

Two Decades of IL-2 Clinical Trials – Lessons Learned and Impact on Development Plans for Anti-CTLA4

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Disclosures

- Consulting fee from BMS/Medarex (ipilimumab)
- Consulting fee from Pfizer (tremelimumab)
- Most of salary from patients who want to get better

- IL-2 was developed in an earlier era
- Rudimentary molecular understanding of immunobiology
- ‘Unlimited’ drug supply
- Major involvement by NCI and NCI-CTEP
- Less hindrance from IP issues
- Less dependence on industry funding to conduct clinical trials
- Pursuit in trials of any reasonable proposal

Goals of IL-2 'Development'

- Dose response
 - Schedule optimization
 - Management/reduction of toxicities
 - Patient selection
 - Determine activity in advanced disease
 - Find predictive biomarker
 - Determine biological effects and mechanisms
 - Demonstrate benefit
 - Improve activity with rational combinations
 - Determine effects in adjuvant setting
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graph TD; A[Dose response] --> B[Patient selection]; C[Schedule optimization] --> D[Find predictive biomarker]; E[Management/reduction of toxicities] --> F[Determine biological effects and mechanisms]; D --> G[Determine effects in adjuvant setting];
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# High Dose IL-2 for Renal Cell Carcinoma

|                                                                          |                             |
|--------------------------------------------------------------------------|-----------------------------|
| <b>Number of Patients</b>                                                | <b>255</b>                  |
| <b>Responders</b>                                                        | <b>37 (15%)</b>             |
| <b>Complete Responders*</b>                                              | <b>17 (7%)</b>              |
| <b>Median Survival (months)</b>                                          | <b>16</b>                   |
| <b>Median duration of response (months)</b><br><b><i>CR patients</i></b> | <b>54</b><br><b>&gt; 80</b> |
| <b>Treatment-related deaths</b>                                          | <b>4%</b>                   |

\* An additional 4 PR had resection of residual disease, alive with DFS > 65 months

# High Dose IL-2 for Metastatic Melanoma

*Atkins et al, J Clin Oncol, 1999*

|                                                                                                  |                                                                                                                                                   |
|--------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Number of Patients</b>                                                                        | <b>270</b>                                                                                                                                        |
| <b>Responders</b>                                                                                | <b>43 (16%)</b>                                                                                                                                   |
| <b>Complete Responders</b>                                                                       | <b>17 (6%)</b>                                                                                                                                    |
| <b>Durable Responses &gt; 24 months</b>                                                          | <b>12 (4.4%)</b>                                                                                                                                  |
| <b>Median Survival</b>                                                                           | <b>12 months</b>                                                                                                                                  |
| <b>Median duration of response</b>                                                               | <b>8.9 months</b>                                                                                                                                 |
| <b>Durable Ongoing Responses &gt; 24 months (in months) (staging based on disease site only)</b> | <b>CR: 24,40,41,59,62,65,72,86, 103,106 (all M1a/b)<br/>PR: 55,92 (both M1c)<br/>+Salvage Surgery (4/5 M1c):<br/>survival: 54,60,64,66,87,103</b> |
| <b>Treatment-related deaths (all sepsis-related)</b>                                             | <b>6 (2.2%)</b>                                                                                                                                   |

# BM Response to Twice-Daily IL2 Regimen

| Date          | 9-27<br>(c1c1)       | 10-10<br>(c1c2) | 12-5<br>(c2c1) |
|---------------|----------------------|-----------------|----------------|
| WBC           | 7600                 | 3000            | 4000           |
| HGB           | 10.3<br>(Transfused) | 7.7             | 12.6           |
| Platelets     | 60,000               | 111,000         | 176,000        |
| LDH           | 2700                 | 440             | 208            |
| Alkaline Phos | 221                  | 614             | 186            |

BM response associated with resolution of thigh mass and pain

# Key Observations from Cumulative IL-2 Experience - 1

- General agreement that durable tumor regression in a small subset (5-10%) = patient benefit
- Selection of patients confounds interpretation of survival data in phase 2 trials
- Median survival is probably not (substantially) improved
- Biology of the tumor is probably more important for activity than tumor 'bulk' or size

# Key Observations from Cumulative IL-2 Experience - 2

- Finding a predictive biomarker has been difficult and elusive
- Poor to no correlation between measured biological effects and outcome
  - Mostly peripheral blood studies
- Mechanism of anti-tumor activity in patients still not completely understood

# More Observations from Cumulative IL-2 Experience

- Suggestive evidence for activity dose–response and dose threshold
- Schedules with greater ‘biological’ activity may have ‘less’ anti-tumor activity
- Multiple combinations with other immune therapies or chemotherapy based on in vitro enhancement of ‘activity’ or biological effect, or in vivo ‘synergy’ in animal models
  - Clinical results almost always inconclusive
  - Activity signals were not sufficiently strong to move beyond phase 1

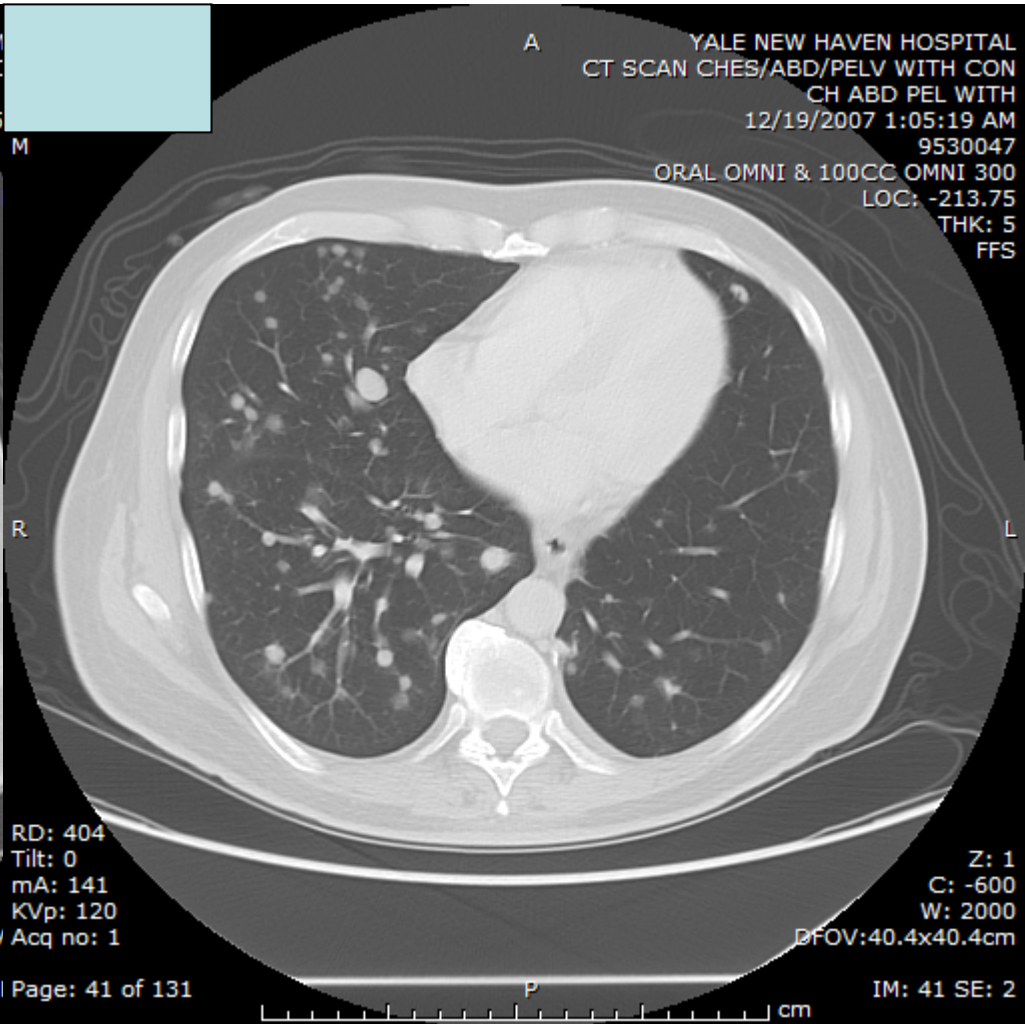
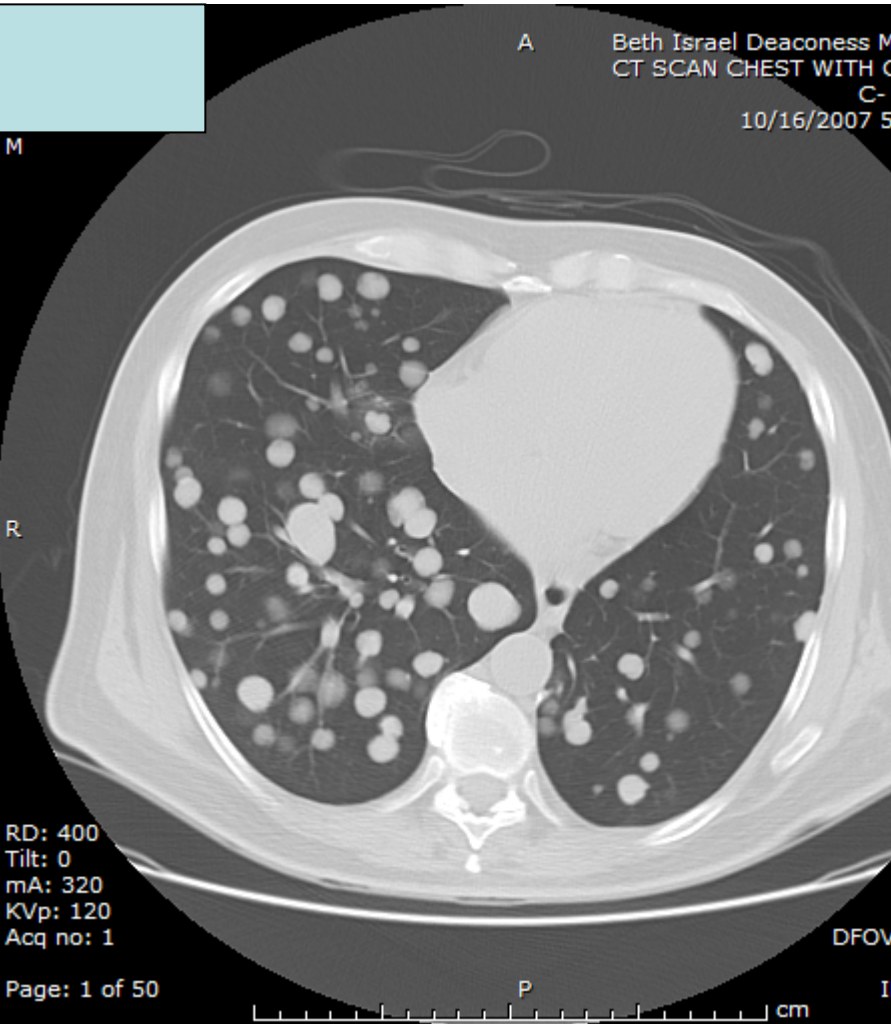
# Does the IL-2 experience inform post-phase 2 anti-CTLA4 development and approval endpoints? (1)

- Reasonable to accept that patients with durable CR/near CR derived benefit from the agent
- Claims of benefit from ‘prolonged SD’, or unexpected prolonged survival in individual patients without response, or improved response to other agents post-progression, **must be verified in phase 3 trials**
- If indeed the ‘benefit’ is limited to the small subset with durable substantial tumor regression, modest-sized randomized studies of anti-CTLA4 compared to standard treatment, using median or overall survival as primary endpoints, may not show significant improvements

## Does the IL-2 experience inform post-phase 2 anti-CTLA4 development? (2)

- In the near-term, highly predictive biomarkers for response are unlikely to be found in blood or sera
- ‘Activity’ in the adjuvant (micro-metastatic) setting is unlikely to be substantially greater than in advanced disease
- Most phase 1 combination studies will produce equivocal signals for further development

# Melanoma, after 2 doses of ipilimumab



# Implications for Anti-CTLA4 Approval Endpoints

- Many experienced clinicians agree on the (presumptive) benefit (durable remission) for small subset of melanoma and RCC patients treated with IL-2 (5-10%)
- Large phase 2 database strongly suggests similar level of activity (benefit, ie durable remission) for anti-CTLA4
- Anti-CTLA4 can produce durable remission in patients progressing on IL-2 and/or DTIC
- Anti-CTLA4 can be used to treat patients unable to tolerate IL-2
- Studies to determine predictive biomarkers are exceedingly difficult and expensive, technology for selecting potential responders 'not there yet'

# Implications for Anti-CTLA4 Approval Endpoints

- Large benefit (although presumptive) in a very small subset may be clinically more meaningful than short extension of survival in high percentage of patients
- Phase 3 survival studies are completed
- Reasonable to propose that anti-CTLA4 merits full approval (now) based on low but consistent durable remission rate in existing phase 2 database