Prognostic Value of Waterfall Plots with the Addition of Nontarget Lesion Data

#11082

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Abstract

Background: In patients with solid tumors, the use of a waterfall plot displaying the best percentage change in sum of the longest diameters of target lesions per patient is a common way to depict anti-tumor activity for cytostatic agents (Booth 2008, Dhani 2009). This representation assumes that the best percentage change represents the maximum anti-tumor activity for each patient. Information about new lesions and/or changes in non-target lesions is not incorporated in the waterfall plot; yet these additional events were found to be significant prognostic factors for overall survival adjusting for change in the target lesions (Litiere 2012, Suzuki 2012).

Methods: We analyzed to Phase III lung cancer trials of 1st and 2nd line combination chemotherapy ± ASA404 (ATTRACT-1, n=1299, ATTRACT-2, n=920). For patients whose best response in the target lesions was shrinkage, we calculated how often this best response was synchronously accompanied by non-target disease progression.

Results:

Best shrinkage (%) in target lesion diameters	Fraction (%) of patients with non-target PD at time of best target lesion response.			
	ATTRACT-1 ASA-404	ATTRACT-1 Control	ATTRACT-2 ASA-404	ATTRACT-2 Control
>30%	20/231* (9)	26/238 (11)	8/68 (12)	8/65 (12)
>0% (some shrinkage)	70/484 (14)	62/460 (13)	35/231 (15)	47/255 (18)
*231 patients achieved at least a 30% shrinkage in the target lesion tumor burden. Of theses 231, twenty patients (9%) had synchronous disease progression outside the target lesions.				

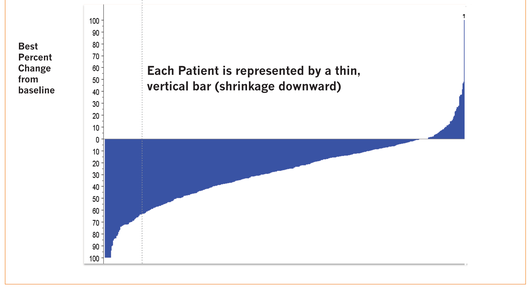
Conclusions: There can be substantial tumor shrinkage in target lesions synchronously with progressive disease outside the target lesions. Therefore, graphical displays of anti-tumor activity should consider incorporating new and non-target lesion information, as well as target lesion tumor burden. We propose an extended waterfall plot presenting a more complete assessment of anti-tumor activity by incorporating non-target lesion information. We illustrate its utility in an additional data set, the RECORD-1 Phase III renal cell cancer trial.

Background

Waterfall plots In oncology

- Depict the best percentage change in the sum of the longest diameters of the target lesion burden per patient (tumor shrinkage below x axis,tumor growth above x axis)
  - Use contiguous histograms sorted in ascending or descending order
  - Recommended as exploratory analyses for Phase II trials by Booth et al (2008) and Dhani et al (2009)
  - Widely used in presentations and publications.
  - Assume best change in target tumor burden corresponds to maximum clinical benefit
- However, waterfall plots may not capture all relevant tumor response information (e.g. new and non-target lesion disease progression)

Standard waterfall plot



Role of components of tumor measurement as predictors of overall survival (OS)

- There were four independent investigations of the role of the tumor measurement components (baseline target lesion tumor burden, change from baseline tumor burden, occurrence of new lesions, non-target lesion disease progression (PD) in predicting overall survival (OS) in 2012
- All four used multivariate Cox proportional hazards models
  - Three used data at 1st post-treatment tumor assessment, one (Litiere et al) used time dependent covariates
- Target lesions modeled with different functional forms
- Three used new lesions and non-target PD as separate covariates, one (Suzuki et al) combined new lesion and non-target PD as one covariate

Importance of new and/or non-target lesions to predict overall survival (OS)

Publication	Number of studies	Tumor types (n=number of patients analyzed)	New lesion HR median, range (p-value median, range)	Non-target PD HR median, range (p-value median, range)
Litiere et al (ASCO 2012)	12 (random sample of 60% stratified by study	7 MBC (n=1069) 3 NSCLC (n=1776) 2 MCRC (n=682)	1.93[a] (1.58-2.22) (<0.001, <0.001-<0.001)	1.49[a] (1.47-1.65) (<0.001, <0.001-0.005)
Mietlowski et al (ASCO 2012)	5	2 MCRC (n=1847) 2 NSCLC (n=1804) 1 OVCA (n=524)	3.02[b] (2.20-3.91) (<0.001, <0.001-<0.001)	1.67[b] (1.19-1.95) (<0.001, <0.001-0.332)
Stein et al (2012 Eur Urology online)	1	1 RCC (n=246)	1.56 (0.053)	1.86 (0.005)
Suzuki et al (2012 Ann Oncology)	1	1 MCRC (n=506)	3.77[c] (<0.001)	3.77[c] (<0.001)
Multivariate Cox proportional model with target lesion data in the model (various functional forms) MBC=metastatic breast cancer; MCRC=metastatic colorectal cancer; NSCLC=non small cell lung cancer; OVCA=advanced ovarian cancer; RCC=renal cell cancer; a= median across 3 tumor types; b=median across 5 studies, c=new and/or non-target lesion PD combined				

Potential issues with the standard waterfall plot

- The four publications all corroborate the importance of all the components of tumor assessment (target lesion measurements, occurrence of new lesions, non-target lesion disease progression) as independent predictors of overall survival.
- There is a need to consider new lesion, non-target lesion and target lesion data in prediction of OS, which is ignored by standard waterfall plots.
- Deaths prior to first post-baseline tumor measurement are also ignored in standard waterfall plots.

Methods

- We explore the frequency at which the best change is accompanied synchronously by disease progression outside the target lesions
- To determine this frequency, we analyzed target lesion data from two Phase III trials in non-small cell lung cancer trials (ASA404 ATTRACT-1 : 1st line and ASA404 ATTRACT-2: 2nd line).
- We propose two alternative waterfall plots (modified and extended).
- The utility of the extended waterfall is illustrated using the RECORD-1 Phase III renal cell cancer study.

Modified and extended waterfall plots proposed to incorporate off-target lesion data

- The modified waterfall plot:
  - Uses a different color (e.g. red) when the best change in the target lesion tumor burden is accompanied by appearance of new lesions and/or non-target PD than when it is not (e.g. blue).
  - May be used as a kind of diagnostic for the appropriateness of the standard waterfall plot.
- Properties of the extended waterfall plot:
  - Patients that die before the first assessment are all assigned the same height and represented on the left.
  - Patients that progress at the first assessment due to nontarget lesion progression or new lesion appearance are assigned a slightly lower height and are represented next.
  - Patients that do not progress at the first assessment are represented by a traditional waterfall plot.
- We show the use of the modified waterfall plot in ATTRACT-1 and the use of the extended waterfall plot in the RECORD-1 study

Description of studies used

Study	Indication	Treatments	N randomized (experimental, control)
ATTRACT-1	1st line NSCLC	Carboplatin/paclitaxel ± ASA404	1299 (649, 650)
ATTRACT-2	2nd line NSCLC	Docetaxel ± ASA404	920 (460 ,460)
RECORD-1	2nd line MRCC	Everolimus + BSC vs. Placebo + BSC	416 (277, 139)
NSCLC=non-small cell lung cancer, MRCC=metastatic renal cell cancer, BSC=best supportive care			

Results

Frequency of best target lesion change with synchronous PD outside target lesions

Best shrinkage (%) in target lesion diameters	Fraction (%) of patients with non-target PD at time of best target lesion response			
	ATTRACT-1 ASA-404	ATTRACT-1 Control	ATTRACT-2 ASA-404	ATTRACT-2 Control
>30%	20/231* (9)	26/238 (11)	8/68 (12)	8/65 (12)
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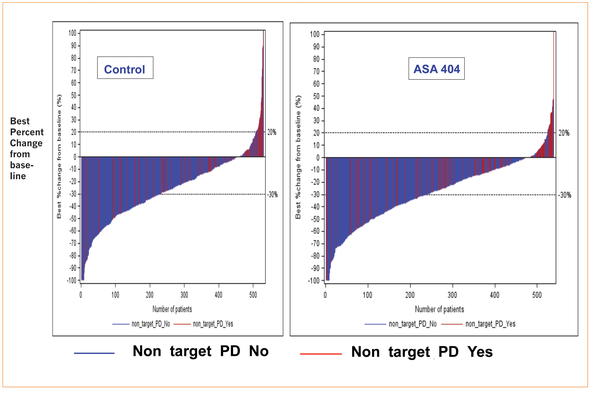
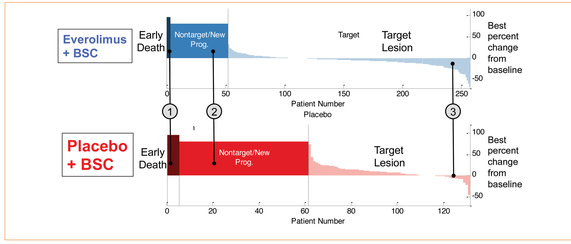
*231 patients achieved at least a 30% shrinkage in the target lesion tumor burden. Of theses 231, twenty patients (9%) had synchronous disease progression outside the target lesions.				

Modified waterfall plot for ATTRACT-1
(tumor shrinkage exhibited below x-axis and tumor growth above x-axis)



The extended waterfall plot demonstrates a more complete measure of patient response.



1. There is a higher proportion of early deaths on placebo.
2. There is a higher proportion of nontarget/new progression events on placebo.
3. There is a lower proportion of patients with shrinking target on placebo among the patients. that didn't progress due to death, nontarget, or new lesions at month 2.

Conclusions

- Standard waterfall plots assume that target lesion activity essentially captures all the relevant information concerning tumor burden.
- New lesion, non-target PD, and early death information are ignored with standard waterfall plots but these appear to be independent predictors of overall survival.
- Furthermore, synchronous PD outside of the target lesions can occur with substantial shrinkage of the target lesions (9-12% when best target lesion shrinkage ≥ 30%)
- The modified and extended waterfall plots are new diagnostics that display information missing from the standard waterfall plot.

References for background and methods

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2. Dhani N, Tu D, Sargent DJ et al (2009). Clin Cancer Res 15:1873-1882.
3. Litiere S, DeVries E, Seymour L et al (2012). ASCO poster, Abstract #10602.
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6. Suzuki C, Blomqvist L, Sundin A et al (2012). Ann Oncol 23: 948-954.

References for 3 Phase III trials

1. ATTRACT-1: Lara PN Jr, Douillard J-Y, Nakagawa K, et al.(2011) J Clin Oncol; 29:2965–2971.
2. ATTRACT-1 (editorial):Lorusso PM, Boerner SA, Hunsberger S (2011). J Clin Oncol;29:2952-2955
3. ATTRACT-2: http://www.cancerresearchuk.org/cancer-help/trials/trials-search/A-trial-ASA404-and-docetaxel-for-non-small-cell-lung-cancer-that-has-continued-to-grow-during-chemotherapy-or-has-come-back-after-treatment
4. RECORD-1: Motzer RJ, Escudier B, Oudard S et al (2010). Cancer 116: 4256-4265.