Assessing the VALue to patients of PROgression Free Survival (AVALPROFS) Quality of Life Results

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1) Background

Patients value quality of life (QoL) not just length of life, but QoL data are limited for drugs that have shown only progression free survival (PFS) or modest overall survival (OS) benefits in clinical trials. Hypothetical studies suggest control of cancer is 'worth' treatment related side effects (SEs). In AVALPROFS we examined this premise contemporaneously. Data showing doctors and their patients are overly optimistic about the benefits of novel drugs have already been published. (Fallowfield et al, 2016)

2) Aims

- To measure QoL and emotional well-being of patients with advanced cancers having drug treatments with PFS/modest OS benefits
- To establish 1) how worthwhile patients felt control of cancer was, given the side-effects experienced and 2) time they required for treatment to continue controlling cancer as severity of SEs increased

3) Methods

- QoL measured at baseline (BL), 6 wks and monthly thereafter using FACT-G [physical (P), functional (F), social (S) and emotional (E) well-being (WB)] and Anti-Angiogenesis (AA) sub-scales
- Study specific interviews with patients at:- BL, 6 wks, progression and if treatment stopped due to toxicity
- Trade-off type questions exploring worthwhileness of treatment given the possible and experienced SEs at different degrees of severity (Grade descriptions modified from CTCAE)

4) Results

- 90/120 (75%) eligible patients (life expectancy of > 6 mths) participated
- Main sites of metastases lung (50%), bone (26%) and liver (21%)
- Treatments included cancer growth inhibitors, monoclonal antibodies +/- chemotherapy

Demographics	N=90	Cancer Site	N=90
Sex: Male; Female	39; 51	Lung	30
Age (Yrs) Mean; Range	65 / 32-85	Melanoma	19
		Breast	18
Partner: Yes	58	Renal	10
Employed: Yes	27	Gynae	7
		Head & Neck	3
Stage of disease III; IV	10; 80	Colorectal	2
		Sarcoma	1

- 36 patients died or progressed during study **(Group A)**
- 4 had treatment breaks and 9 stopped due to toxicity **(Group B)**
- 41 remained on treatment in study for 6 mths without progression **(Group C)**

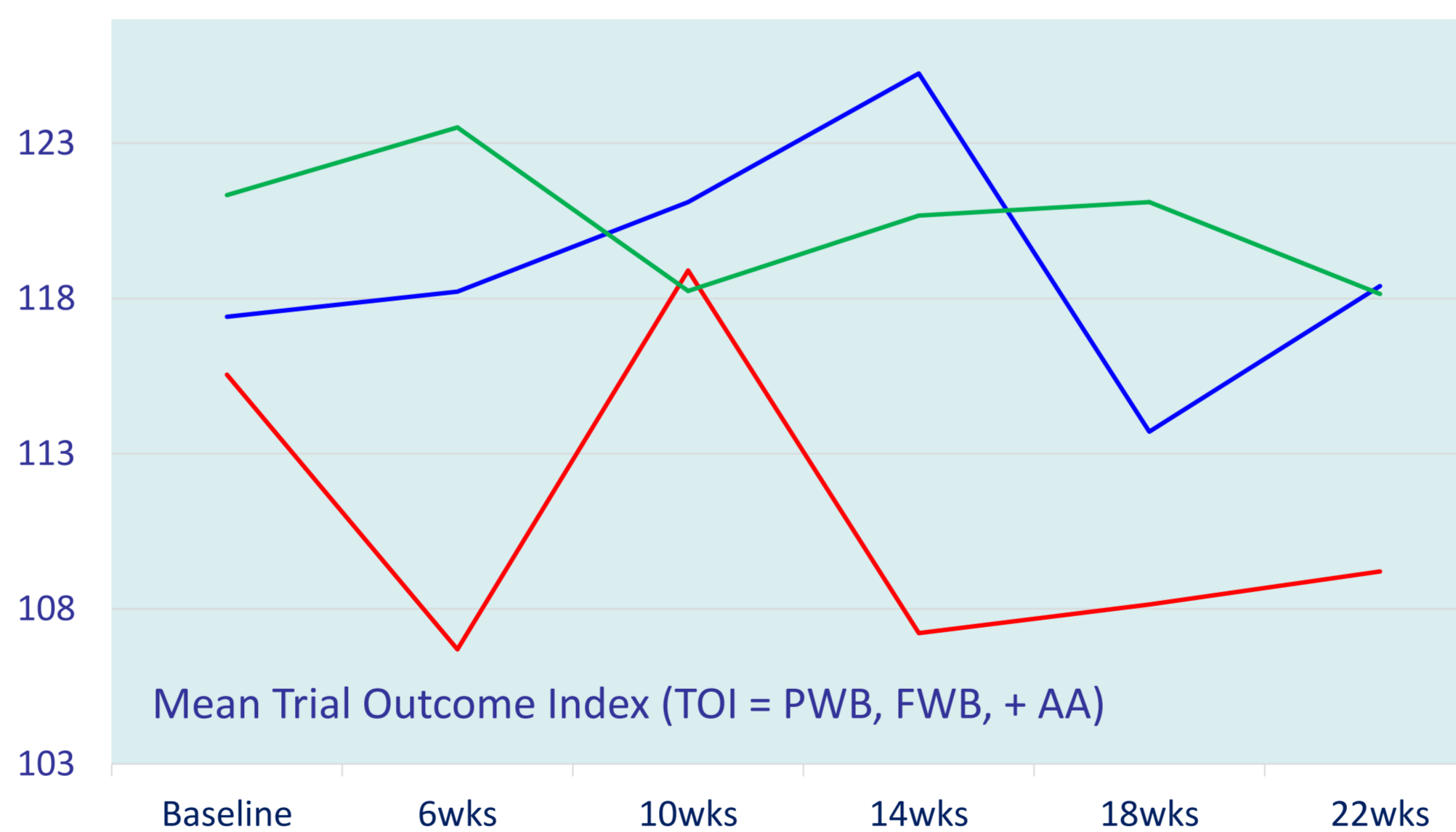## 5) Treatment related side effects

- By 6 wks 66/69 (96%) were experiencing treatment related SEs
- Worst SEs were fatigue (35%), diarrhoea (17%) & skin rash (15%)
- Only 1 patient with progression expressed regret about treatment

"I feel some regret that I have spent time taking something that made me ill and didn't work, it made me worse" (Grade II skin rash, fatigue)

6) QoL

- Questionnaire completion as shown in the table below, declined from 99% (89/90) to 53% (48/90) at 22 wks. Dropout was highest in groups **A** and **B**

Group	BL	6wks	10wks	14wks	18wks	22wks
A	35	17	14	8	7	5
B	13	13	10	9	7	5
C	41	39	38	37	36	38

Mean FACT-G over time (high scores = good QoL)

Mean Trial Outcome Index (TOI = PWB, FWB, + AA)

- Good QoL (FACT-G and TOI) was maintained over time by **Group C**

- MIDs (clinically relevant changes) were used in responder analyses to determine proportions who declined, improved or did not change from BL at each time point
- Fewer **Group A** and **B** patients improved or stayed the same compared to **Group C**

Group	A	B	C
FACT-G	14%	38%	64%
TOI	19%	46%	59%

7) Emotional well-being

- Patients who stayed on treatment without signs of progression, were less worried about dying at 6 mths (24%) than they were at BL (41%)
- Many felt that they had to try treatment even if outcome was not good

"It's been horrendous, haven't been any benefits at all, QoL down hugely since I last saw you, but no regrets I had to try it" (Grade III dyspnoea, fatigue, nausea and Grade II diarrhoea)

8) Trade-off type questions

Is (or would) the benefit of the drug in terms of controlling the cancer be worth the following Grades of SE severity?

Interview	Grade I	Grade II	Grade III
Baseline Yes - worthwhile	95%	88%	44%
6 weeks Yes - worthwhile	97%	89%	52%

With this Grade SE how long do you require the treatment to control the cancer for you to consider it a worthwhile treatment for you?

	Grade I	Grade II	Grade III
Baseline Min 6 mths benefit	17%	29%	34%
6 weeks Min 6 mths benefit	15%	25%	35%

- As the possible severity of SEs increased patients were less inclined:-
  - at BL to feel that the benefit in terms of controlling cancer **would be** worthwhile (X^2=75.6004. p < 0.00001)
  - or at 6 wks that benefit **was** worthwhile (X^2 = 50.6896 p < 0.00001)
- At Grade III >1/3rd required treatment to control cancer for ≥6 mths

"To have severe side-effects I'd want more return from treatment. 6 mths is not enough, at least a year controlling the cancer"

9) Summary & Conclusions

- Despite life expectancy ≥6 mths being an entry criterion many (40%) patients died or progressed during the 6 mths study
- Those who remained on treatment in study without signs of progression reported good QoL and emotional well-being
- Side effects experienced (especially fatigue, diarrhoea and skin rash) were problematic enough for 14% to have breaks or stop treatment
- Most felt treatment worthwhile but as SE severity increased they required much lengthier periods for it to continue controlling the cancer
- These periods were substantially longer than the PFS shown in clinical trials for most of the drugs used
- More research into ameliorative interventions for worst SEs is needed to make treatment with drugs offering only PFS worthwhile

Ref: Fallowfield LJ, Catt SL, May SF, Matthews L, Shilling VM, Simcock R, Westwell S & Jenkins VA "Therapeutic aims of drugs offering only PFS are misunderstood by patients and oncologists may be overly optimistic about likely benefits." *Supportive Care in Cancer* 2017 25 (1): 237-244.