
Open Label

ARM A (FULL DOSE)
-ADENO Pem 500mg/m^2 + Carbo AUC 5 Q21d x 4 → maint Pem Q21d OR
-OTHERS: Pacli 175 mg/m2 + Carbo AUC 5 Q21d x 4

ARM B (LOW DOSE)
Same chemo meds as Arm A but 75% dose

Evaluation: Clinical- Q 3 wks in both arms; Radiologic-Q 3 cycles, then every 2-3 months
Duration of Therapy: until PD, unacceptable toxicity or consent withdrawal.

Treatment Plan

- Arm A:
  - AdenoCA: Pem 500 mg/m^2 + Carbo AUC 5 Q 3 weeks x 4→maint Pem. If Pembrolizumab is affordable: Pembro 200mg Q 3 weeks for max 35 cycles
  - All other histologies: Pacli 175 mg/m^2 + Carbo AUC 5 Q 3 weeks x 4. If Pembrolizumab is affordable: Pembro 200mg Q 3 weeks for max 35 cycles
- Arm B:
  - Same chemo meds as Arm A, but at 75% dose
  - Pembrolizumab, if affordable, will be given at full dose.

Sample Size

- Non-inferiority is defined as an increase in HR <1.33 in Arm B-dose reduced chemotherapy regimen) as compared to Arm A-Standard full dose regimen.
- One-year survival of ≥ 33% and 23% are assumed in the standard arm and experimental arm, respectively.
- As the nature of treatment is palliative, a slight increase in the risk of death will be considered clinically non-significant and may be offset by a decrease in toxicity or cost.
- Type 2 error of 20%
- One-sided type I error of 5%
- Equal allocation between both arms
- Accrual over 2 years and a study duration of 4 years
- We will require 220 events and sample size of 308 patients.

Ethics committee comments…

Ethics committee comments-July 2020

IEC comments were as follows:

1. Is doublet full dose chemotherapy the standard of care in elderly frail patients? The IEC has concerns that the toxicity in this 'standard' arm will be unacceptably high.
2. Is there phase 2 data for this particular comparison?
3. Sample size 308 - are we expecting outcomes to be similar in adeno and squamous tumors? Please clarify.
4. What proportion of each tumour type is likely to be accrued?
5. The use of pembrolizumab depending on affordability is unethical. How will the PI ensure that equal proportions of patients in each arm received pembrolizumab? In addition, there are concerns that the addition of pembrolizumab to full dose doublet chemotherapy may not be tolerated. PI to standardize the use of pembrolizumab between arms. It is not clear why participants should bear the cost of immunotherapy.
6. For PFS, why is "Lost to follow up" considered an event? It should be censored data.
7. FACT and MMSE are available in English only. PI to use standard validated translations of these questionnaires in regional languages.
8. The use of growth factor needs to be standardized. Dose modification guidelines need to be clearly stated.
9. Compensation for study related toxicity needs to be provided to patients in both arms.
10. Informed consent document: Risk benefit to be re-written
11. Overall, the IEC feels that there is inadequate evidence to support the safety and tolerability of the full dose doublet chemotherapy in elderly frail patients. PI to clarify if this is standard of care in our institute.
12. Risk and benefit in the ICF should be revised to include all the possible side-effects. Treatment for study related injury should be mentioned in the budget. Treatment of study related injury should apply to both arms.

Status: Revisions with major modifications for resubmission

Ethics committee comments-Oct 2020

IEC comments were as follows:

1. The background information provided deals mainly with either elderly or frail patients, and not the population of frail AND elderly patients, who are likely to have far more complications. The only reference provided for the combination of frail and elderly patients deals with a different cancer (esophago gastric) which has different implications from lung cancer. There is inadequate data to support the use of full dose chemotherapy in elderly and frail patients. Early phase data is needed before embarking on a phase 3 trial
2. The IEC has concerns about the age cut-off of 60 years used in the study. A 60 year-old with a good PS is eligible for full dose chemo and may be harmed by randomization to low dose chemo. The IEC feels that the age criteria for inclusion in the study need to be revised
3. The inferiority margin chosen is very large and needs justification.
4. Please provide the entire correspondence from Dr Kanesvaran. At present, we can only see his response email, without knowing what the question asked to him was. Also, his reply seems to suggest that full dose chemo is SUPERIOR to low dose which goes against the premise of this trial

Status: Revisions with major modifications for resubmission

Ethics committee comments-May 2021

IEC comments were as follows:

1. The frailty score in the GI questionnaire is a 17 point score. There would be a wide margin in the score obtained (3-17) across the age group. This needs to be made tighter. They could be sub-grouped/stratified
2. It is very unclear why the PI, citing a lack of evidence is going to a phase III study instead of going for a phase II study or phase three study with an early interim analysis or a doing it in a defined group group of patients, maybe 60-70 years instead of selecting all patients above 60 years of age.
3. The explanation given regarding the unequal distribution of Pembrolizumab in the two arms due to affordability issues (response letter dated 07/09/2020 discussed in the October meeting of IEC-II) was not acceptable to the IEC as there is clear evidence that Pembrolizumab would definitely impact the OS.
4. Criteria for discontinuation are extremely subjective and very prone to bias-"Progressive disease (PD), either radiological (scans read by oncologic radiologists, but no central review) or clinical, as determined by the

Ethics committee comments-May 2021 (contd)

investigator, unacceptable toxicity as determined by the patient or investigator, the investigator determines that continuation of treatment is not in the patient's best interest." PI to introduce objective, unbiased and blinded criteria for discontinuation.

5. Mr.Ravindran Kanesvaran has only commented on age and performance status and not on frailty.
6. Sample size calculation: A 10% difference in OS (33% relative increase) is unacceptable. Also, the protocol mentions one-sided 5% alpha in the sample size calculation but in the statistical analysis, it mentions "Tests will be conducted as follows: non inferiority tests at one-sided $\alpha=0.025$ level; superiority tests at two-sided $\alpha=0.05$ level; and two-sided CIs at 95%." Please clarify why a one sided alpha of 2.5% is chosen and why superiority/two-sided tests are planned. Please re-calculate the sample size using a more reasonable margin of non-inferiority.
7. The IEC still has concerns about subjecting frail elderly patients to full dose chemotherapy with the likelihood of excessive toxicity.
8. Early monitoring and three monthly reporting of all AEs is essential
9. All study assessments to assess response / discontinuation to be made by an independent blinded radiologist and documented on EMR
10. Please hand over the study to another researcher from the same DMG who will be the new PI.

Status: Revisions with major modifications for resubmission

My questions?

- Is the study ethically appropriate in the current form?
- What changes should I make to the design of the study, to make it acceptable to the ethics committee?
  - Should I include all patients, rather than frail older patients?
  - Should I restrict the age criteria to only a particular cohort like 60 to 70 years, as suggested by the IEC? What would the rationale of this be?
  - Should this be a phase II design rather than a phase III non-inferiority RCT?