Community Oncology Working Group (COWG): "Optimal use of systemic therapy in the palliative setting"

When to start systemic therapy: Indications for initiation of treatment vs. watchful waiting

Ian F Tannock MD, PhD, DSc
Princess Margaret Hospital and University of Toronto

ESMO, Madrid

Potential conflicts of interest

I have advised multiple companies about design of trials for prostate cancer for which I have received contributions to my research fund.

I have chaired international company-sponsored trials for hormone-refractory prostate cancer (TAX-327, VENICE)

I do not accept personal remuneration from companies

If a patient has a cancer with:

symptoms that are due to their cancer, and

a good chance of "responding" to drugs

with low-moderate toxicity

The decision to recommend treatment is straight-forward

The decision is much more difficult if:

the patient is minimally symptomatic and/or

the probability of "response" is low and/or

the available treatment is toxic

There are only two goals of any new treatment:

To allow the patient to live longer

and/or

To allow the patient to live better

If systemic therapy is to be palliative….

…. then it must improve either the duration or the quality of survival

We base our decisions on results of clinical trials. But…

- Many clinical trials have a 1° outcome measure other than OS or QoL
- DFS and PFS are commonly used in phase III trials of systemic therapy – response rate often in phase II trials
- DFS and PFS has been used for registration of new drugs but all the above endpoints are poorly correlated with OS and QoL
- They are also subject to considerable bias

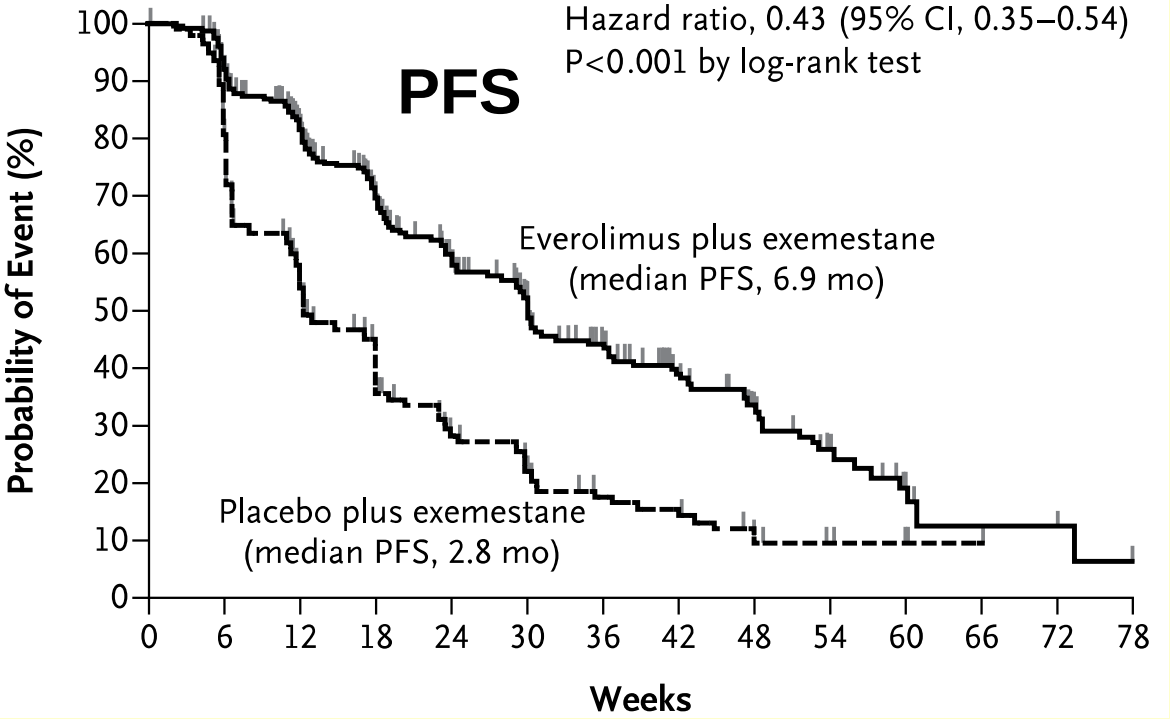
What should we call an agent that leads to a substantial chance of tumour response and/or increases PFS, but has no effect on survival or Quality of Life, and adds toxicity?

HARMFUL

Everolimus in Postmenopausal Hormone-Receptor–Positive Advanced Breast Cancer

José Baselga, M.D., Ph.D., Mario Campone, M.D., Ph.D.,

N Engl J Med 2012;366:520-9.



SAEs due to treatment: 11% vs. 1%

Early stopping due to SAE or withdrawn consent: 24% vs. 6%

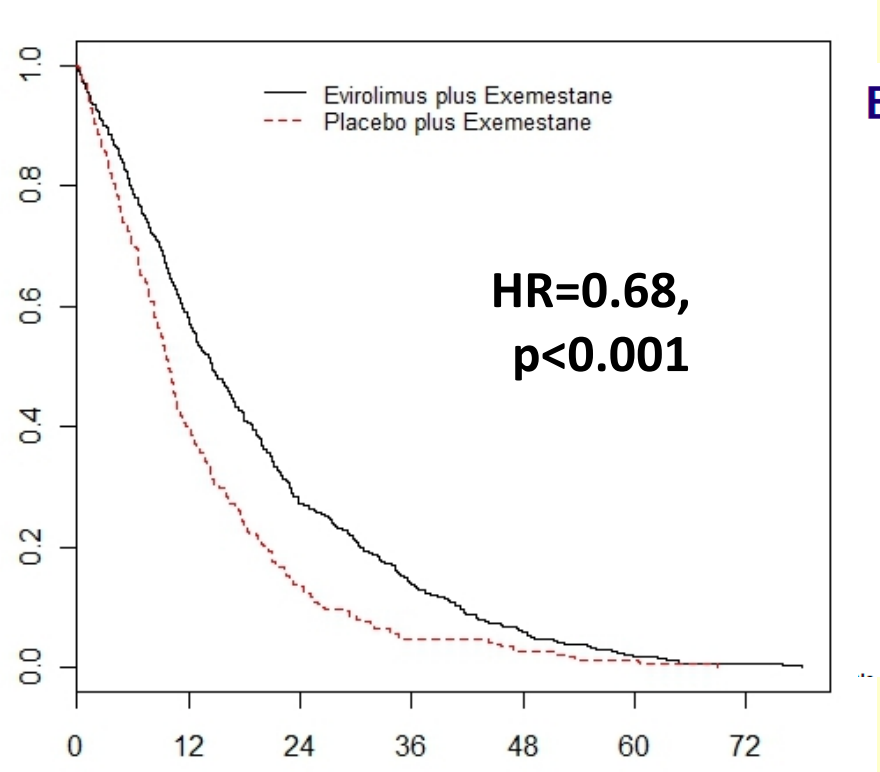
Toxic deaths: 7 vs. 1

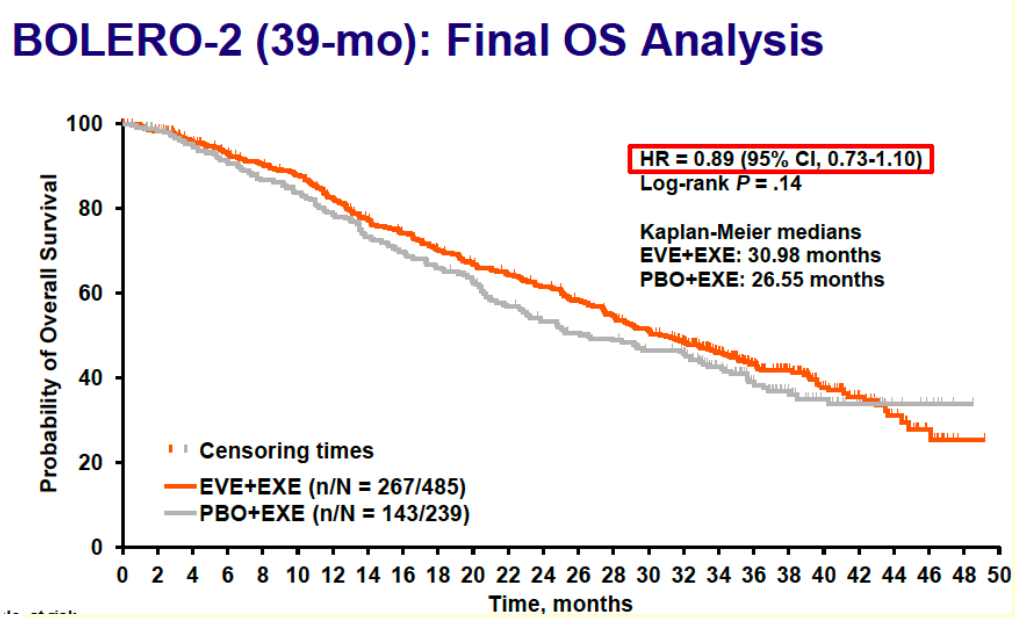
This result led to registration of everolimus + exemestane for postmenopausal ER+ women ($$$$)

Censoring bias: Patients who withdraw from a study (for toxicity or other reasons) are censored if they have not satisfied criteria of progression. A better representation might be difference in "time on treatment"

Bolero-2: Time on treatment (courtesy of Greg Pond)

… and survival results became available recently





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Treatments also add toxicity that is often poorly captured in clinical trials

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Reporting of Serious Adverse Drug Reactions of Targeted Anticancer Agents in Pivotal Phase III Clinical Trials

Bostjan Seruga, Lynn Sterling, Lisa Wang, and Ian F. Tannock

J Clin Oncol 29:174-185. © 2010

58% of potentially fatal adverse events are not in the initial FDA drug label, and 39% are not reported in any published randomized trial

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Efficacy vs. Effectiveness

Efficacy is the difference in outcome in an ideal population such as those with minimal comorbidity and high PS selected to take part in a RCT

Effectiveness is the difference in outcome in the real world – evaluated by health outcomes research applied to a population

A small difference in outcome in an RCT (i.e. in efficacy) with an agent that adds toxicity is likely to disappear when applied in routine practice (it may not be effective)

Clinical trials may not reflect routine clinical practice

Translating clinical trials to clinical practice: outcomes of men with metastatic castration resistant prostate cancer treated with docetaxel and prednisone in and out of clinical trials*

Annals of Oncology 24: 2972–2977, 2013

A. J. Templeton[1], F. E. Vera-Badillo[1], L. Wang[2], M. Attalla[1], P. De Gouveia[1], R. Leibowitz-Amit[1], J. J. Knox[1], M. Moore[1], S. S. Sridhar[1], A. M. Joshua[1], G. R. Pond[3], E. Amir[1] & I. F. Tannock[1]*

Men receiving 3-weekly docetaxel for CRPC	*Routine practice at PMH*	*On-trial patients at PMH*	*P-value*	*TAX-327 trial*
Number	314	43		335
Median survival (95%CI)	13.6 mos (12.1-15.1)	20.4 mos (17.4-23.4)	0.007	19.3 mos (17.6-21.3)
% septic neutropenia	9.6%	0%	<0.001	3%

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Quality of life and/or symptom control in randomized clinical trials for patients with advanced cancer

F. Joly[1], J. Vardy[2], M. Pintilie[3] & I. F. Tannock[2*]

Ann Oncol. 2007 Dec;18(12):1935-42.

Most cancer trials are directed to palliation of incurable cancer, but few phase 3 trials include QL or PROs as a primary outcomes

QL is often criticized as "Subjective", but this word has 2 meanings

1. **Opposite of objective, unreliable**
2. **Important to the subject (i.e. to the cancer patient)**

QL or PROs related to a major symptom (e.g. pain) can be measured reliably and objectively. This must be done by the patients themselves. There are several well validated questionnaires.

Most useful are the FACT and EORTC questionnaires

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Assessment of QL in a Clinical Trial

It is essential to define a primary PRO or measure of QL as the primary palliative endpoint – too often trials collect huge amounts of data that is impossible to analyze.

Measure this primary QL endpoint in each patient at baseline.

Specify an improvement in the primary criterion of QL, and its duration, for a patient to have a palliative response.

Measure QL repeatedly, and determine the proportion of patients in each arm who satisfy criteria of response.

Many trials report time-dependent changes in "average QL". This has no meaning since some patients improve and others deteriorate, while the number of patients assessed declines over time.

All of these factors need to be taken into account, especially when starting drug treatment for a minimally symptomatic patient

We should also recognize that:

Many patients have an inaccurate view of the benefits of drug treatment

Some patients will accept toxicity for even a small chance of benefit

Others require much higher chance of benefit to accept treatment

Patients' Expectations about Effects of Chemotherapy for Advanced Cancer

N Engl J Med 2012;367:1616-25.

Jane C. Weeks, M.D., Paul J. Catalano, Sc.D., Angel Cronin, M.S., Matthew D. Finkelman, Ph.D., Jennifer W. Mack, M.D., M.P.H., Nancy L. Keating, M.D., M.P.H., and Deborah Schrag, M.D., M.P.H.

RESULTS

Overall, 69% of patients with lung cancer and 81% of those with colorectal cancer did not report understanding that chemotherapy was not at all likely to cure their cancer.

CONCLUSIONS

Many patients receiving chemotherapy for incurable cancers may not understand that chemotherapy is unlikely to be curative, which could compromise their ability to make informed treatment decisions that are consonant with their preferences.

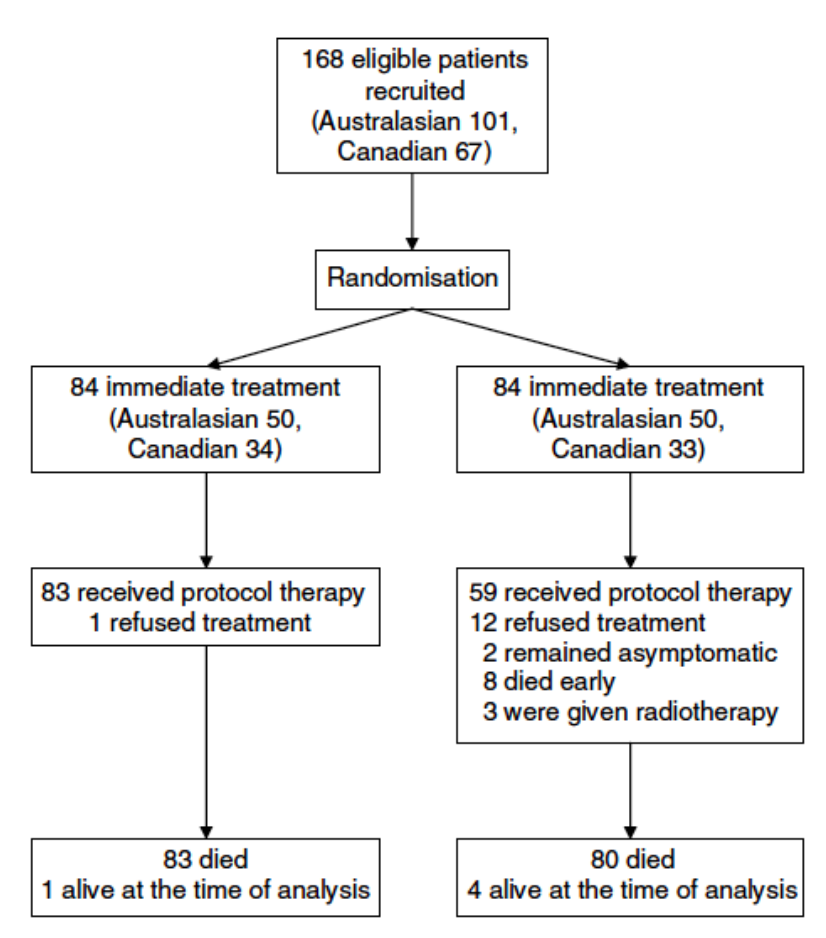
For most common incurable cancers, there is minimal evidence to support (or even evidence against):

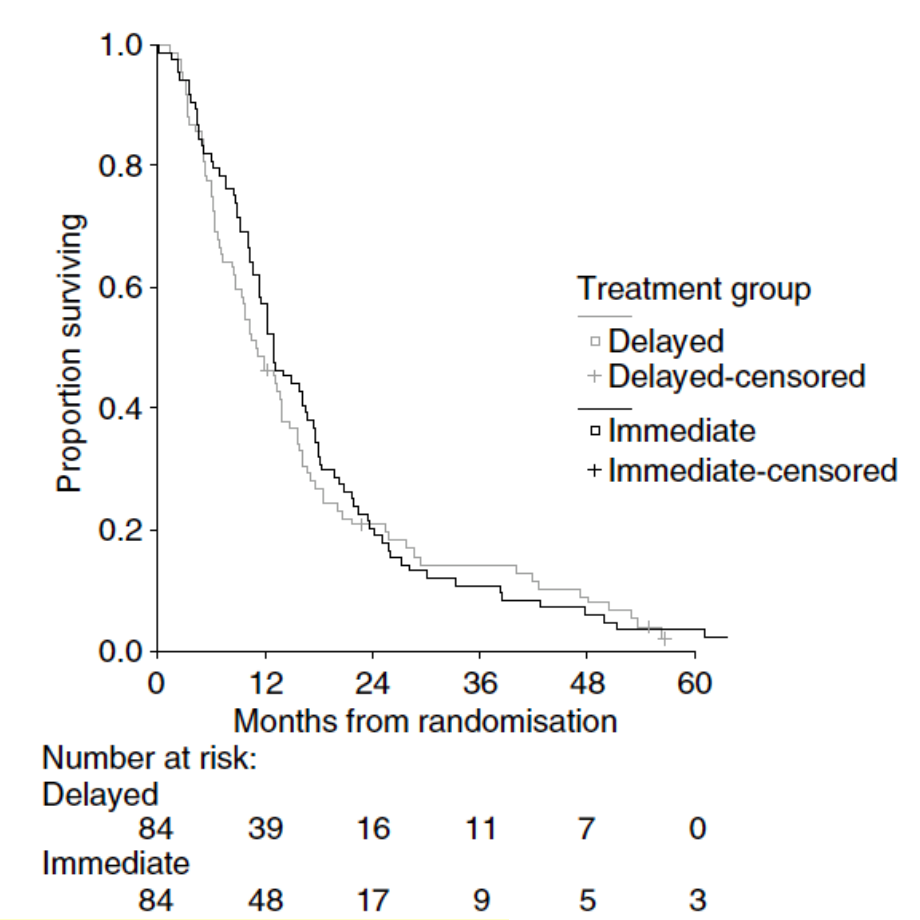
- Starting chemotherapy when the patient is minimally symptomatic
- Longer versus shorter duration of chemotherapy

A meta-analysis of two randomised trials of early chemotherapy in asymptomatic metastatic colorectal cancer

British Journal of Cancer (2005) 93, 1236–1243

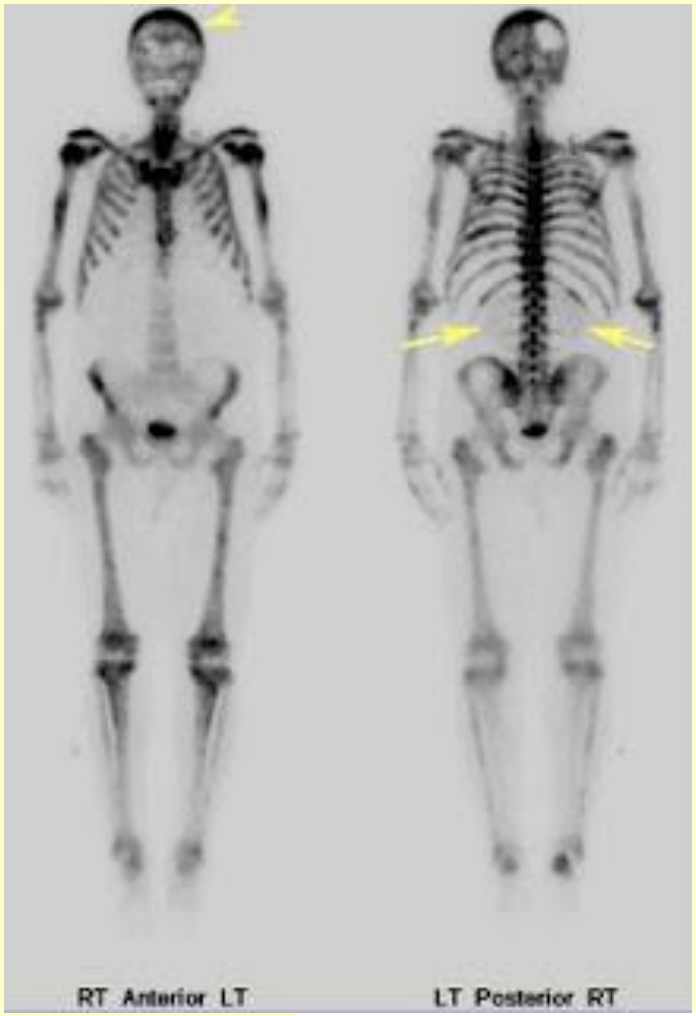
SP Ackland[*,1,2], M Jones[1,3], D Tu[4], J Simes[1,3], J Yuen[1,3], A-M Sargeant[4], H Dhillon[1,3], RM Goldberg[6], E Abdi[1,7], L Shepherd[4] and MJ Moore[4,5]





A hypothetical patient

- **Mr Kemal:** 67 y.o. man with progressive metastatic prostate cancer, refractory to hormonal therapy
- Despite multiple bone metastases he is minimally symptomatic and active
- Would you start chemotherapy?

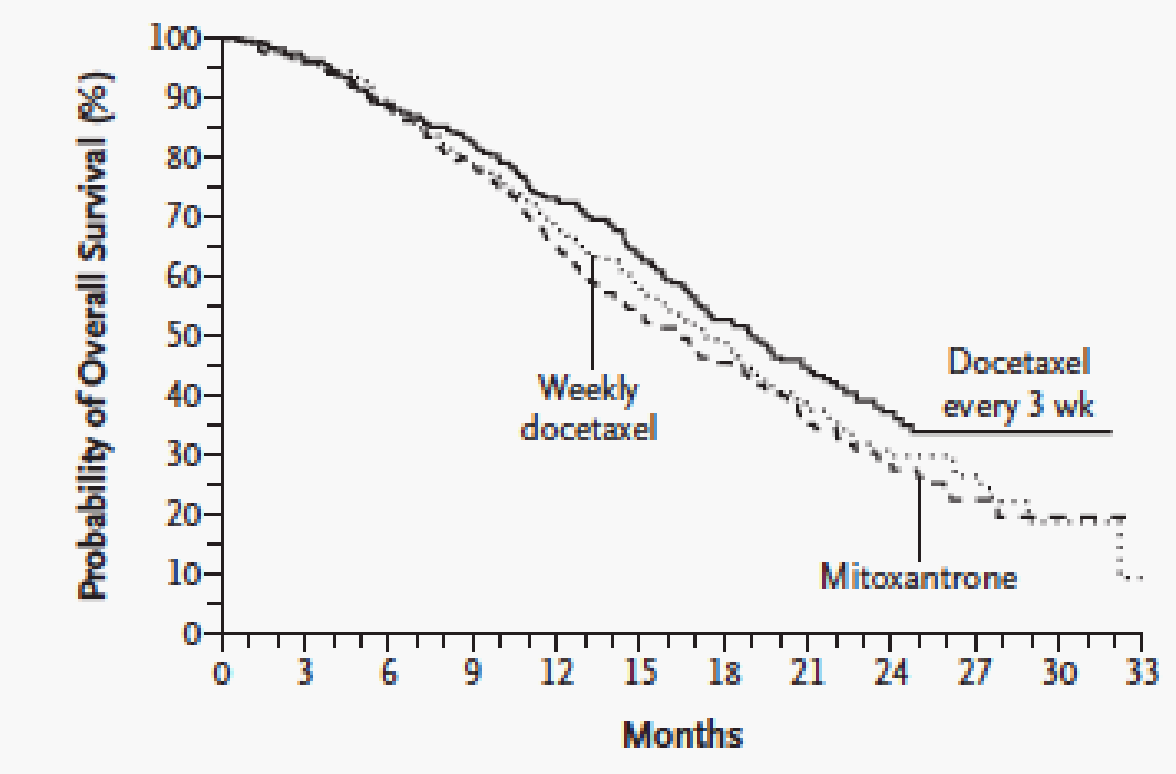


Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer

N Engl J Med 2004;351:1502-12

Ian F. Tannock, M.D., Ph.D., Ronald de Wit, M.D., William R. Berry, M.D.,

Docetaxel and prednisone has been standard 1st-line chemotherapy since the TAX-327 RCT showed improved survival and symptom control compared to previous standard



TAX-327: Secondary endpoints

TAX-327 2° endpoints	Docetaxel q 3wk	Docetaxel wkly	Mitox q 3wk
Pain Response Rate	34.6% p=0.01	31.2% p=0.08	21.7%
PSA Response Rate	45.4% p=0.0005	47.9% p<0.0001	31.7%
QOL Response rate	21.9% p=0.009	22.6% p=0.005	13.1%

Some important questions….

Which is more important?

3-month improvement in survival

Improved pain and quality of life?

– but only if there is initial pain and impaired QoL

When to start chemotherapy?

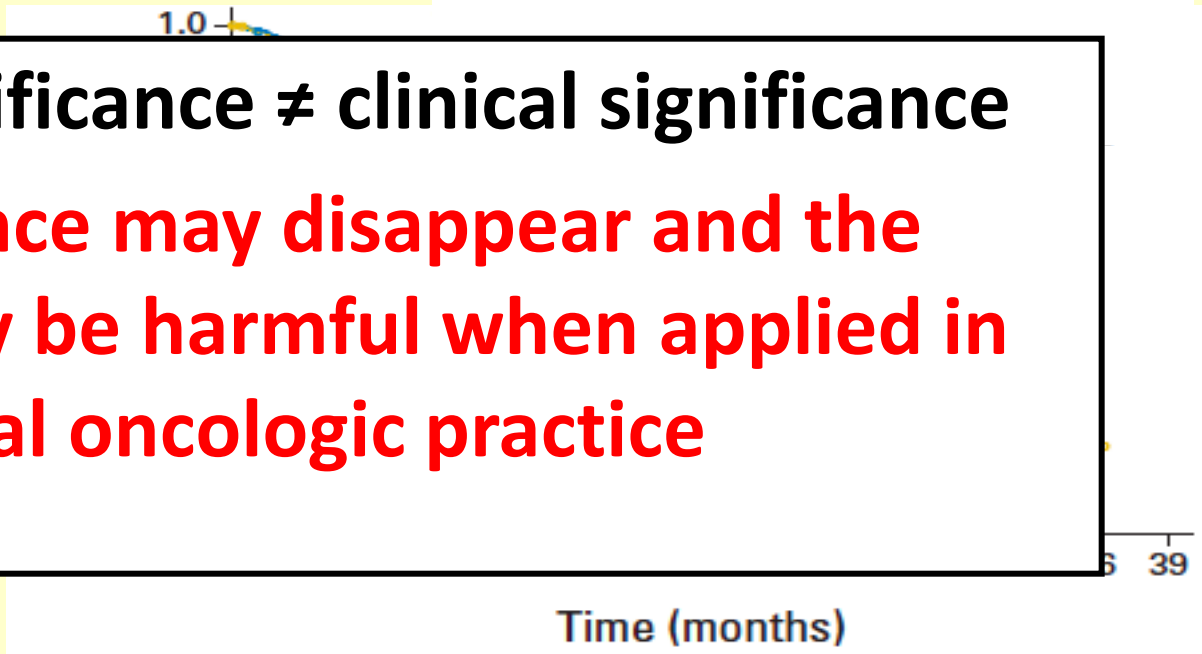
You cannot make a well patient better – but you can cause symptoms from treatment - No evidence that starting chemo in asymptomatic men is better than waiting for symptoms.

As long as FDA and EMA register drugs on basis of p < 0.05, Pharma will do large trials to detect small differences

Addition of Aflibercept to Fluorouracil, Leucovorin, and Irinotecan Improves Survival in a Phase III Randomized Trial in Patients With Metastatic Colorectal Cancer Previously Treated With an Oxaliplatin-Based Regimen

J Clin Oncol 30:3499-3506. © 2012

Eric Van Cutsem, Josep Tabernero, Radek Lakomy, Hans Prenen, Jana Prausová, Teresa Macarulla, Paul Ruff, Guy A. van Hazel, Vladimir Moiseyenko, David Ferry, Joe McKendrick, Jonathan Polikoff, Alexia Tellier, Rémi Castan, and Carmen Allegra



Statistical significance ≠ clinical significance

This difference may disappear and the treatment may be harmful when applied in general oncologic practice

A 48 year old woman has lesions of 2 cm and 3 cm in the right lower lobe of her lung 4 years after nephrectomy for clear cell carcinoma of the kidney.
A bone scan, MRI brain, and CT scans reveal only the two pulmonary metastases. She is well and asymptomatic.

Which of the following treatments would you recommend?

A. Sunitinib
B. Temsorilimus
C. Interferon-α and Bevacizumab
D. Surgical resection of the metastases
E. Surgical resection followed by a targeted agent

Acknowledgements

My thanks to many present and former fellows, who undertook much of the work presented, and stimulated many of the ideas that led to it. Especially:

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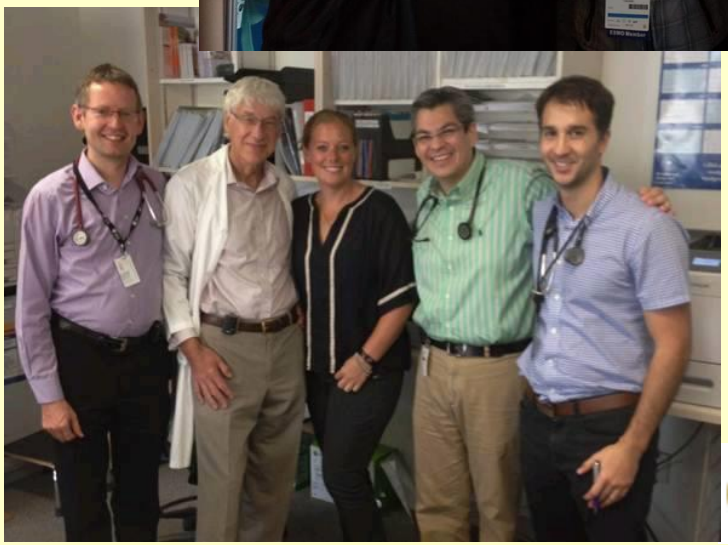

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