Mathematical Modelling of Immune Kinetics in Advanced Cancer through Meta-Analysis of Complete Response Rates: Immune Synchronization Emerges as the Likely Determinant of Clinical Response.

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Abstract

Introduction: Recent evidence suggests that the failure of the immune system to eradicate cancer cells is due to the tumor co-opting the normal regulatory/suppressive and homeostatic mechanisms of the immune system, thus avoiding immune based destruction. A small percentage of patients with complete responses (CR; no evidence of tumor) result from many systemic therapies. CR's usually underpin long-term survival.

Methods: Data from numerous studies using standard chemotherapy, targeted therapies and immune modulatory therapies were mathematically analysed, using Meta-Analysis techniques, to evaluate the Complete Response (CR) Rates.

Results: 68 studies using standard chemotherapy for 13 cancer types treated with 8 drug classes were analysed by meta-analysis and showed a CR rate of 7.4%. A range of targeted therapies (B-raf; Mek) and immune based therapies (CTLA-4; PD-1; PD-L1) were also assessed which showed similar findings. Meta-Analysis of 62 IL-2 based therapies showed a similar CR rate also. Over 8000 patients were examined across the Meta-Analyses.

Conclusions: 130 clinical trials, including of over 8000 patients, has demonstrated that the CR rate of 5-10% for patients treated with widely divergent therapies. This remarkably fixed. The probability of this occurring by chance alone is extremely close to zero, and is both scientifically and clinically implausible. Therefore, an underlying predictive operative biological mechanism must apply. It is highly likely that the known principles of immune kinetics between effector and regulatory homeostatic functions must therefore determine a degree of immune synchronization to produce these observed CR's. We have derived a mathematical model and equation using the principles of controlled homeostatic systems, which can be used to explain our Meta-Analysis findings, and the clinical efficacy.

Meta Analysis Data Set 160 trials /studies = 9,964 patients

Agent	% CR Rate	Study No.	Authors	No. of Patients /Trials
IL2 High Dose Combo M/A	4.40%	14	Coventry, Ashdown 2013	1066 in 14 trials
IL2 High Dose Mono M/A	6.60%	13	Coventry, Ashdown 2013	2741 in 19 trials
IL2 Intermediate Dose Comb M/A	2.60%	16	Coventry, Ashdown 2013	400 in 5 trials
IL2 Intermediate Dose Mono M/A	1.60%	15	Coventry, Ashdown 2013	184 in 2 trials
IL2 Low Dose Combo M/A	5.20%	18	Coventry Ashdown 2013	362 in 11 trials
IL2 Low Dose Mono M/A	4.50%	17	Coventry, Ashdown 2013	286 in 13 trials
IL-2 Meta Analysis (M/A) 62 Trials	5.60%	12	Coventry, Ashdown 2013	5312 in 62 trials, 1988-2012

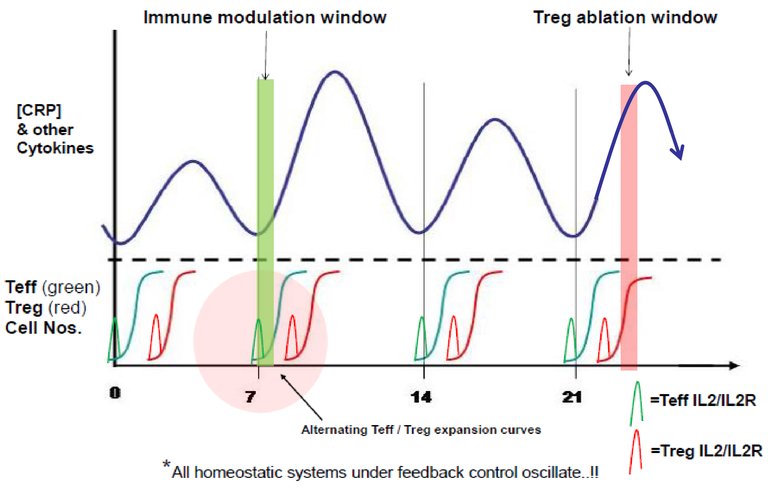
Agent	% CR Rate	Study No.	Authors	No. of Patients /Trials
Ipilimumab+ Nivolumab BMS	6%	29	Wolchok 2013	86
Ipilimumab	10%	2	Farolfi 2012	36
Ipilimumab + gp120 esc	6%	5	Prieto2012	85
Ipilimumab + surgery	7.50%	6	Ku 2010	53
Ipilimumab +gp120	7%	3	Prieto 2012	56
Ipilimumab +IL2	17%	4	Prieto2012	36
Tremelimumab	15.70%	24	Huang 2011	19
Temelimumab	0%	25	Kirkwood 2010	241
Tremelimumab	5.10%	27	Ribas 2008	39
Tremelimumab	2.20%	28	Comacho 2009	89
Tremelimumab + INFa2b	11.40%	23	Tahinni AA 2012	35
Tremelimumab MART-1 DC	12.50%	26	Ribas 2009	16

Agent	% CR Rate	Study No.	Authors	No. of Patients /Trials
Meta Analysis, cytotoxic agents	7%	21	Coventry, Ashdown 2013	2756 in 68 trials, 2000-2008
Temozolomide Meta Analysis	7.12%	22	Yatomi Clarke 2013	541 in 9 trials 2010-2013

Agent	% CR Rate	Study No.	Authors	No. of Patients /Trials
Dabrafenib (Break II)	7%	11	Ascierto 2013	75
Dabrafenib /Mek150/1	6%	8	Flaherty 2012	54
Dabrafenib Mono	4%	9	Flaherty 2012	54
Dabrafenib/Mek 150/2	9%	7	Flaherty 2012	54
Vemurafenib	6.25%	1	Ravnan 2012	32
Vemurafenib	6%	10	Sosman 2012	132

Agent	% CR Rate	Study No.	Authors	No. of Patients /Trials
PD-1 Mab (mono) BMS	3.30%	30	Wolchok, 2013	30
PD-1 Mab Merck	9.70%	20	Hamid O, 2013	103
PD-1L Mab Genentech	7%	19	Gordon, AACR 2013	30

Immune Regulation Kinetics in Cancer – a Cyclical Phenomenon



The Dynamic homeostatically oscillating Immune Cycle creates narrow periodic recurring therapeutic windows.

These therapeutic windows occur as a result of transient ½ life cytokine/receptor interactions on the opposing, alternating synchronously dividing immune cells (Teffs & Tregs) within a repeating ~7day cycle.

Collectively, this physiologic overlay creates a near fixed barrier and constrains the probability of a late stage patient achieving a CR via Treg ablation or immune modulation with certain agents.

This probability is defined as an ~12hr window every ~7 days and equals ~0.07 or 7%. (see equation below)

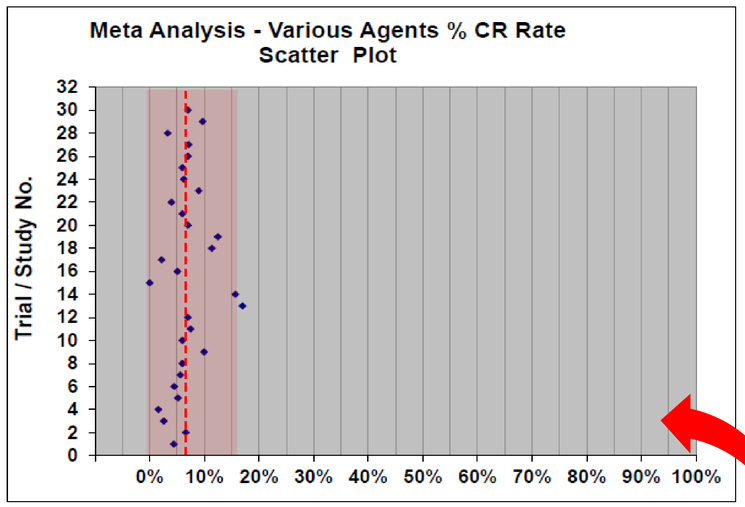
Methodology for Dice Simulation of CR Outcome

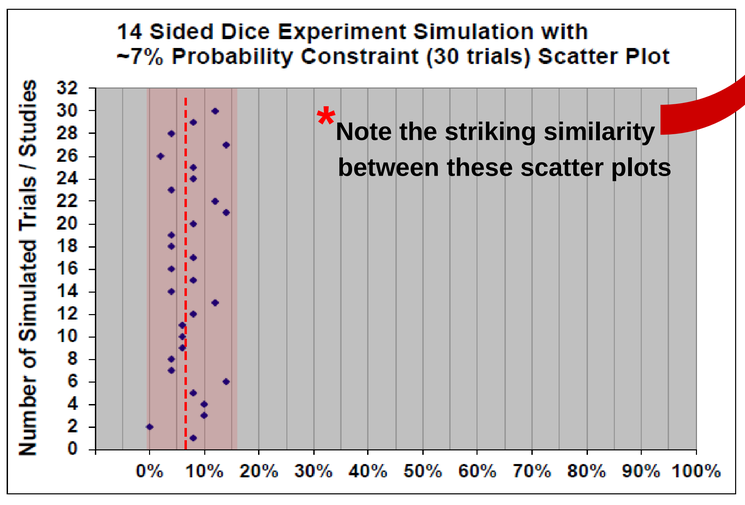
- A number was chosen randomly (5)
- Toss 14 sided dice 50 times
- Record % frequency the 5 occurs
- Repeat 30 times
- Probability constraint is 1/14 or 7%
- Expect an approximate dispersion from 0% - 15% in frequency
- Graph as a Scatter plot

If there is a similar probability constraint governing a late stage patient achieving a CR, then the Scatter Plots for clinical trial % CR Rates and the 14 sided dice simulation should look the same / similar.

Trial	%Frequency
1	8%
2	0%
3	10%
4	10%
5	8%
6	14%
7	4%
8	4%
9	6%
10	6%
11	6%
12	8%
13	12%
14	4%
15	8%
16	4%
17	8%
18	4%
19	4%
20	8%
21	14%
22	12%
23	4%
24	8%
25	8%
26	2%
27	14%
28	4%
29	8%
30	12%

Comparison between Dice Simulation and Meta Data





The Complete Response Probability Equation

$$0.07_{(P_{CR})} \approx \frac{W_{Rx}}{\lambda_{IC}}$$

λ_{IC} = Immune Cycle Periodicity (~7 days or 168hrs)

W_{Rx} = Width of Therapeutic Window (~12hrs)

$P_{(CR)}$ = Probability of a CR (12/168, or 0.07, or 7%)

Conclusion

The principal determinant of CR efficacy is constrained by the probability of fortuitous therapeutic Immune Synchronization and Modulation in the *Time Domain.*

A conjunction of events, including the random timing of therapy, with respect to an endogenous homeostatically oscillating tumor immune response creates recurring narrow therapeutic "windows", and thus restricts this CR efficacy to approximately a random 7% of patients.

We propose that intentional immune synchronization of therapy will lead to a significant increase in the Complete Response Rates