



Radiological Dynamics and Resistance Types of Advanced Melanoma Treated with Anti-PD-1 Monotherapy

Xue Bai^{1,2}, Michelle S. Kim³, Gyulnara Kasumova³, Lu Si¹, Bixia Tang¹, Chuanliang Cui¹, Xiaoling Yang^{1,4}, Xiaoting Wei¹, Justine V. Cohen², Donald P. Lawrence², Christine Freedman², Riley M. Fadden², Krista M. Rubin², Tatyana Sharova³, Dennie T. Frederick³, Keith T. Flaherty^{2,5}, Ryan J. Sullivan^{2,5}, Jun Guo^{1,5,6}, Genevieve M. Boland^{3,5,6}



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¹ Peking University Cancer Hospital, ² Massachusetts General Hospital Cancer Center, ³ Department of Surgical Oncology, Massachusetts General Hospital, ⁴ Shanxi Bethune Hospital, ⁵ Senior authors, ⁶ Corresponding authors: Dr. Jun Guo, email: guoj307@126.com, Dr. Genevieve M. Boland, email: gmboland@partners.org



Disclosure

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Background



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Background

- Radiological data taken at different time points are associated with survival in anti-PD-1 monotherapy treated advanced melanoma patients¹⁻⁵
- No tumor growth tempo-focused study so far
- No literature addressing the radiological evolution of patients who achieve a PR or SD
- Although the SITC taskforce has defined the resistance types to anti-PD-1 monotherapy (primary versus secondary)⁶, clinical data describing their clinical differences and evolving trajectories is still lacking

1. Joseph RW, et al. Clin Cancer Res, 2018;
3. Osgood C MF, et al. JCO, 2019; 37(15_suppl);
5. Wang M, et al. Ann Oncol, 2019;

2. Betof Warner A, et al. JCO, 2020;
4. Patrinely JR, et al. Cancer, 2020;
6. Kluger HM, et al. JTC, 2020



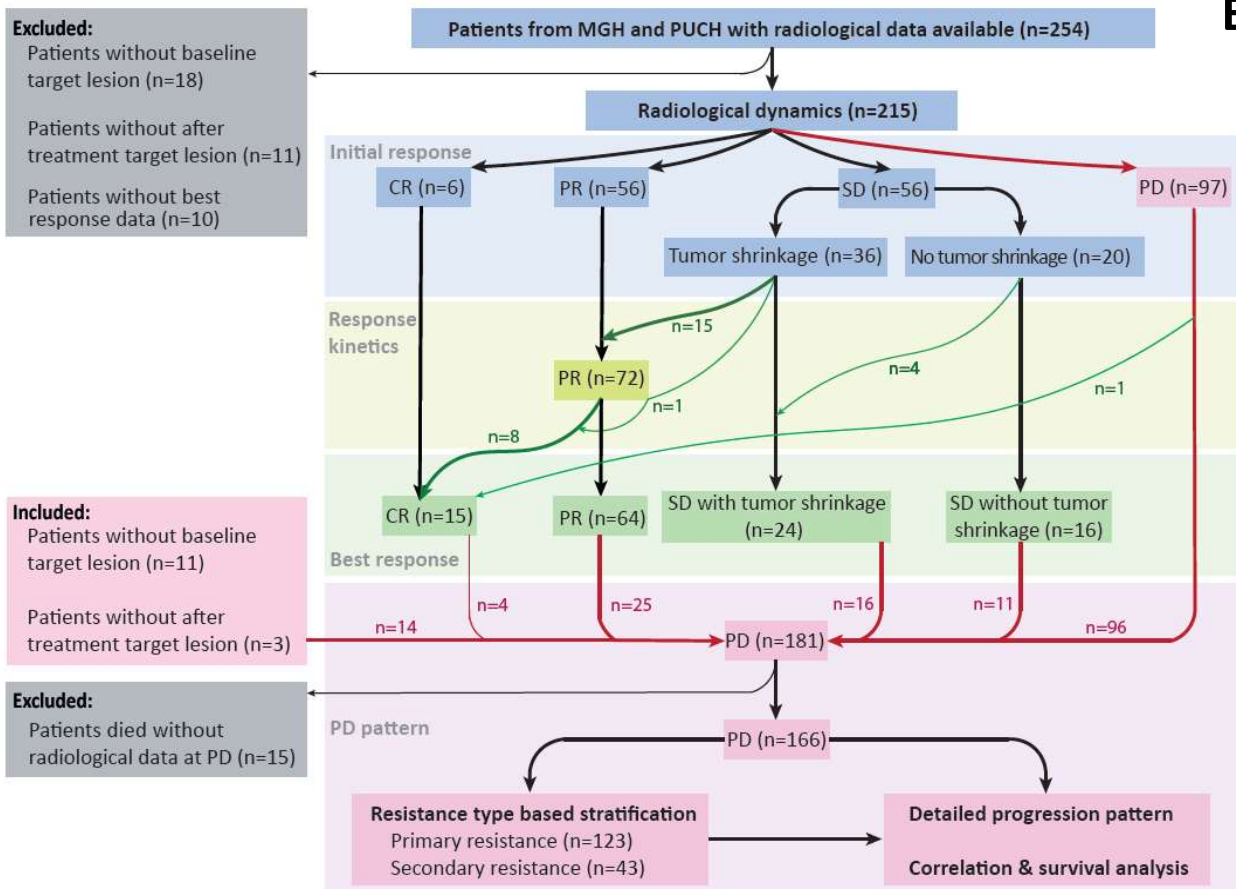
Study Design



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Research Schema



Endpoints

✓ Radiological dynamics

- Tumor size at different time points
- Tumor growth tempo
- Evolving trajectories of PR & SD patients

✓ Heterogeneous progression pattern

- Widespread vs. non-widespread
- Radiological parameter
- Tumor growth tempo (radiographic & LDH)
- Correlation with post-PD survival

✓ Resistance type (SITC taskforce defined)

- Progression pattern
- Tumor growth tempo (radiographic & LDH)
- Further treatment
- Correlation with post-PD survival



Radiological dynamics

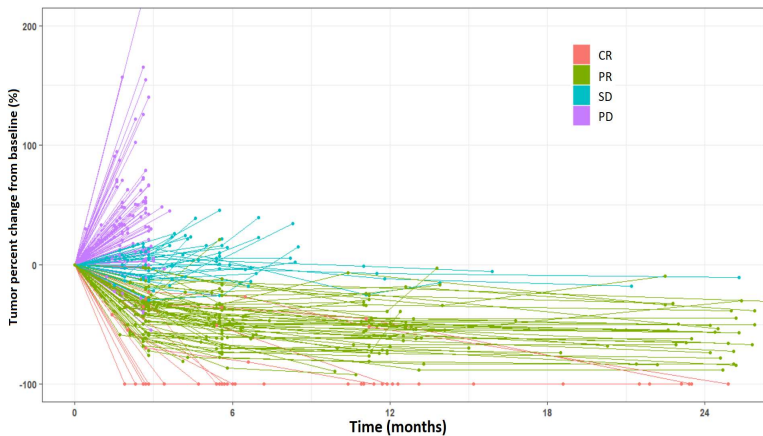


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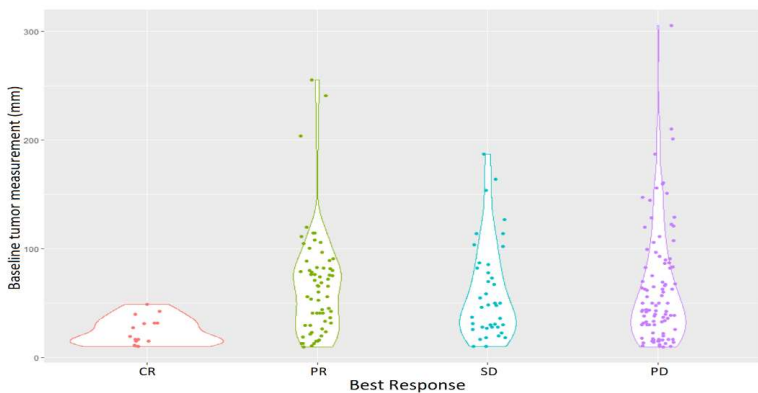
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Radiological dynamics

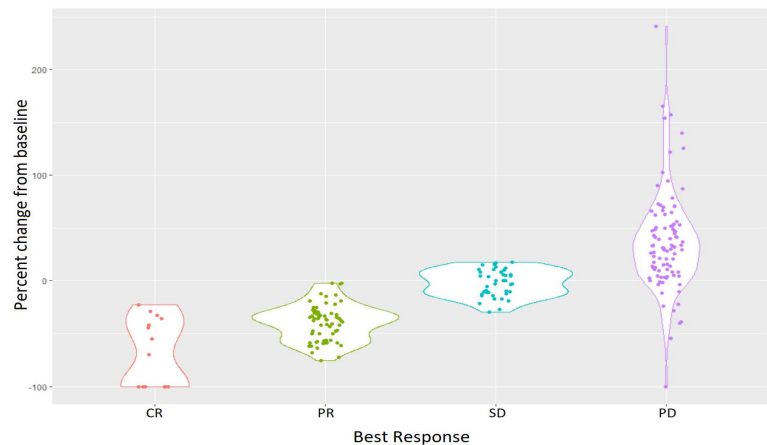
- The most dramatic tumor size change occurred within first 3 months
- The median tumor percent change at first evaluation was -70% in CR patients, -37% in PR patients, and -1% in SD patients
- CR patients had the smallest tumor size at baseline
- Tumor size change was correlated with disease progression



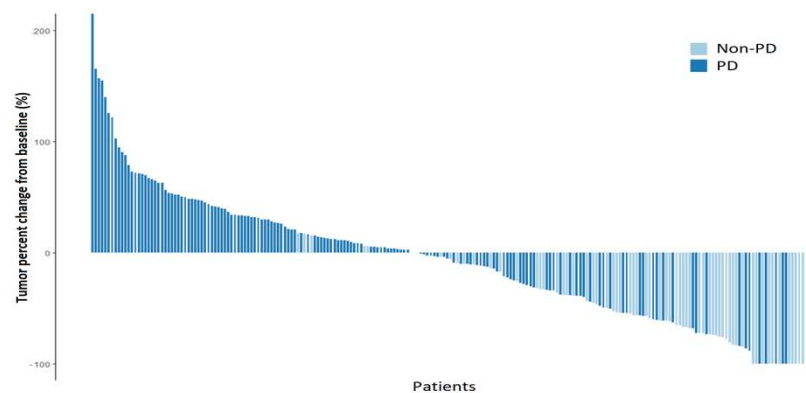
Spider plot of the entire cohort



Baseline tumor size & best response



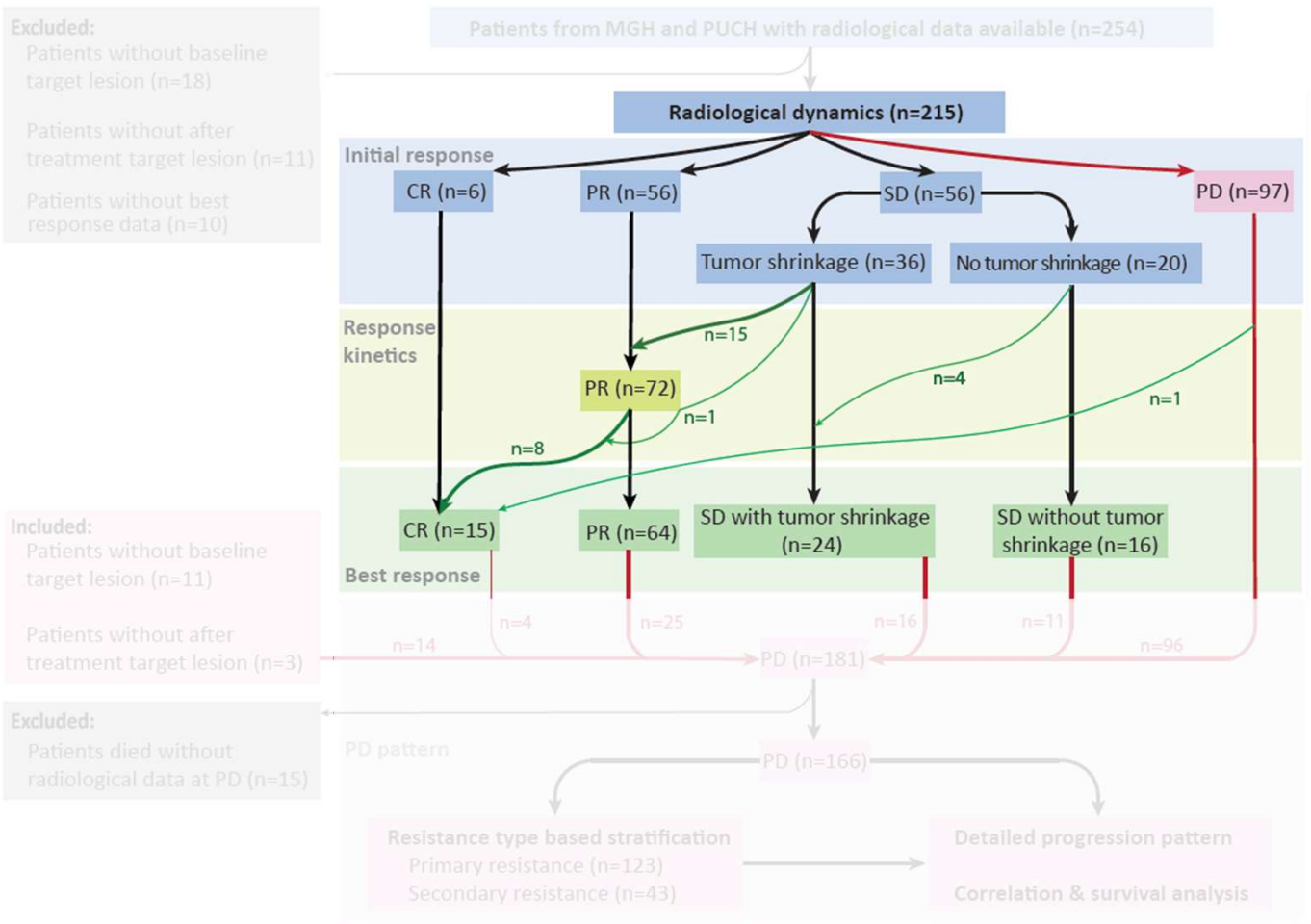
Median tumor % change at 3-month evaluation from baseline



Tumor size change & PD

Radiological dynamics

- CR patients: median duration of CR was 20.9 months
- PR patients: 8 (11.1%) experienced further tumor regression and achieved CR, median duration of PR was 46.0 months, median duration of the eventual CR in this subgroup was not reached
- SD patients: median duration of disease control from the time of first response assessment scan was 6.3 months. One (1.7%) patient achieved CR, 15 (26.8%) PR, all with tumor shrinkage at first evaluation



Radiological dynamics & survival

Radiological dynamics were independently correlated with both PFS & OS

Survival type	Variable type	HR (95% CI)	P value
PFS	Tumor response depth	0.873 (0.847 to 0.900)	<.001
	Time to maximal tumor reduction	0.830 (0.788 to 0.874)	<.001
OS	Tumor response depth	0.917 (0.880 to 0.957)	<.001
	Time to maximal tumor reduction	0.897 (0.851 to 0.946)	<.001

*Response depth and time to maximal tumor reduction were both treated as continuous variables, interpreted as HR per 10 percent increase in the tumor response depth and per 1-month increase for time to maximum decrease or minimum increase of tumor before or at PD compared with baseline measurement. Other covariates included ethnicity (Caucasian vs. non-Caucasian), melanoma subtype (cutaneous, acral, mucosal, ocular, and melanoma of unknown primary), M stage (M0, M1a, M1b, M1c, and M1d), baseline LDH level (elevated vs. normal), previous systemic treatment (yes vs. no), baseline target lesion size (continuous variable).



Progression Pattern



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Progression patterns

- Progression patterns are heterogeneous
- Primary resistance dominates

Progression Pattern	
Categorical metrics	Number (%)
Resistance type	
Primary resistance	123 (74)
Secondary resistance	43 (26)
Number of involved organ(s)	
1	80 (48)
2	50 (30)
>=3	36 (22)
General progression pattern	
Enlargement only	41 (25)
New lesion(s) only	42 (25)
Both	83 (50)
LDH at PD	
Normal	72 (43)
Elevated	79 (48)
NA	15 (9)
Continuous metrics	Median (range)
Target lesion size at PD (mm)*	49.0 (0 to 415.0)
Tumor enlargement dynamics#	
Percent change from last evaluation (%)	26.2 (-100.0 to 241.0)
Percent change from last evaluation (%) per month	10.0 (-28.6 to 109.1)
LDH elevation dynamics\$	
Percent change from last evaluation (%)	6.2 (-33.7 to 354.6)
Percent change from last evaluation (%) per month	7.9 (-49.7 to 409.2)



Resistance Type



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Resistance types

- Primary resistance dominates
- Primary resistance was associated with
 - More broad progression
 - More involved organs
 - More frequent LDH elevation
 - More rapid tumor growth
 - More rapid LDH elevation speed

Progression pattern	Resistance type		
	Primary resistance (n=123)	Secondary resistance (n=43)	P value
General progression pattern			<.001
Enlargement only	34 (28)	7 (16)	
New lesion(s) only	19 (15)	23 (54)	
Both	70 (57)	13 (30)	
Number of involved organ(s)			<.001
1	49 (40)	31 (72)	
2	39 (32)	11 (26)	
≥3	35 (28)	1 (2)	
LDH at PD			.005
Normal	48 (39)	24 (56)	
Elevated	67 (54)	12 (28)	
NA	8 (7)	7 (16)	
Target lesion size at PD (mm)*	64.0 (0 to 415.0)	29.2 (0 to 229.0)	<.001
Tumor enlargement dynamics#			
Percent change from last evaluation (%)	31.3 (-100.0 to 241.0)	3.3 (-71.4 to 120.0)	.001
Percent change from last evaluation (%) per month	13.2 (-28.6 to 82.2)	0.8 (-14.6 to 109.1)	.001
LDH elevation dynamics§			
Percent change from last evaluation (%)	12.3 (-33.7 to 354.6)	2.1 (-25.4 to 42.6)	.003
Percent change from last evaluation (%) per month	13.3 (-49.7 to 409.2)	2.4 (-36.3 to 41.7)	.003

NA, not available. *13 patients with no available target lesion size data at PD. #18 patients with no available tumor enlargement dynamics data.
 §24 patients without LDH dynamics data at PD.



Post-PD Survival



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Post-PD survival (PPS)

Association with longer PPS

- **Response pattern**
 - Response depth
 - PFS
- **PD pattern**
 - Less widespread PD pattern
 - Fewer involved sites
 - Smaller target lesion size
 - Slower tumor growth
- **Resistance type**
 - Secondary resistance

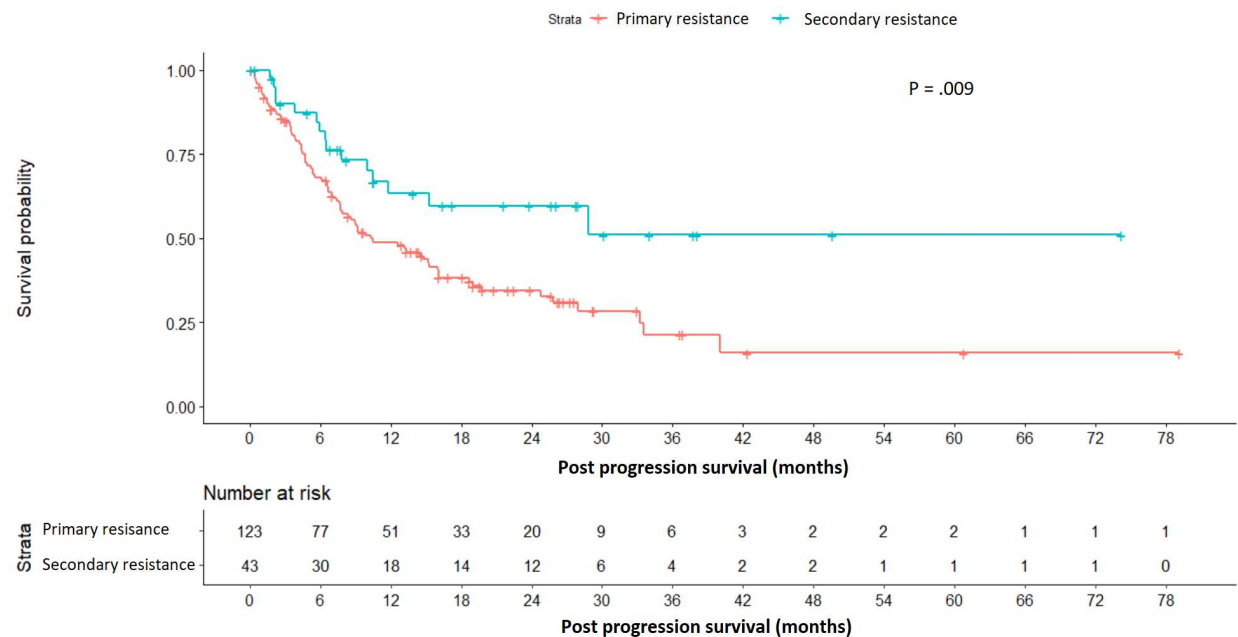
PPS (months)~		
Bivariate analysis	HR (95% CI)	P value
Response pattern		
Tumor percent change (%) ^{\$}	1.005 (1.002 to 1.009)	.005
Time to nadir (months) ^{\$}	0.959 (0.904 to 1.018)	.17
PFS (months) ^{\$}	0.959 (0.921 to 0.998)	.04
PD pattern		
General PD pattern [%]	2.261 (1.469 to 3.480)	<.001
Number of involved organ ^{\$}	1.427 (1.187 to 1.715)	<.001
Target lesion measurement ^{\$}	1.010 (1.004 to 1.016)	<.001
Enlargement dynamics ^{\$}	1.017 (1.005 to 1.029)	.006
LDH elevation at PD [^]	2.735 (1.695 to 4.413)	<.001
LDH elevation dynamics [!]	1.007 (1.004 to 1.009)	<.001
Resistance type [#]	0.503 (0.288 to 0.879)	.02

~Cox proportional hazards regression model, adjusted for baseline target lesion size. ^{\$}As continuous variables. [%]Dichotomous outcome, defined as both new lesion(s) & enlargement vs. either new lesion(s) or enlargement only, with the latter as the reference group). [^]Dichotomous variable (normal vs. elevated, normal as the reference). [!]Continuous variable, compared with last pre-PD LDH level, unit as percent change per month. [#]Dichotomous variable, primary resistance as the reference group.

Post-PD survival (PPS)

Resistance type

- **Primary resistance**
 - Median PPS of 10.3 months (95% CI, 7.7 to 16.1)
- **Secondary resistance**
 - Median PPS not reached (95% CI, 11.8 to not reached)





Conclusions



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Conclusions

- Radiological dynamics were heterogeneous, yet significantly correlated with survival.
- Primary and secondary resistance are distinct clinical manifestations
- We propose the possibility of resistance pattern-based therapeutic decision-making and clinical trial design, if further validated by future prospective studies