

Supplementary Figure 2: SITC ICI Combination Resistance Definitions

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease

Definitions of Primary Resistance for ICI Combinations

Treatment combination	Exposure requirement	Best response	Confirmatory scan requirement
IO-Chemotherapy ^{3*}	6–8 weeks**	PD ≤ 6 months***	Not required
IO-Targeted ⁴	8–12 weeks**** (at least 2 cycles of ICI component)	PD or SD < 6 months	Not required
IO-IO ⁵	12 weeks and/or a minimum of 2 cycles of both drugs	PD or SD < 6 months	At least 4 weeks after PD, if clinically feasible

*For patients that experience recurrent disease after stopping therapy for reasons other than toxicity, no uniform clinical definitions of resistance applicable across disease states could be described

**For rapidly progressing disease, any exposure is adequate

***Timing of RECIST progression regardless of best response

****In the absence of toxicity or progression while on treatment

Secondary Resistance for ICI Combinations

Treatment combination	Exposure requirement	Best response	Confirmatory scan requirement
IO-Chemotherapy ^{3*}	> 6 months	PD > 6 months**	Not required
IO-Targeted ⁴	> 6 months	CR, PR, or SD ≥ 6 months	Not required
IO-IO ⁵	> 6 months	CR, PR, or SD ≥ 6 months***	At least 4 weeks after PD, if clinically feasible

*For patients that experience recurrent disease after stopping therapy for reasons other than toxicity, no uniform clinical definitions of resistance applicable across disease states could be described

**Timing of RECIST progression regardless of best response

***For aggressive tumors such as mesothelioma and NSCLC, 3 months is required

Resistance for ICI Combinations in the Adjuvant Setting

Treatment combination	Exposure requirement	Best response
IO-Chemotherapy ^{3*}	Undefined	Undefined
IO-Targeted ⁴	A minimum of 6 weeks to adjuvant therapy completion	Recurrence < 12 weeks after the last administered dose
IO-IO ⁵	Completion of regimen	≤ 12 weeks or recurrence on therapy after the last administered dose**

*Definitions could not be agreed upon given current data availability

**Primary resistance is deemed undeterminable if progression occurs > 12 weeks after the last administered dose

Resistance for ICI Combinations in the Neoadjuvant Setting

Treatment combination	Exposure requirement	Best response
IO-Chemotherapy^{3*}	Undefined	Undefined
IO-Targeted⁴	Minimum of 6 weeks	< 50% tumor death in resection specimen
IO-IO^{5**}	Completion of regimen	≤ 12 weeks or recurrence on therapy after the last administered dose***

*Definitions could not be agreed upon given current data availability

**Definitions are only applied in scenarios where postoperative therapy is not applied and major pathologic response was achieved. Resistance cannot be determined if major pathologic response is absent

***Primary resistance is deemed undeterminable if progression occurs > 12 weeks after the last administered dose