# Clinical Outcomes of Interleukin-2 Therapy in Advanced Cancer: Meta-Analysis of over 60 Trials.


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## Abstract


**Introduction:** 20 years of Interleukin-2 (IL2) therapy for cancer shows clinical complete responses (CR) reported at 5%–20% for advanced malignant melanoma, renal cell carcinoma, and other cancers. Strong durable CR's and long-term 5–10 year survivals can occur.

**Methods:** A meta-analysis was performed of Low, Intermediate and High Dose IL2 therapy, alone or in combination.

**Results:** 62 trials of 5312 patients treated using IL2 were identified. An overall CR rate of 6% was determined. All doses and regimens were capable of producing CR's.

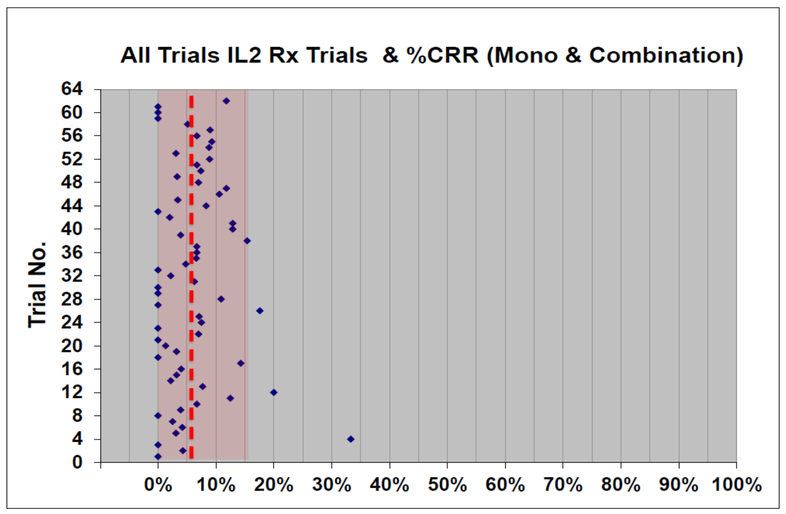
**Conclusion:** Finally, after over 20 years of use and investigation of IL2, the mechanisms of action of IL2 as a 'homeostatic' cytokine are becoming clearer. The physiological feedback of IL2 actions over T-cell effector and regulatory functions indicate that there is a homeostatic balance, which is capable of being manipulated by exogenous (therapeutic) IL-2 towards either net responsiveness or tolerance. This is underpinned by transient expression of IL-2 receptor levels on the respective effector or regulatory populations. In this regard, the timing and frequency of IL2 administration will necessarily determine the clinical outcome through 'immune synchronization'. The way forward is to monitor systemic inflammation, to determine the optimal time for IL2 dose delivery; and not to give up on the patient too early because non-responsiveness can be turned into responsiveness with repetitive accurate dosing. This phenomenon is just becoming apparent with other therapies, showing that the solution to the problem is obtainable by carefully coordinated and timed therapeutic administration.


## Meta Analysis Trial Data

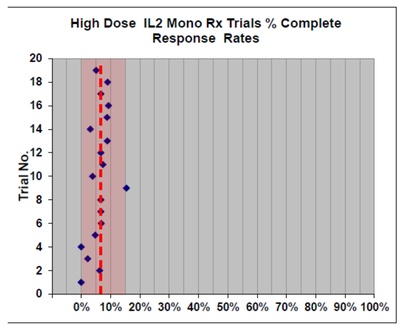
62 Trials – 5312 Patients

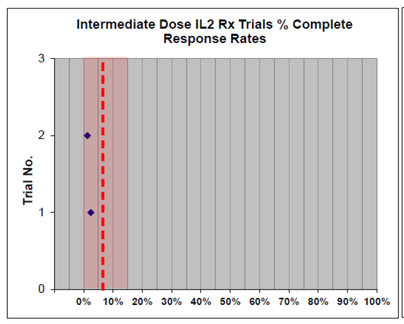
| Number of Trials 1986-2012 | Number of Patients | Complete Responses | % Complete Response |
|---|---|---|---|
| All Trials = 62 (total) | 5312 | 298 | 5.6 |
| HD IL2 (total 33) | 3807 | 239 | 6.3 |
| HD IL2 (mono 19) * | 2741 | 181 | 6.6 * |
| HD IL2 (combo 14) | 1168 | 64 | 5.6 |
| ID IL2 (total 11) | 713 | 24 | 3.4 |
| ID IL2 (mono 2) | 184 | 3 | 1.6 |
| ID IL2 (combo 9) | 400 | 11 | 2.6 |
| LD IL2 (total 17) | 792 | 35 | 4.4 |
| LD IL2 (mono 6) | 286 | 13 | 4.5 |
| LD IL2 (combo 11) | 362 | 19 | 5.2 |

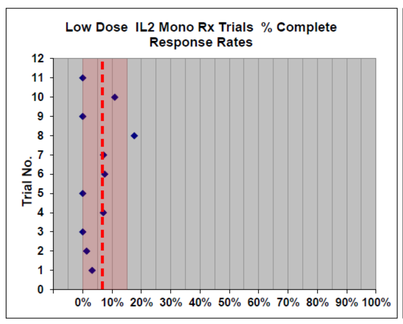
Combo = +/or: TILs, LAKs, ChemoRx, Vax, peptides, other cytokines, Mabs, TKIs



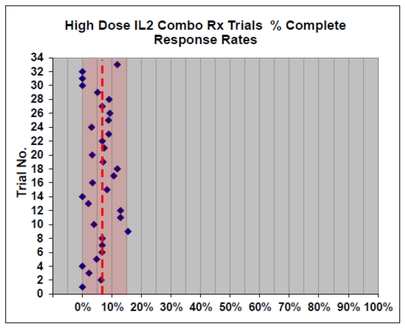

## Mono IL2 Rx % CR's

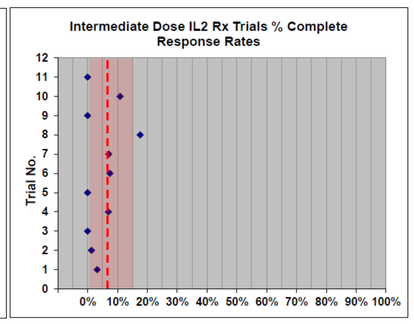


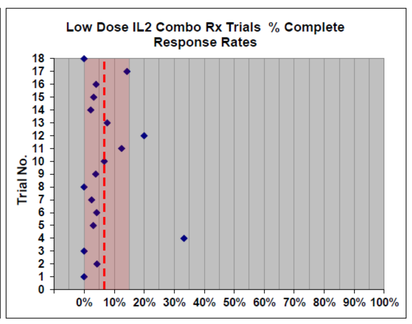




## Combination IL2 Rx % CR's



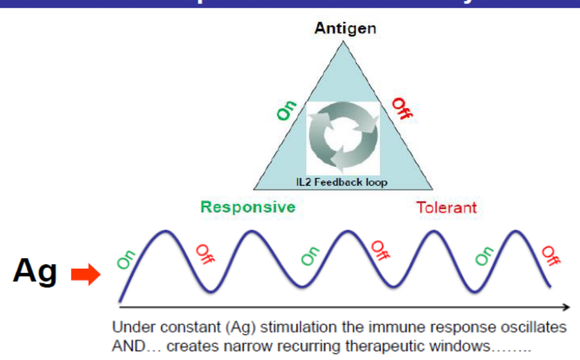




## Using Reported Aspects of Immune Kinetics to Derive an Equation to explain the CR Rate

- The immune Response is a "Bi-stable" System that can exist in either of one of two states, responsive or tolerant .
- This "Bi-stable" System has an IL2 Feedback mechanism
- Under constant stimulation via persistent cancer cell antigen release, this "Bi-stable" System's IL2 Feedback mechanism causes the immune response to continuously oscillate or cycle.
- This oscillation or cycle via the transient alternating interaction of IL2 and its receptor on T eff then Tregs creates narrow ~12hr recurring therapeutic windows every ~7 days.
- The immune kinetics stated above implies exogenous (therapeutic) IL2 can favour tumor responsivness and deliver a complete response in a late stage cancer ~7% of the time.
- This creates a probability barrier of the patient being successfully treated and derives the following equation.

### The Immune Response – A Bi-stable System with Feedback




## The Complete Response Probability Equation

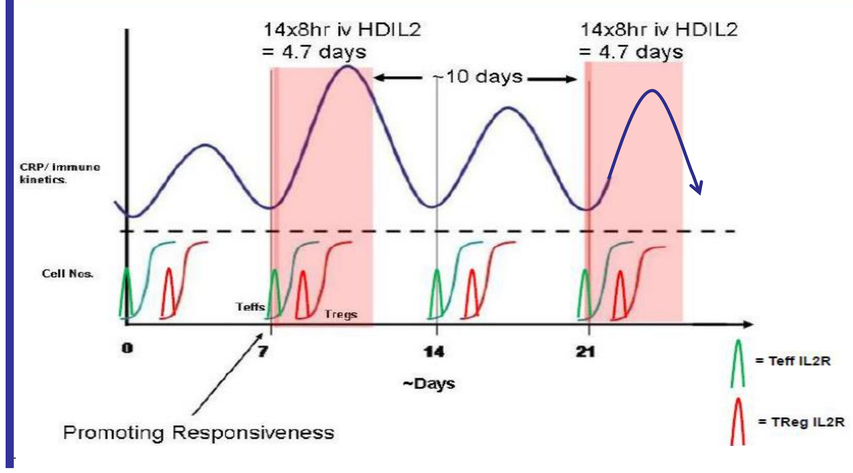
$$0.07_{(P_{CR})} \approx \frac{W_{Rx}}{\lambda_{IC}}$$

$\lambda_{IC}$ = Immune Cycle Periodicity (~7days)

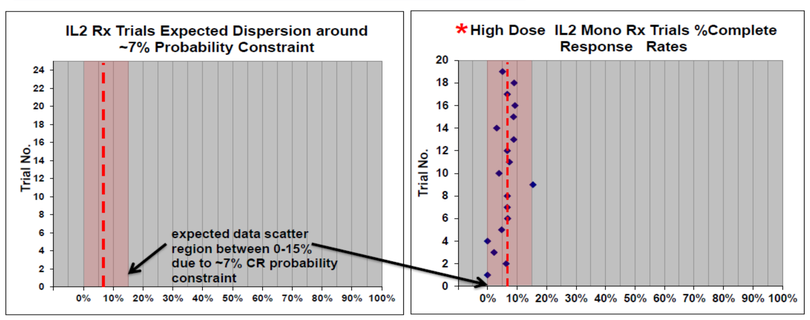
$W_{Rx}$ = Width of Therapeutic Window (~12hrs)

$P_{(CR)}$ = Probability of a CR (1/14, or 0.07, or ~7%)

## HD IL2 Rx and interactions with the Regulated Immune Response Cycle




## A Simple Probability Simulation & Test




The Complete Response Probability Equation (CRPE) defines the average ~7% complete response rate and the likely spread or dispersion / variation (~0%-15%) seen in the CR rate across multiple clinical trials with IL2 Rx.

## Conclusion

The near fixed average complete response rate seen with IL2 therapy is caused by Immune Synchronization due to a conjunction of fortuitous immunologic events.

## Implications

We reason that monitoring the patient's immune fluctuations to accurately synchronize the IL2 therapy with the correct phase of the patient's Immune Cycle, will increase the Complete Response Rate and reduce toxicity.