Supplementary Online Content

Ferrara R, Mezquita L, Texier M, et al. Hyperprogressive disease in patients with advanced non–small cell lung cancer treated with PD-1/PD-L1 inhibitors or with single-agent chemotherapy. Published online September 6, 2018. doi:10.1001/jamaoncol.2018.3676

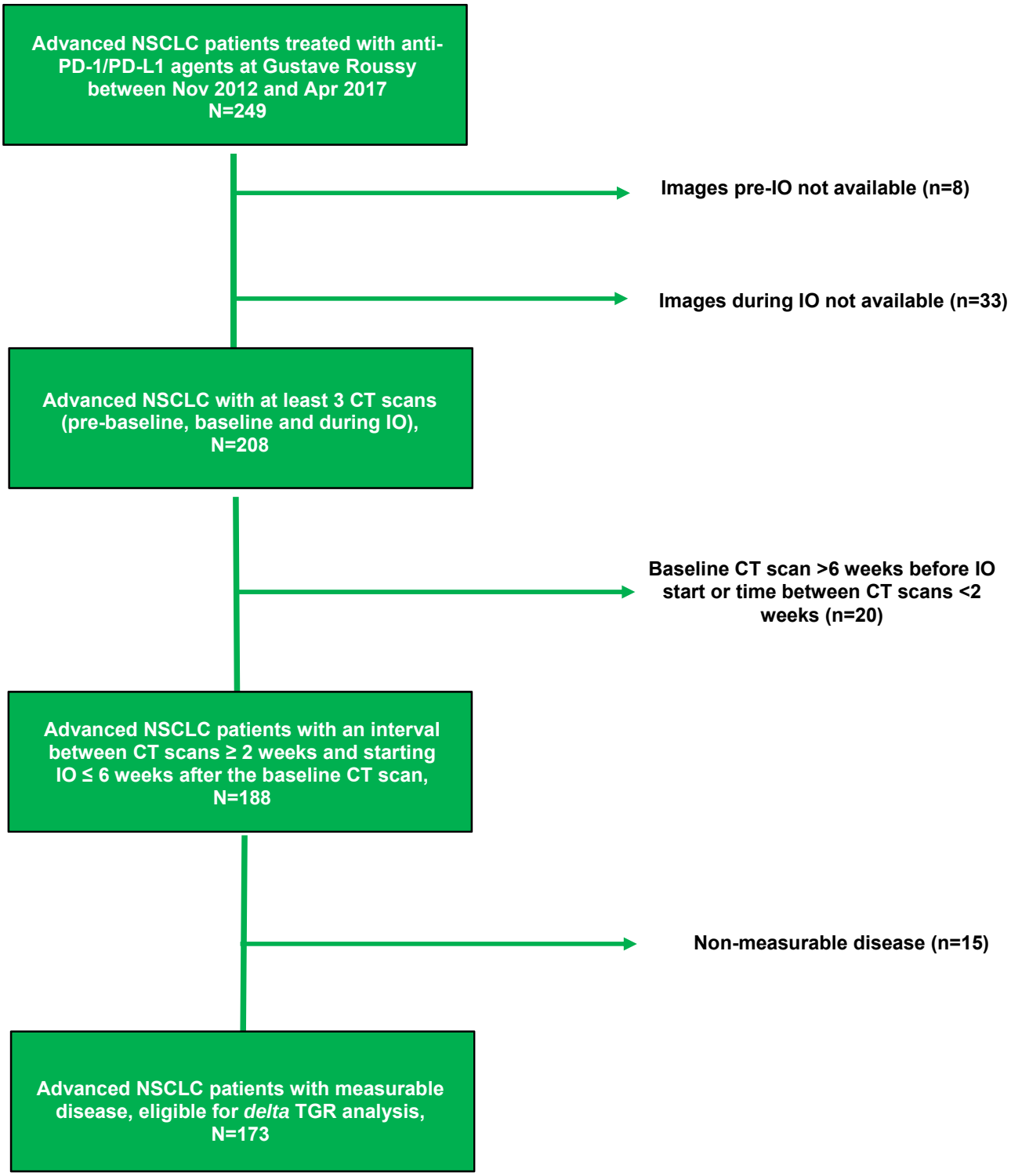
This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Supplemental Methods

Computation of tumor growth rate (TGR) and timing of TGR assessment

Assuming tumor growth follows an exponential law, Vt, tumor volume at time t (expressed in months in the tumor evaluation) is equal to Vt = V0 exp (TG.t), where V0 is volume at baseline, and TG is the growth rate. We approximated the tumor volume (V) by V=4 π R3/3, where R, the radius of the sphere, is equal to D/2. Consequently, TG is equal to TG=3 log(Dt/D0)/(t1-t0), where log represents natural logarithms and t1-t0 is the time between evaluations in months. TGR results were reported as a percent increase in tumor volume per month using the following transformation: TGR=100 [exp(TG)−1], where exp(TG) represents the exponential of TG[1]. The algorithm for TGR calculation is publicly available online (https://github.com/chferte/TumorGrowthRate/blob/master/TGR_calculator.R). Tumor volume was evaluated at three timepoints: before treatment with IO or chemotherapy [(n-1) CT scan], at baseline [baseline (n) CT scan], and once during treatment [(n+1) CT scan]. TGR was then calculated before [(n) CT scan vs (n-1) CT scan] and during [(n+1) CT scan vs (n) CT scan] for both the PD-1/PD-L1 inhibitor cohort and single-agent chemotherapy cohort.

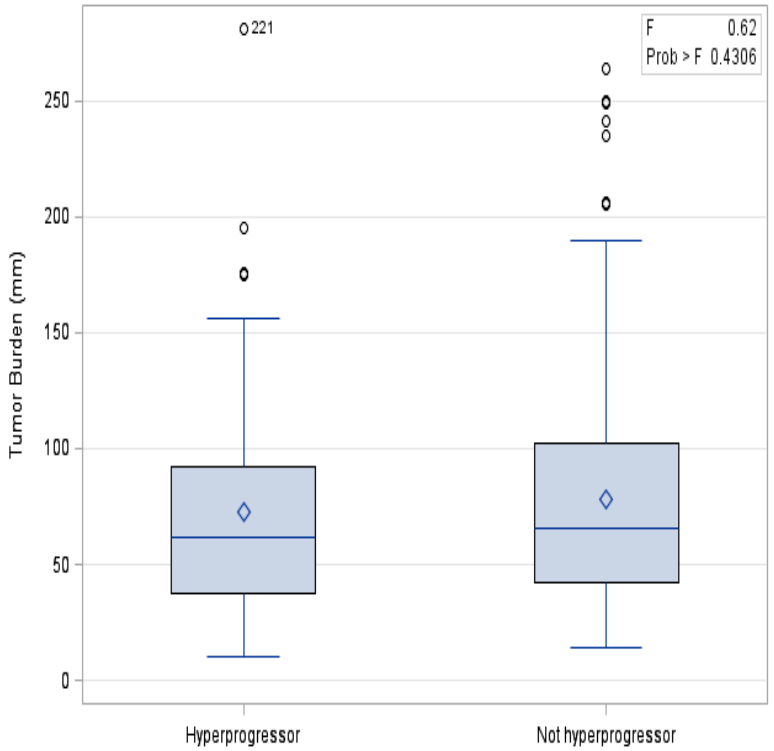
eFigure 1. Flowchart for *delta* TGR Evaluation in the Immunotherapy Cohort (From a Single Institution)



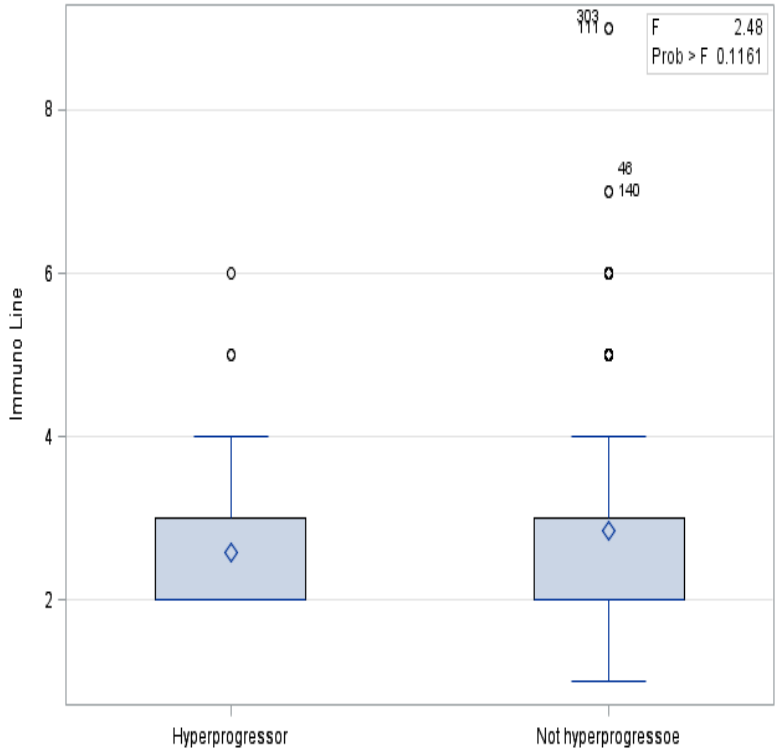
Out of 249 patients treated with PD-(L)-1 inhibitors at Gustave Roussy, 76 (~30%) were excluded because of unavailability of CT scans before (3%) or during IO (13%), inadequate time intervals between CT scans (8%) or absence of measurable disease (6%).

eFigure 2. Box Plots Showing Baseline Tumor Burden (A) and Number of Previous Lines (B) Distributions According to HPD Status (Immunotherapy Cohort)

(A)

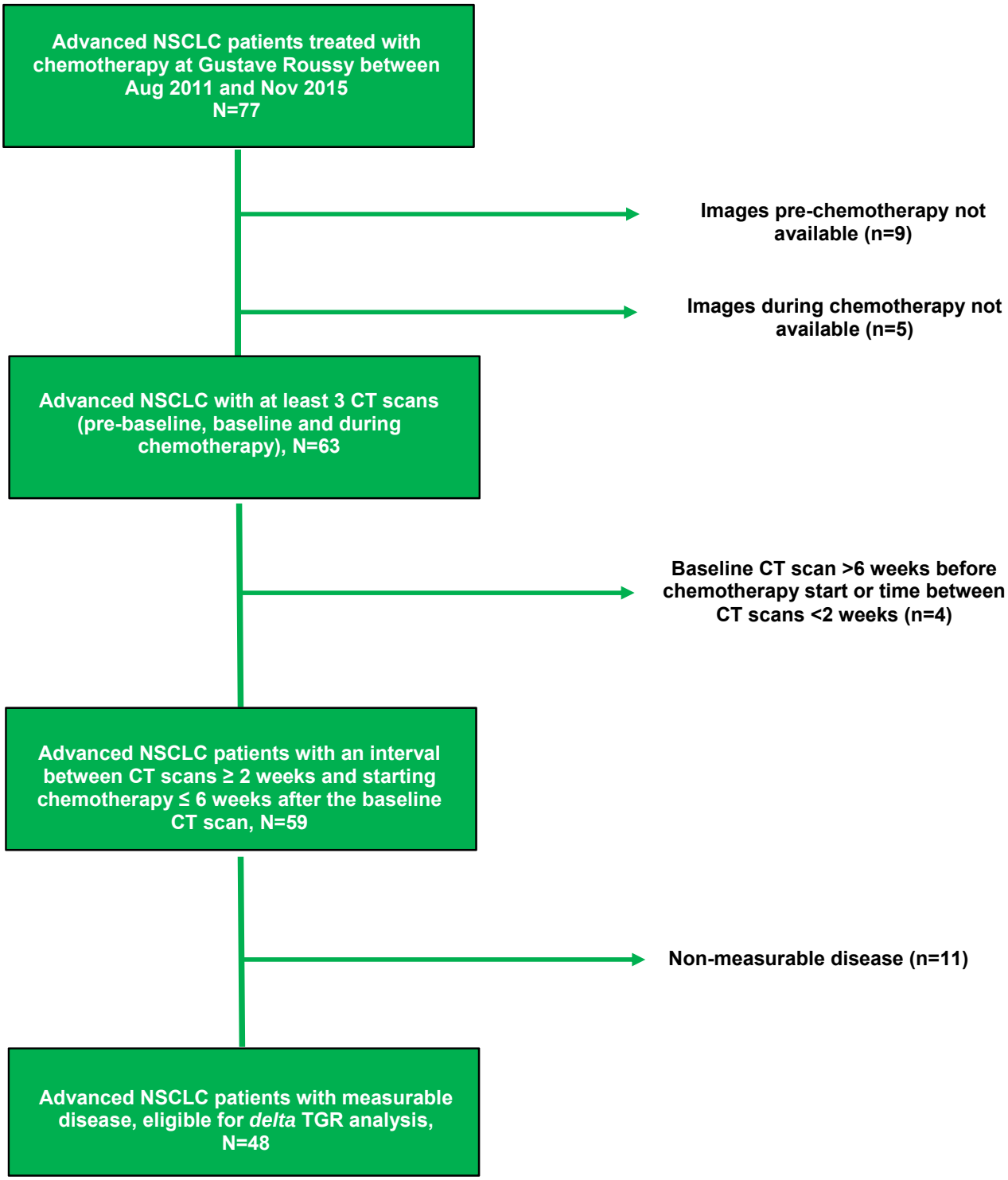


(B)



(A) No significant difference in the mean tumor burden at baseline according to HPD status (72 mm HPD vs 78 mm non-HPD, p=.43). (B) No significant difference in the mean number of lines before immunotherapy according to HPD status (2.6 HPD vs 2.8 non-HPD, p=.11).

eFigure 3. Flowchart for *delta* TGR Evaluation in the Chemotherapy Cohort (From a Single Institution)



Out of 77 patients treated with single agent chemotherapy at Gustave Roussy, 29 (~38%) were excluded because of unavailability of CT scans before (12%) or during chemotherapy (6%), inadequate time intervals between CT scans (5%) or absence of measurable disease (14%).

eTable 1. Typical and Atypical Response Patterns to PD-1/PD-L1 Inhibitors and Single-Agent Chemotherapy

Best response	PD-1/PD-L1 inhibitors (N=406) No. (%)	Single agent chemotherapy (N=59) No. (%)
CR/PR	77 (19%)	6 (10%)
SD	158 (39%)	35 (59%)
PD	170 (42%)	18 (31%)
Pseudoprogression[a]	19 (4.7%)	0 (0%)

[a] Progressive disease (PD) followed by complete/partial response (CR/PR) or stable disease (SD) lasting more than 6 months

eTable 2. TGR Analysis in the Immunotherapy and Single-Agent Chemotherapy Cohorts

	PD-1/PD-L1 inhibitors (N=406) No. (%)	Single-agent chemotherapy (N=59) No. (%)
TGR pre-treatment		
≤ 0	75 (18%)	14 (24%)
> 0	331 (82%)	45 (76%)
TGR on-treatment		
≤ 0	167 (41%)	39 (66%)
> 0	239 (59%)	20 (34%)
***delta* TGR[a]**		
≤ 0%	266 (66%)	47 (80%)
>0% and ≤50%	78 (19%)	9 (15%)
> 50%	62 (15%)	3 (5%)

a TGR on treatment minus TGR pre-treatment

eTable 3. Patient Characteristics in the Chemotherapy Cohort

	N=59 No. (%)
Age	
≥ 65 years	28 (47%)
Smoking status	
Never smoker	6 (10%)
Former/current	53 (90%)
Histology	
Non-squamous	47 (80%)
Stage [a]	
III	7 (12%)
IV	52 (88%)
No. metastatic sites at baseline	
> 2	16 (27%)
Mutational status	
EGFR mutation	4 (7%)
ALK rearrangement	3 (5%)
KRAS mutation	17 (29%)
Wild-type [b]	9 (15%)
Other alterations	11 (19%)
Missing	15 (25%)
Performance status	
≥ 2	8 (13%)
Chemotherapy line (range 2-8)	
> 2	17 (29%)
Chemotherapy drugs	
Taxanes [c]	43 (73%)
Pemetrexed	7 (12%)
Vinorelbine	4 (7%)
Gemcitabine	5 (8%)

[a] TNM stage (7th Edition) at advanced disease detection, [b] wild-type for *EGFR* mutation, *ALK* rearrangement and *KRAS* mutation, [c] single agent docetaxel or paclitaxel

eReference

1. Ferté C, Fernandez M, Hollebecque A, et al. Tumor growth rate is an early indicator of antitumor drug activity in phase I clinical trials. *Clin Cancer Res*. 2014;20(1):246-252.