Preliminary Design of a Basket Trial for Cancer Cachexia

Susie Collins, Pfizer

Early Clinical Development

Pfizer WORLDWIDE RESEARCH, DEVELOPMENT AND MEDICAL

SCIENCE FOR LIFE-CHANGING IMPACT

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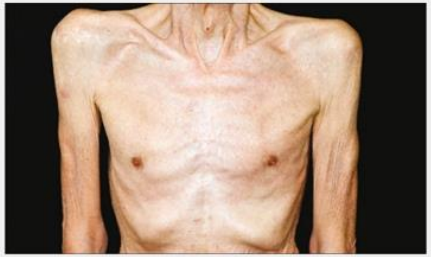
What is Cachexia?

Cachexia is a multifactorial metabolic disorder that occurs with several chronic diseases including cancer, heart failure, chronic obstructive pulmonary disease, and chronic kidney disease

It manifests as marked involuntary body weight loss, muscle wasting, and reduced appetite, progressing to significant functional impairment and increased risk of death

↓ appetite, ↑ energy expenditure, ↑ lipolysis, ↑ muscle wasting = ↓ body weight



Diagnostic Criteria[†]

- Weight loss >5% OR
- BMI <20 and weight loss >2% OR
- Sarcopenia and weight loss >2%

Additional Signs and Symptoms[††]**:**

- **Reduced food intake;** systemic inflammation
- **Marked physical disability and ADL* decline**; fatigue and weakness
- **↑ rates of treatment-related toxicities** (e.g. cancer chemotherapy) resulting in reduced or missed doses
- **Impacted QoL**; psychological impacts of food aversion, eating difficulties, weight loss, loss of control and physical decline leading to death

† *Fearon et al. Lancet Oncology, 2011 May; 12(5):489-95*
†† *Baracos et al. Nature Reviews Disease Primers, 2018 Jan; 18;4:17105*
* ADL – Activities of Daily Living

Sarcopenia - loss of muscle mass, strength and function related to aging

What is Cachexia?

High prevalence of cachexia, affecting ~9 million patients across multiple chronic diseases

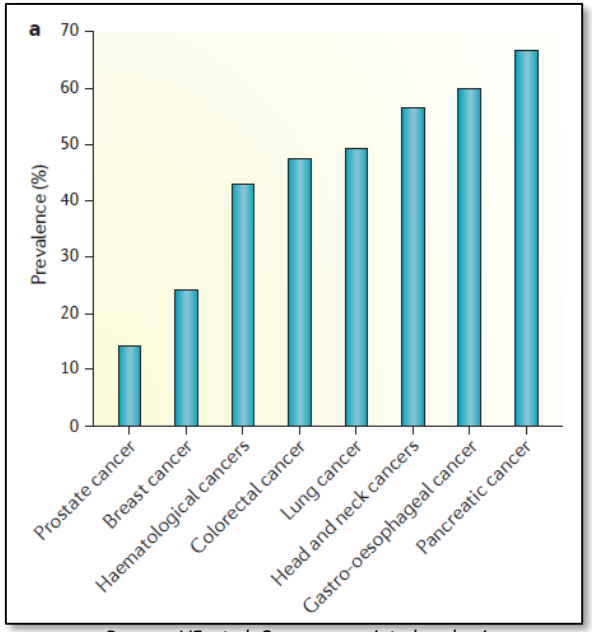
Table 1 Estimated clinical impact of cachexia in different chronic illnesses in Europe in 2014. Estimates are assumed to be rather conservative

	Prevalence of illness in population (%)	Patients at risk (%)	Prevalence in patients at risk (%)	Absolute number of patients with cachexia[a]	1-year mortality of patients with cachexia (%)
COPD, moderate	3.5	15	35	1.4 m	15–25
Chronic HF, NYHA II–IV	2.0	80	10	1.2 m	20–40
Cancer, all types	0.5	90	30	1.0 m	20–60
Rheumatoid arthritis, severe	0.8	20	10	120,000	5
End-stage chronic kidney disease	0.1	50	50	185,000	20

[a] Assumptions are based on a total population of 742 million in Europe. By comparison, the assumed population of the US is 300 million, and of Japan 100 million

von Haehling & Anker, J Cachexia Sarcopenia Muscle (2014) 5: 261-263

The prevalence of cachexia by cancer site



Baracos VE, et al. Cancer-associated cachexia. Nature Reviews Disease Primers. 2018: 18;4:17105

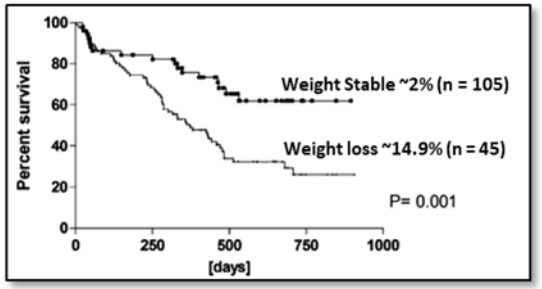
In some cancers, >50% patients have cachexia: lung, head and neck, gastro-oesophageal and pancreatic

What is Cachexia?

Cachexia carries a significant burden, including higher re-admissions, lower quality of life and higher mortality

Pancreatic Cancer

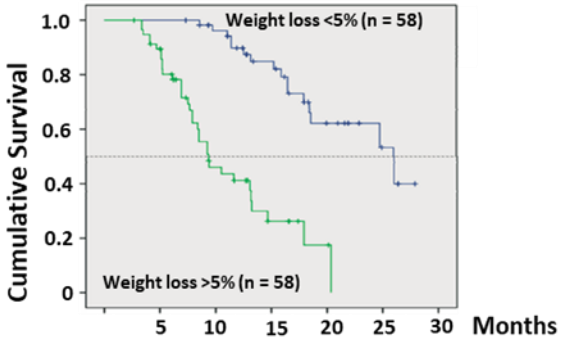
Poor survival prognosis in resectable PDAC patients with preoperative weight loss



Bachmann et al, J Gastrointest Surg (2008) 12:1193–1201

NSCLC

Poor survival in Stage IIIB/IV patients receiving second line chemotherapy with >5% weight loss



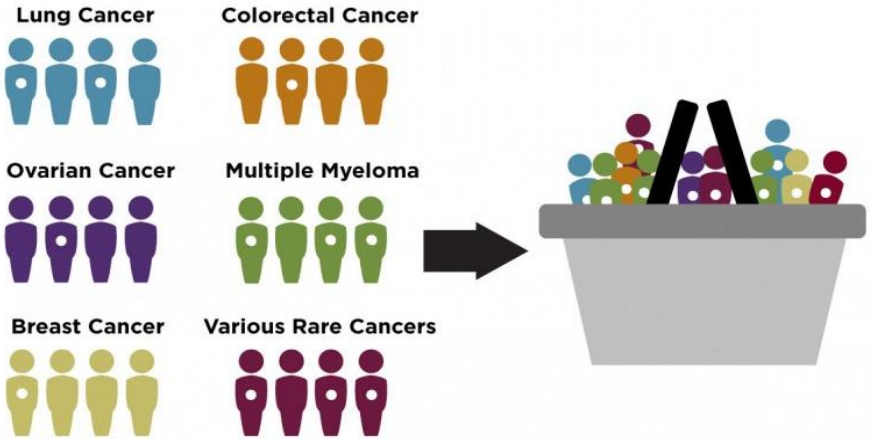
Currently there are no approved drugs for cancer cachexia (with only Megace approved for AIDS cachexia)

Pfizer's Clinical Asset

- Pfizer's early clinical development portfolio currently has several projects targeting cachexia
- One of these projects is investigating development for cancer cachexia
- Traditionally, cancer clinical trials have focussed on testing a compound in patients with a single tumour type, e.g. pancreatic cancer
- Becoming increasingly used, however, are basket trials

Basket Trials – What are they?

- Basket trials are relatively new (this decade) and have predominantly been used in cancer trials
- They test the effect of one drug on a single mutation in a variety of tumour types, at the same time
- It is the presence of the mutation that is important, not the location of the tumour



In our scenario, being cachectic is equivalent to having the mutation

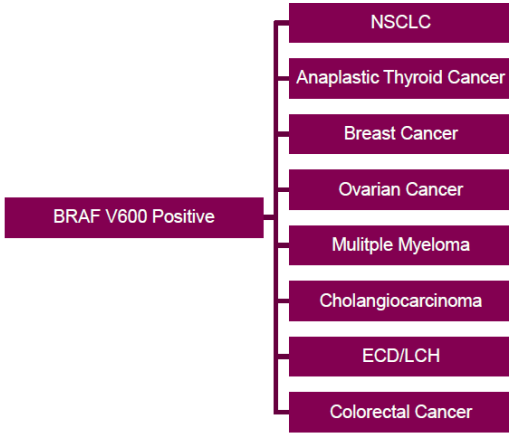
- Usually designed as a single-arm (i.e. no placebo) trial with overall response rate (ORR) as the endpoint

In our scenario, we have parallel arms and have lean body mass change from baseline as the endpoint

Basket Trials – What are they?

- Historically, the most common use of basket trials has been early/mid-stage clinical research to help evaluate which potential locations of cancer should be tested in larger trials

  Example: One of the first basket trials evaluated vemurafenib (Zelboraf) in multiple non-melanoma cancers with BRAF V600 mutations



- Vemurafenib was originally approved by the FDA (2011) for the treatment of melanoma with BRAF V600E genetic mutation
- A basket study was conducted involving patients with BRAF genetic mutation
- It was determined that vemurafenib was also effective in treating a rare blood cancer known as Erdheim-Chester Disease (ECD), where patients have BRAF V600 genetic mutation (FDA approval 2017)

- More recently, the FDA has considered a basket trial evidence for more general approval

  Example: Pembrolizumab (Keytruda) was approved (May 2017) for an expanded indication to treat microsatellite instability-high cancer based only on genetic abnormality, regardless of origin or site of cancer

Basket Trials – What are they?

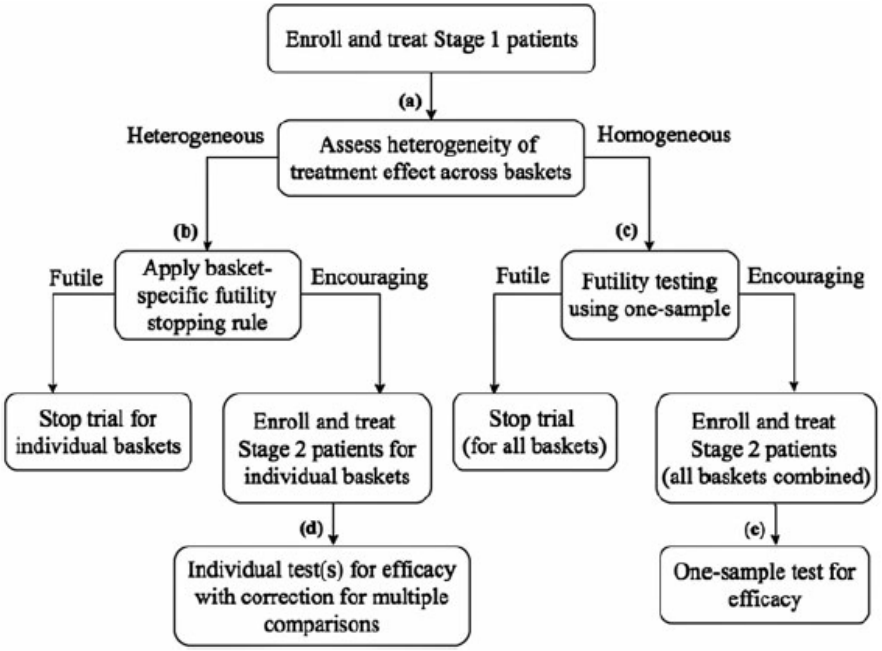
A basket trial can be conducted as separate parallel cohorts in different tumour types, within one protocol. No information is shared between baskets

- Simple, familiar and easy to implement
- Sample size, decision criteria, analysis, conclusions are the same as if they were separate studies. Therefore, the total sample size is N x number of baskets
- Answers the question “Does the treatment work in each population?”
- Gain some operational efficiencies from using one protocol rather than separate ones

However, you gain more if you can pool the treatment effect across the different tumour types

Basket Trials – Preliminary Design

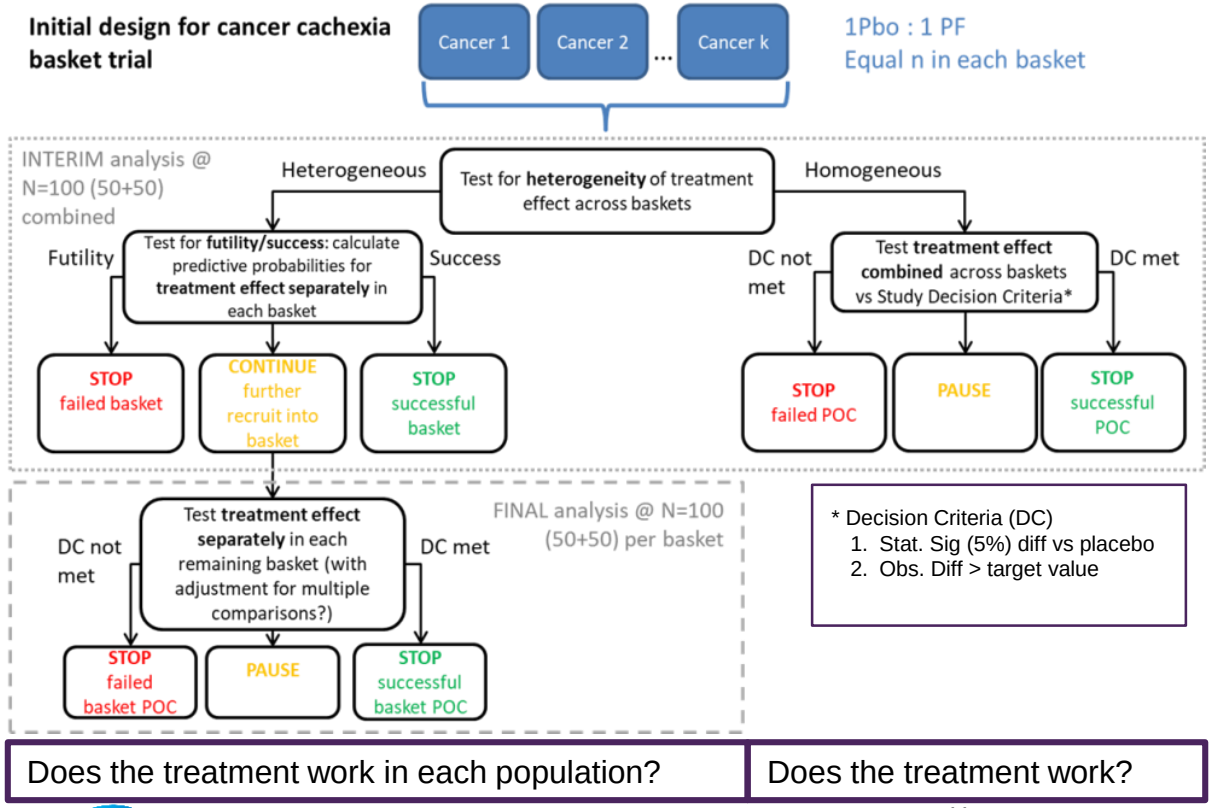
Design by Cunanan et al (2017)*



- First stage of the study is similar to a parallel independent two-stage Simon design
- Endpoint is response rate
- At the interim stage, heterogeneity of response rates across baskets is tested using a contingency test and path (b) or (c) is then taken
- Test for futility is carried out (either in each basket or combined) based on the minimum number of responses needed in Stage 1 to warrant enrolling additional subjects in Stage 2
- Futile baskets/study are stopped; Non-futile baskets/study are continued and additional subjects enrolled

** Cunanan et al. Statistics in Medicine 2017 Jan; 36 1568–1579*

Basket Trials – Preliminary Design



Adapted for a continuous endpoint and to include Bayesian predictive probabilities for testing futility: -

- Enrol patients from several tumour types
- Interim analysis - test for heterogeneity of the treatment effects
- If homogeneous: pool the data across tumour types, analyse and assess against decision criteria
- If heterogeneous: analyse each tumour type separately for futility/success, continue to recruit any non-futile tumour types and then analyse separately at the end of the study and assess against end of study decision criteria

The timing of the interim was chosen so that the combined sample size had sufficiently good Operating Characteristics, i.e. sufficient probabilities of achieving both efficacy decision criteria for chosen true treatment differences

Basket Trials – Interim Analysis

At the interim analysis, the test for futility/success assesses the likelihood of end-of-study success using Bayesian predictive probabilities

Bayesian Predictive Probabilities

What is the probability, given the data that we have gathered so far, and the planned additional number of subjects to be recruited, that at the end of the study we will meet our criteria for success?

- Data-so-far are the Prior in the calculations
- High predictive probability (e.g. > 80-90%) is an early indication of study success
- Low predictive probability (e.g. < 10-20%) indicates it is likely the study will fail if continued as planned

Predictive Probability = $1 - \Phi\left(\frac{A}{B}\right)$ where $A = \Delta + z_\pi \sigma_\delta - \bar{x}_\delta^I$

$$B = \sigma\sqrt{(1-i)\left(\frac{1}{n_A^I} + \frac{1}{n_P^I}\right)}$$

$$\sigma_\delta = \sigma\sqrt{i\left(\frac{1}{n_A^I} + \frac{1}{n_P^I}\right)}$$

$\Phi(.)$ is the cumulative $Normal(0,1)$ distribution function

Δ is the given target value

π is the probability of the true treatment effect passing a given target value Δ, i.e. $P(\delta > \Delta) > \pi$

z_π is the π^{th} quantile of $Normal(0,1)$

$\bar{x}_\delta^I = \bar{x}_A^I - \bar{x}_P^I$ where $\bar{x}_A^I$ is the mean of the interim active data and $\bar{x}_P^I$ is the mean of the interim placebo data

σ^2 is the group variance

$i = n_A^I/n_A = n_P^I/n_P$ is the information fraction at interim (i.e. interim relative size)

n_A^I and n_P^I are the number of subjects for the interim active and placebo data, respectively

Full derivation is given in: -

Walley RJ, Smith CL, Gale JD & Woodward P (2015) Advantages of a wholly Bayesian approach to assessing efficacy in early drug development: a case study: Pharm Stat, 14(3) 205-15

Basket Trials – Interim Analysis

Operating Characteristics for this interim can be assessed to ensure the interim is worthwhile. Key points of interest should be considered: -

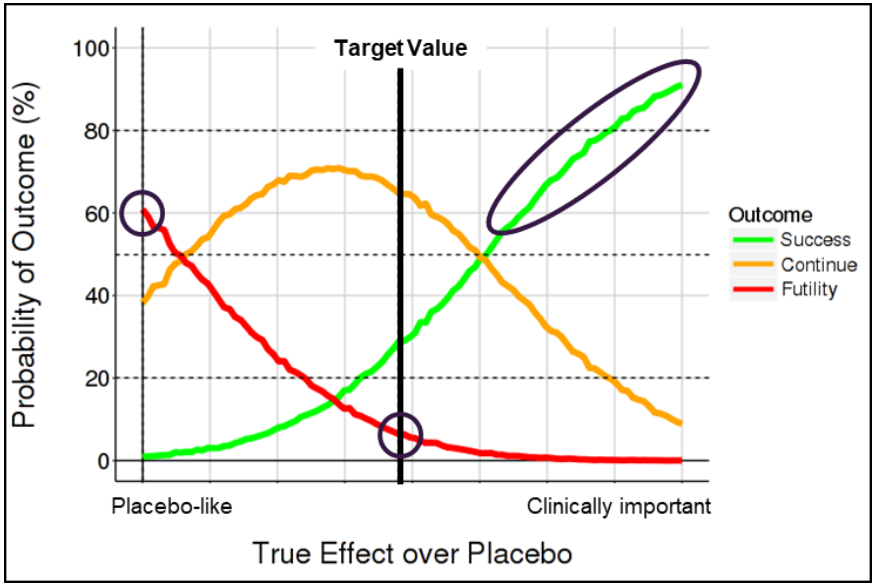
- Probability of success for compounds that have true effects of clinical interest
- Probability of futility for compounds which are truly placebo-like

  e.g. an interim with only a 10% chance of declaring futility for placebo-like drugs is not useful. Probability of stopping for a placebo-like drug should be ≥ 50%
- Probability of stopping if the true effect is at study target value should be ≤ 20%

Example

Success: Predictive probability for DC2* > 80%

Futility: Predictive probability for DC1* < 10%



* Decision Criteria (DC)
  1. Stat. Sig (5%) diff vs placebo
  2. Obs. Diff > target value

Basket Trials - Advantages

- Allows more than one tumour type to be studied in one protocol, i.e. we are not putting all our eggs into one basket (just into one basket trial) - useful if unclear which tumour type to choose
- Allows a more precision medicine approach to clinical development
- Gain information about the treatment effect in several different tumour types
- If the treatment effect is homogeneous, then the sample size is smaller compared with a traditional design
- Operational efficiencies compared with separate protocols
- Recruitment rates may vary. This could allow a shorter time to completion if recruitment is quicker in one tumour type compared to another

Basket Trials - Disadvantages

- The test for homogeneity may lack power and so likely to end up down the homogeneity path
  - Simulation work can be used to investigate the appropriate timing and power of the test
  - If combine, negative baskets will dilute a signal in other baskets. May result in a lack of efficacy overall (and it is not powered to test the separate baskets)
  - If combine and the study completes, you conclude the treatment either works or doesn't work (but not whether it works in each basket and it is not powered to test the separate baskets)
  - The variability is likely to be increased by combining across baskets (so the sample size may not be appropriate/may need adjusting)
- If heterogeneous
  - If you don't combine and the treatment works in only one basket, the sample size is higher compared with a traditional design for one tumour type, although smaller than doing separate parallel studies
  - If you don't combine, the study size will increase up to the equivalent of doing separate parallel studies
- Recruitment rates may vary. Need to wait for all baskets to be recruited for interim analysis. Could cause a delay depending on the difference in recruitment rates. Also, the final study could be biased to the easier to recruit tumour type (if homogeneous)

Basket Trials – Questions to address

A number of questions should be considered before using such a trial: -

- Do we need to know whether the treatment works, or do we need to know which tumour type the treatment works in?
- Is the compound effect likely to be similar across tumour types? If not, a basket trial should not be considered as the first study
  - Is the weight loss similar across tumour types?
  - Is the Placebo response likely to be similar across tumour types?
  - Is the Treatment effect (vs placebo) likely to be similar across tumour types?
- Is the recruitment rate similar across tumour types?
- When would it be appropriate to perform an interim analysis and what is the power of the test for heterogeneity?

The Pfizer project team have concluded this design is probably not appropriate for their First-in-Patient study largely because it is a new mechanism and efficacy has not yet been established. It remains an option for later development

Questions?