Ethical tension in placebo-controlled randomized trials for cancer:

a review of recently published trials

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Introduction: Cancer and Placebo

- Until recently placebo not used in cancer trials
  - No placebo effect / chemotherapy ➔ not necessary?
  - Prognosis ➔ unethical?
  - Challenge with molecularly targeted agents
    - Efficacy: Stable disease
    - Long term, costs

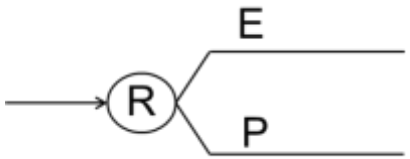
- Placebo outcomes
  - Symptom control
    - 0-27% per trial
  - Tumor response (ORR, WHO)
    - 0-7% per trial, 11 patients (2.4%)
  - Stable disease
    - 52% of trials

37 placebo RCT
1977-1997
(Chvetzoff and Tannock JNCI 2003)

40 placebo RCT - Molecularly targeted agents
1977-2012
(LeTourneau, Paoletti at al. JCO 2013)

Introduction

- Placebo-controlled randomized trials (P-RCT)
  - Necessary / desirable for cancer
  - "Placebo-only" 1:1 trial
    - Might not be feasible
      - Scientific, practical, ethical reasons
    - Some alternative strategies are proposed

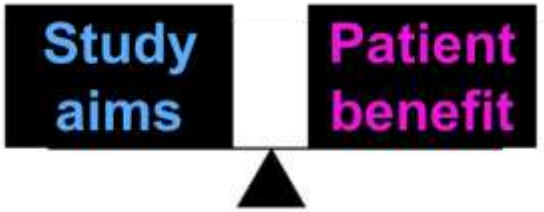


(ICH E10, 2000; Daugherty CK, et al. JCO, 2008)

- Objective

Describe the frequency of "alternative" strategies for randomized placebo-controlled trials for cancer

➔ Review of published P-RCT



Methods

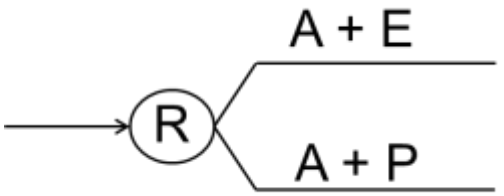
- Sample of cancer P-RCT, 2014
  - Pubmed/Medline (October 2014)

    Cancer [Tiab] and **Placebo** [Tiab]

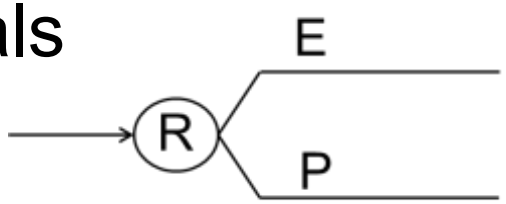
    and **Randomized Controlled Trial** [Ptype]
  - Inclusion criteria
    - P-RCT, evaluating clinical endpoints
  - Exclusion criteria
    - Protocol without results
    - Secondary analysis

Alternative strategies using placebo (1)

- "Add-on" placebo controlled trial
  - If proved active standard treatment (A)
  - A + E (experimental) vs. A + Placebo of E

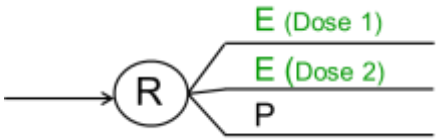


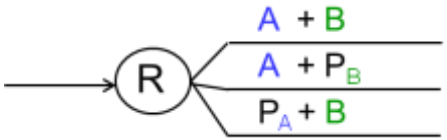
  - As opposed to placebo "only" trials
    - E vs. Placebo of E
    - Salvage therapy
      - After failure to standard therapy



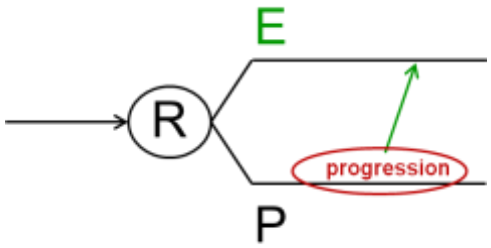
Alternative strategies using placebo (2)

- Additional control groups
  - Dose-finding
  - Factorial design

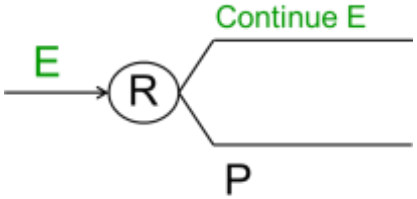




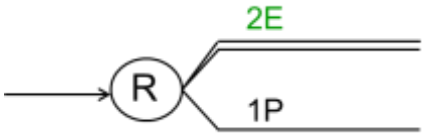
- Early escape / rescue treatment
  - Access E upon progression
  - “one-way crossover”



- Randomized maintenance

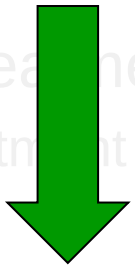


- Unbalanced randomization (ratio 2:1…)



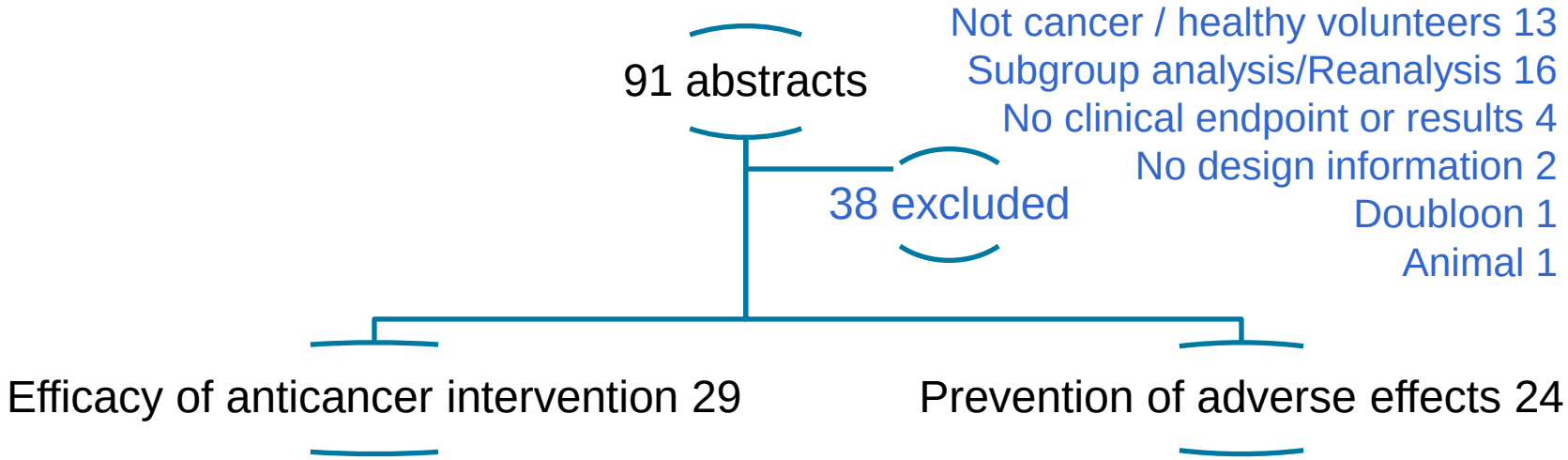
- Stopping rules

Alternative strategies



Decrease exposure to placebo

Results: 53 eligible trials



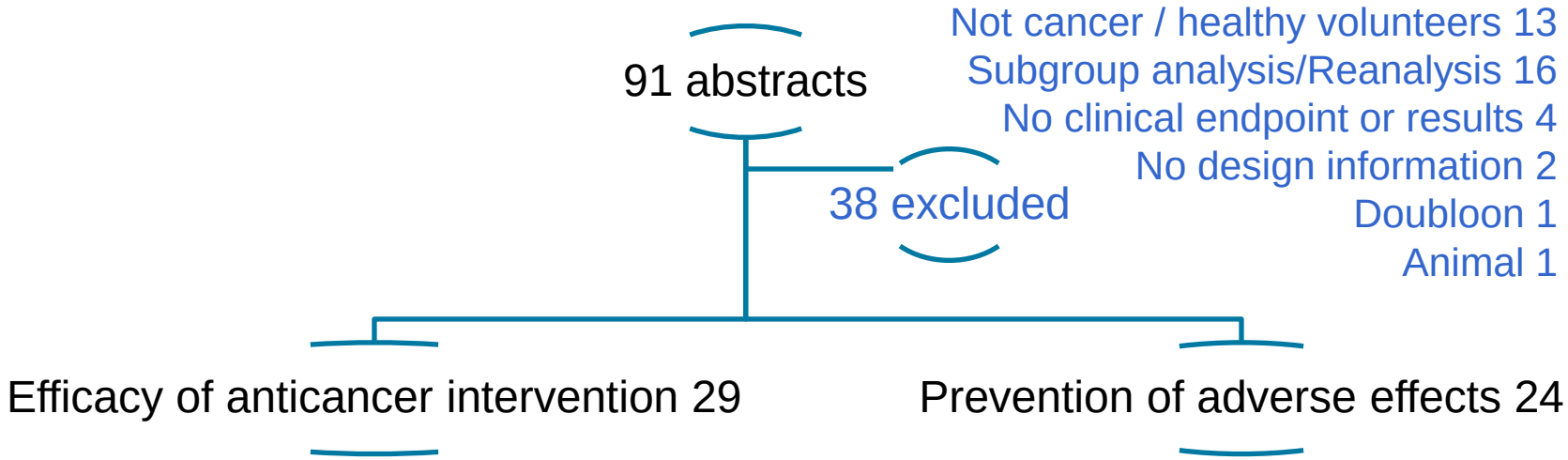
29 “Treatment” P-RCT

- 20 Phase III (69%), 9 phase II
- Molecularly targeted agents 16
- Cancer
  - Lung 7
  - Prostate 5
  - Breast 3
  - Other: pancreas ovary, urothelial, liver, uterus, gastric, oesophagus, brain, neuroendocrine, thyroid

24 “Symptom” P-RCT

- Symptom
  - Urogenital 5
  - Neuropathy 4
  - Gastrointestinal 3
  - Bone 3
  - Other: fatigue, pain, metabolic, surgical complication

Results: 53 eligible trials



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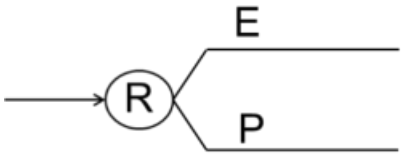
Results (2) Design in 29 “Treatment” P-RCT

	n	%
Alternative strategy (any)	27	93.1
Add-on	20	69.0

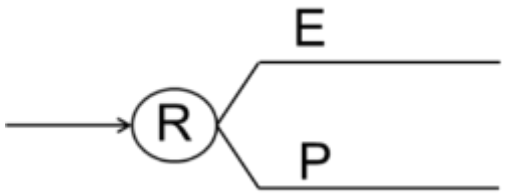
Results (2) Design in 29 “Treatment” P-RCT

	n	%
Alternative strategy (any)	27	93.1
Add-on	20	69.0
Stopping rule	15	51.7
Unbalanced randomization	5	17.2
"Cross-over"	5	17.2
Maintenance	2	6.8
Factorial	1	3.4
Dose-finding	1	3.4

9 “placebo only”



Placebo “only” RCT, no alternative design



Cancer	Clinical Setting	Treatment	Primary Endpoint
Cervix	Low grade intraepithelial neoplasia (CIN1) HPV+	Green tea*	CIN1 and HPV clearance
Esophagus	Advanced Failure to chemotherapy	Gefitinib	Survival

*phase II. OS overall survival.

Placebo “only” RCT, alternative strategies

Cancer	Clinical Setting	Treatment
Urothelial	Advanced Responders to chemo.	Sunitinib*
Lung	Unresectable Responders to radiochemo.	Tecemotide

*phase II. SD stable disease, OR objective response, OS overall survival, PFS progression free survival.

Placebo “only” RCT, alternative strategies

Cancer	Clinical Setting	Treatment
Urothelial	Advanced Responders to chemo.	Sunitinib*
Lung	Unresectable Responders to radiochemo.	Tecemotide
Gastric	Advanced, Failure to chemo.	Ramucimumab
Liver	Advanced, Failure to sorafenib	Everolimus
Thyroid	Advanced/metastatic Refractory	Sorafenib
Entero-pancreatic	Advanced	Lanreotide
Oral carcinoma	Unresectable	Recombinant adenoviral gene

*phase II. SD stable disease, OR objective response, OS overall survival, PFS progression free survival.

Placebo “only” RCT, alternative strategies

Cancer	Clinical Setting	Treatment	Design strategy	Primary Endpoint
Urothelial	Advanced Responders to chemo.	Sunitinib*	Maintenance Crossover	Progression
Lung	Unresectable Responders to radiochemo.	Tecemotide	Maintenance 2:1 Stop Rule	Survival
Gastric	Advanced, Failure to chemo.	Ramucimumab	2:1 Stop Rule	Survival
Liver	Advanced, Failure to sorafenib	Everolimus	2:1 Stop Rule	Survival
Thyroid	Advanced/metastatic Refractory	Sorafenib	Crossover	Progression
Entero-pancreatic	Advanced	Lanreotide	Crossover	Progression
Oral carcinoma	Unresectable	Recombinant adenoviral gene	3-arm factorial 1:1:1	Response Survival

*phase II. SD stable disease, OR objective response, OS overall survival, PFS progression free survival.

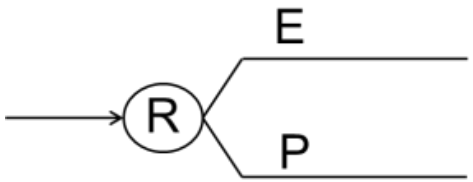
Discussion

- First study to describe alternative strategies in P-RCT

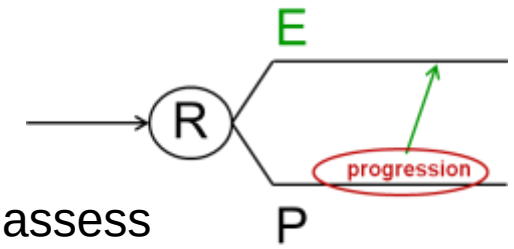
- Preliminary results
  - Delay in pubmed
    - Randomized Controlled Trial [Ptype]
  - ~ 250 abstracts, 2014 year

Discussion

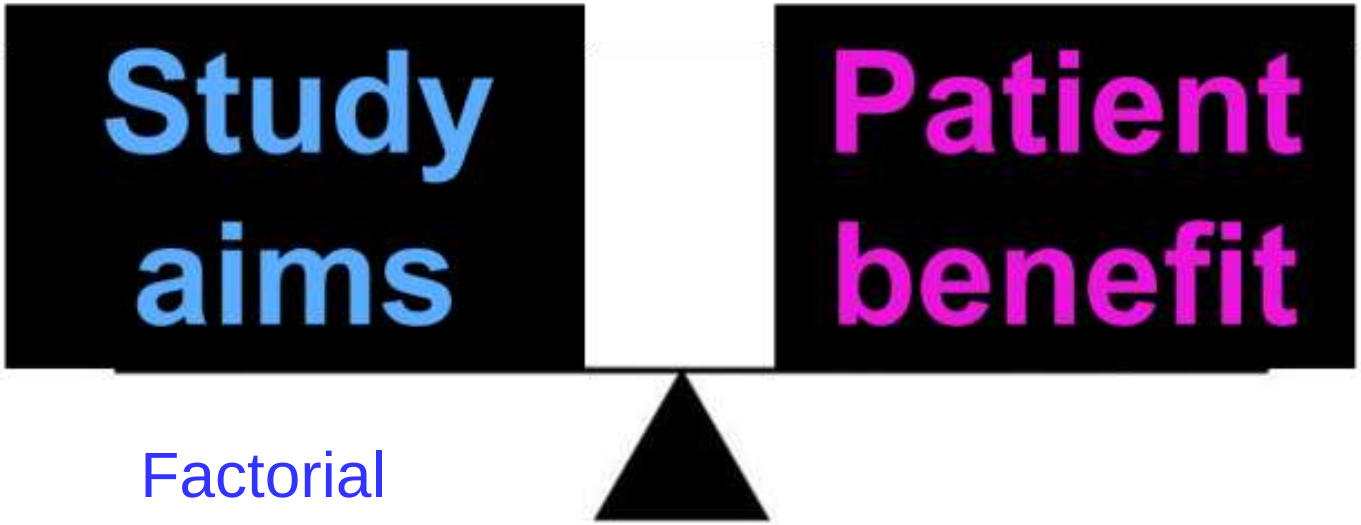
- Majority of cancer “Treatment” trials use alternatives strategies to classical 1:1 P-RCT
  - “Placebo only” rare
  - Advanced disease/salvage therapy (8/9)



- Most frequent “alternative” strategies
  - Add-on (70%)
  - Stopping rules (52%)
  - Unbalanced randomization (17%)
  - “Cross-over” (17%)
    - Patients access E after progression
    - Long-term outcomes (mortality) difficult to assess
    - Controversy :“Misguided” ethics? (Prasad V, Grady C, CCT 2014)



Discussion



Factorial
Dose-finding
Maintenance
Add-on
Unbalanced randomization
Adaptive/stopping rule

"Cross-over"

Add-on
Unbalanced randomization
Adaptive/stopping rule

Conclusion

- Alternatives to 1:1 placebo “only” RCT are very frequent
  - Adress specific scientific questions
  - Try to adress ethical tension of placebo in cancer patients

- Some more analysis needed
  - Evolution?
  - Ethical/scientific balance for “cross-over” trials

Aknowledgement

- C Grady, L Colloca (Dept of Bioethics, NIH, Bethesda, USA)
- T Fojo (National Cancer Institute, NIH, Bethesda, USA)
- I Tannock (Princess Margaret Cancer Centre, Toronto, Canada)

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