Recent Advances In Joint Models For Cancer And The New Statistical Challenge Of Immunotherapy Clinical Studies

Statistical Issues And Challenges With Immunotherapies: Introduction (i.e. the Perspective of Clinical Oncologists)

Emilio Bria
U.O.C. Oncologia Medica, U.O.S. Neoplasie Toraco-Polmonari, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica del Sacro Cuore, Roma
emilio.bria@unicatt.it

Bordeaux (FRA), January 25th, 2019
Disclosures

- Advisory Boards / Honoraria / Speakers’ fee / Consultant for:
  - MSD, Astra-Zeneca, Celgene, Pfizer, Helsinn, Eli-Lilly, BMS, Novartis, Roche

- Research Support / Grants from:
  - A.I.R.C. (Associazione Italiana Ricerca sul Cancro)
  - I.A.S.L.C. (International Association for the Study of Lung Cancer)
  - L.I.L.T. (Lega Italiana per la Lotta contro i Tumori)
  - Fondazione Cariverona
  - Astra-Zeneca
  - Roche
  - Open Innovation
• Impact of Immunotherapy (IO) in Medical Oncology
• Patients’ Selection and Predictive Factors for IO
• Treatment End-points for IO
• Evidences for Real-World beyond Clinical Trials
Statistical Issues And Challenges With Immunotherapies

Presentation Outline

• Impact of Immunotherapy (IO) in Medical Oncology
  • Patients’ Selection and Predictive Factors for IO
  • Treatment End-points for IO
  • Evidences for Real-World beyond Clinical Trials
Lung Cancer Prognosis in last century (Stage III-IV)

- Stage IV Non-‘something-else-disease’ (NSCLC)
- Chemo Doublets reaching a ‘plateau’
- If fit, 100% of patients received chemotherapy
- ORR ranging from 15 to 30%

- Stage III (Locally Advanced)
- IPD Meta-Analysis [N=1,205]
- 25% Grade 3-4 AEs
- ORR ranging from 15 to 45%

Schiller J et al, NEJM 2002

Auperin E et al, J Clin Oncol 2010
## ONCOGENE Addiction
### ['Stupid’ Disease]

<table>
<thead>
<tr>
<th>Single Dominant Driver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small Mutational Load</td>
</tr>
<tr>
<td>(LOW Tumor Mutation Burden)</td>
</tr>
<tr>
<td>Targeted TKIs COULD work</td>
</tr>
<tr>
<td>Immunotherapy MAY NOT</td>
</tr>
<tr>
<td>Resistance, late, same/other pathway</td>
</tr>
<tr>
<td>Traditional Intermediate End-points MAY work as surrogate</td>
</tr>
</tbody>
</table>

### Multiple Drivers & Passengers

- Large Mutational load (HIGH Tumor Mutation Burden)
- Targeted TKIs COULD work
- Immunotherapy MAY NOT effective
- Resistance common, early
- Traditional Intermediate End-points MAY work as surrogate

---

**Advanced NSCLC in >2016: ‘Operative’ Classification according to Molecular Biology**

**IFCT (France) [N=13,425 pts]**

- EGFR 12%
- KRAS 32%
- BRAF 2%
- HER2 1%
- ALK 5%
- PIK3CA 2%

---

*Adapted from G. Sledge, ASCO 2011*
Advanced NSCLC in >2016: ‘Operative’ Classification according to Molecular Biology

IFCT (France) [N=13,425 pts]

- **Full WT 15%**
- **Unknown 32%**

**NON-ONCOGENE Addiction**
[‘Smart’ Disease]

- **Multiple** Drivers & Passengers
- Large Mutational load (HIGH Tumor Mutation Burden)
- (Un)Targeted TKIs are NOT effective
- Immunotherapy MAY effective
- Resistance common, early
- Traditional Intermediate End-points does NOT correlate with efficacy

Adapted from G. Sledge, ASCO 2011

Statistical Issues And Challenges With Immunotherapies

Barlesi F et al, Lancet 2016
The Evolving View of Lung NSCLC

The Immune System: an ‘Ideal’ anti-cancer Weapon

Why I-O May Work

- Diverse Attack
  - T-Cells, antibodies, NKs, etc.
- Precise Targeting
  - Can distinguish minute chemical alterations
- Recall
  - After effective priming immunity can last for a lifetime

Hurdles

- The wall of cancer’s defence against immune attack:
  - Regulatory immune cells
  - Suppressive cytokines
  - Immune checkpoint

Modified - Topalian S, ASCO 2015
Statistical Issues And Challenges With Immunotherapies

FDA approvals for Immune Checkpoint (IC) Inhibitors

**AGENT** | **TARGET**
--- | ---
Ipilimumab | CTLA-4
Tremelimumab | CTLA-4
Nivolumab* | PD-1
Pembrolizumab* | PD-1
Atezolizumab | PD-L1
Durvalumab | PD-L1
Avelumab | PD-L1

Topalian S, ESMO 2017
Peters S, ESMO 2017
NSCLC: Treatment Choices are Driven by Biomarkers

- PD-L1 TPS 0-49% 59%
- mEGFR 15%
- re-ALK 5%
- re-ROS1 1%
- PD-L1 TPS>50% 20%

Suggested Median Time-to-report by Guidelines: <3-4 wks
‘Real-World’ Median Time from diagnosis to 1-line therapy: 30-34 days*

*Gobbini E et al, Lung Cancer 2017
Statistical Issues And Challenges With Immunotherapies

Head-to-Head Pembrolizumab Better than Chemo (PD-L1 ≥50%)

1934 Screened Patients, 500 (30%) PD-L1 TPS ≥50%, 61.5% Men, 18.5% Squamous, 90.5% C/F Smokers

Statistical Issues and Challenges With Immunotherapies

Head-to-Head Pembrolizumab Better than Chemo (PD-L1 ≥50%)

1934 Screened Patients, 500 (30%) PD-L1 TPS ≥50%, 61.5% Men, 18.5% Squamous, 90.5% C/F Smokers

PFS

<table>
<thead>
<tr>
<th>Events, n</th>
<th>Median, mo</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>73</td>
<td>10.3</td>
<td>0.50 (0.37-0.68)</td>
</tr>
<tr>
<td>Chemo</td>
<td>116</td>
<td>6.0</td>
<td></td>
</tr>
</tbody>
</table>

(Updated) OS

No. of Events | HR (95% CI) | P
---|-------------|----
Pembrolizumab | 73 | 0.63 (0.47 to 0.86) | .002* |
Chemotherapy  | 96 |

No. of Events | HR (95% CI) | P
---|-------------|----
Pembrolizumab | 73 | 0.63 (0.47 to 0.86) | .002* |
Chemotherapy  | 96 |

Censoring rate (55% of pts with event)
Statistical Issues And Challenges With Immunotherapies

Head-to-Head Pembrolizumab Better than Chemo (PD-L1 ≥50%)

(Updated) OS Adjusted* to Cross-Over to IO

*Three statistical methods were applied:
  • Simplified 2-stage
  • Rank-preserving structural failure time (RPSFT)
  • Inverse probability of censoring weighting (IPCW) methods

<table>
<thead>
<tr>
<th></th>
<th>No. of Events</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>73</td>
<td>0.63 (0.47 to 0.86)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>96</td>
<td>0.49 (0.34 to 0.69)</td>
</tr>
<tr>
<td>Crossover-adjusted chemotherapy</td>
<td>96</td>
<td></td>
</tr>
</tbody>
</table>

Median OS (months) (95% CI)

- 30.0 (19.3 to NR)
- 14.2 (9.8 to 19.0)
- 8.7 (7.3 to 11.5)

Reck M et al, J Clin Oncol 2019
Chemotherapy Enhances Anti-Cancer Immune Response: Rational Partner for Immunotherapy

- Increasing T-cell penetrance in the tumor
- Eliminating immunosuppressive cells: T-regulatory cells
- Enhancing effector T-cell function
- Enhancing maturation and activation of dendritic cells toward antigen presentation
- Inducing immunogenic cell death
- Eliminating immunosuppressive cells: T-regs, myeloid-derived suppressor cells, M2 macrophages
- Improving recognition of tumor antigens by T-cell

Statistical Issues And Challenges With Immunotherapies

- Chemotherapy Enhances Anti-Cancer Immune Response
- Rational Partner for Immunotherapy

- Improving recognition of tumor antigens by T-cell
- Increasing T-cell penetrance in the tumor
- Enhancing effector T-cell function
- Eliminating immunosuppressive cells: T-regulatory cells
- Enhancing maturation and activation of dendritic cells toward antigen presentation
- Inducing immunogenic cell death
- Eliminating immunosuppressive cells: T-regs, myeloid-derived suppressor cells, M2 macrophages
Statistical Issues And Challenges With Immunotherapies

Pembro + Chemo Better than Chemo (regardless of PD-L1)

Gandhi L et al, AACR 2018, NEJM 2018

KN 189 [Non-Squamous]

KN 407 [Squamous]

PDL1 [TPS] <1%

PDL1 [TPS] 1-49%

PDL1 [TPS] ≥50%
NSCLC: Treatment Choices are Driven by Biomarkers

Suggested Median Time-to-report by Guidelines: <3-4 wks
‘Real-World’ Median Time from diagnosis to 1-line therapy: 30-34 days*

*Gobbini E et al, Lung Cancer 2017
Censoring rate: 38% of pts with OS event

Censoring rate: 59% of pts with PFS event

Gandhi L et al, ACR 2018, NEJM 2018

Paz-Ares L et al, ASCO 2018, NEJM 2018
Statistical Issues And Challenges With Immunotherapies

Pembro + Chemo Better than Chemo (regardless of Histology & PD-L1)

- **PDL1 [TPS] <1%**
  - KN 189 [Non-Squamous]
  - KN 407 [Squamous]

- **PDL1 [TPS] 1-49%**

- **PDL1 [TPS] ≥50%**

Gandhi L et al, AACR 2018, NEJM 2018

Paz-Ares L et al, ASCO 2018, NEJM 2018
RT induce Immunogenic Tumor Death and PD-L1 expression

• RT DNA and membrane damage activates transcription factors and signalling pathways
• That modulates the immunophenotype and immunogenicity of tumour cells

• RT induced Damage-associated molecular patterns (DAMPs mediate robust immunomodulation and de facto underlie the immunogenicity of cancer cell death
• Chemotherapeutics results in variable level of DAMPs with consequent activation of a therapeutically relevant anticancer immune response

• RT initiates production of IFN/STING
• Activates Pro-Death Signaling in tumor cells
• Induced PD-L1 expression
• Initiates release of tumor antigens
• Generates Chemotactic Signals recruiting Myeloid cell populations
Durvalumab after Concurrent CT-RT improves Prognosis

Statistical Issues And Challenges With Immunotherapies

**PFS**

- Durvalumab vs Placebo
- Stratified HR, 0.52 (95% CI: 0.42, 0.65)
- Two-sided p<0.0001

**OS**

- Median OS
- Durvalumab: 183/476 (38.4) months
  - (95% CI, 34.7 – NR)
- Placebo: 116/237 (48.9) months
  - (22.9 – NR)

**OS HR 0.68**

- (99.73% CI, 0.47–0.99), p=0.00251

**Regulatory Approval is Pending (PD-L1>1%)**

Antonia S et al, WCLC 2018, NEJM 2018
Statistical Issues And Challenges With Immunotherapies

IO: Unexpected Activity in Neoadjuvant Treatment of NSCLC

**NIVOLUMAB**
[26 pts, Stage I-IIIa]

**ATEZOLIZUMAB**
[43 pts, Stage I-IIIa]

Major Pathological Response
(≤10% Viable Tumour Cells)

Forde PM et al, NEJM 2018

Rusch V et al, WCLC 2018
Statistical Issues And Challenges With Immunotherapies

Presentation Outline

- Impact of Immunotherapy (IO) in Medical Oncology
- **Patients’ Selection and Predictive Factors for IO**
- Treatment End-points for IO
- Evidences for Real-World beyond Clinical Trials
Challenges to address in IO Clinical Trials

- Who to treat
  - Patient characteristics
    - Autoimmune disease
    - Viral infection
    - Elderly
    - Brain metastasis
    - BM transplant
    - Limited PS
  - Predictive biomarkers
  - Combinations
    - Chemotherapy
    - Radiation
    - Immuno-oncology agents

- How to treat
  - Dosing
    - Frequency
    - Duration

- How to evaluate endpoints
  - Pseudoprogression
  - Hyperprogression
  - Toxicity evaluation

Baik CS et al, Clin Cancer Res 2017
Efficacy 'Plateaus' of Immunotherapy: Advanced Melanoma

- 20% Of Patients overcome 3 yrs, no (very few) additional deaths in 10 years!
- Are we dealing with CURED patients?

A treatment selection factor is (clearly) required!

Schadendorf D et al, JCO 2015
Statistical Issues And Challenges With Immunotherapies

Biomarkers for Immunotherapy

Current (and Validated) Option for Clinical Practice:
- PD-L1 (IHC) on Tumor Tissue

Unmeet Medical Need:
- Validated Biomarkers in Tissue and Blood

Potential Utility of Liquid Biopsy in Immunotherapy:
- Diagnostic
- Prognostic
- Predictive of Response
- Monitoring
- Mechanisms if Resistance

Current tools:
- Calculation of circulating TMB
- Detection of bPDL1
- Allelic Fraction Variation Dynamic

Nishino A et al, NRCO, 2017
Statistical Issues And Challenges With Immunotherapies

Pts Unselected for PD-L1: Second Line Nivolumab

A treatment selection factor is (clearly) required!

Horn L et al, J Clin Oncol 2017
Statistical Issues And Challenges With Immunotherapies

OAK [Phase III]: Atezolizumab vs. Docetaxel

Quantitative Effect according to PD-L1

A treatment selection factor is (clearly) required!

Rittmeyer A et al, Lancet 2017
A treatment selection factor is (clearly) required!...beyond PD-L1
**Statistical Issues And Challenges With Immunotherapies**

**TMB as Biomarker in Lung Cancer: ‘Evolutionary Road’**

**TMB as a Biomarker for I-O Therapies: LUNG CANCER**

**First report of TMB effect on response to I-O in melanoma**

**Rooney:** Genetic properties of tumor associated with cytolytic activity

**IMvigor210:** TMB associated with response in 2L+ bladder

**FIR/BIRCH/POPLAR:** TMB associated with efficacy in 1L and 2L+ NSCLC

**KEYNOTE-012/KEYNOTE-028:** TMB associated with best overall response in 1L+ solid tumors

**CheckMate 026:** High TMB associated with survival in 2L+ SCLC

**CheckMate 032:** High TMB associated with survival in 2L+ SCLC

**CheckMate 038:** TMB associated with survival in IPI-naïve patients with 2L+ melanoma

**CheckMate 027:** High TMB associated with survival in 2L+ SCLC

**CheckMate 227:** High TMB associated with survival in NIVO+IPI patients in 1L NSCLC

**OAK/POPLAR:** TMB analysis in 2L+ NSCLC

**BFAST and B-FIRST:** TMB analysis in 1L NSCLC

**Zehir:** Prospective sequencing of over 10,000 tumors using MSK-IMPACT assay

**FDA approval/authorization of FoundationOne CDx and MSK-IMPACT**

**Chan T, ASCO 2018**
Statistical Issues And Challenges With Immunotherapies

Neoantigen Intratumor Heterogeneity (ITH) & Clonal Neoantigens

Tumor Mutational Burden (TMB) & Antitumor Immunity

Sensitivity to PD-1 blockade enhanced in tumors enriched for clonal neoantigens.

Wolchok JD, Chan T, Nature 2014

McGranahan et al, Science 2016
Statistical Issues And Challenges With Immunotherapies

TMB according to Oncogene-Addiction

Oncogene-Addicted

Non- Oncogene-Addicted

Lower % of TMB-high
Worst Outcome with I-O

Higher % of TMB-high
Better Outcome with I-O

Spigel D et al, ASCO 2016
Correlation between Tumor Mutational Burden and Objective Response Rate with Anti–PD-1 or Anti–PDL1 Therapy in 27 Tumor Types.
**Tumor Mutational Burden (TMB) According to Disease**

(Non-oncogene-addicted) NSCLC has High Somatic mutation frequencies (high TMB)

Somatic mutation frequencies observed in exomes from 3,083 tumour/normal pairs.

*Lawrence M et al, Nature 2013*

Effect of TMB on OS after ICI treatment [1,662 patients]

Cox regression HR for OS [Solid black circles represent HRs with p<0.05]

*Samstein et al, Nature Gen 2019*
TMB IS predictor for PFS benefit of I-O vs. Chemo

CM 026: NIVO vs. Chemo
TMB by WGS [21,522 genes]

CM 227: NIVO + IPI vs. Chemo
TMB by NGS [324 genes]

Statistical Issues And Challenges With Immunotherapies

Carbone D et al, NEJM 2017

Helmann J et al, NEJM 2018
TMB IS NOT predictor for OS benefit of I-O vs. Chemo

CM 026: NIVO vs. Chemo
TMB by WGS [21,522 genes]

<table>
<thead>
<tr>
<th>TMB</th>
<th>HR (95% CIs)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 10 mut/Mb</td>
<td>0.77 (0.56, 1.06)</td>
<td>0.108</td>
</tr>
<tr>
<td>&lt; 10 mut/Mb</td>
<td>0.78 (0.61, 1.00)</td>
<td>0.049</td>
</tr>
</tbody>
</table>

CM 227: NIVO + IPI vs. Chemo
TMB by NGS [324 genes]

<table>
<thead>
<tr>
<th>TMB</th>
<th>HR (95% CIs)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 10 mut/Mb</td>
<td>0.77 (0.63, 0.94)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

NB: data derived from press release on BMS website and cumulated according to a Random Effect Model [Heterogeneity p=0.95]
Statistical Issues And Challenges With Immunotherapies

bTMB (Blood/Tissue) as a predictor of benefit of Atezolizumab

- Training Set: POPLAR, Validation Set: OAK

Gandara D et al, Nature Med 2018
• The higher the value, the higher the benefit........which cut-off?

Gandara D et al, Nature Med 2018
TMB is independent from PD-L1 (over)expression

High TMB does not overlap with PD-L1 overexpression

Categorical PD-L1 (0-3) IHC Staining

Continuous PD-L1 (%) IHC Staining

Gandara D et al, Nature Med 2018

Helmann J et al, NEJM 2018
Feasibility of TMB (tissue/blood) & Positivity Rate

**POPLAR** | **OAK** | **B-F1RST**
---|---|---
Samples | 273 | 850 | 152
Evaluable | 211 (77.2%) | 642 (75.5%) | 119 (78%)
Positivity (bTMB) | 30% | 27% | 18%

CM 227

N=1739

1004 (57.7%)

44% high TMB

299 (17%)
B-F1RST: Prospective Evaluation of bTMB as Biomarker

Statistical Issues And Challenges With Immunotherapies

Overall Response Rate (%)

- ITT (N = 152)
  - PR (n = 8)
  - SD (n = 7)
  - PD (n = 12)

- BEP (n = 119)
  - PR
  - CR

- High (n = 49)
  - PR
  - CR

- Low (n = 70)
  - PR
  - CR

- High (n = 28)
  - PR
  - CR

- Low (n = 91)
  - PR
  - CR

- High (n = 19)
  - PR
  - CR

- Low (n = 100)
  - PR
  - CR

bTMB Subgroups

- ≥ 10 Cutoff
  - P = 0.0595

- ≥ 16 Cutoff
  - P = 0.0002

- ≥ 20 Cutoff
  - P < 0.0001

Kim ES et al, ESMO 2018
Statistical Issues And Challenges With Immunotherapies

Neoadjuvant Nivolumab in Resectable Stage I-IIIA

Association between Mutational Burden and Pathological Response to PD-1 Blockade

No. Of Sequence Alterations in Pretreatment Tumor

Correlation between No. Of Sequence Alterations and Percentage Of Residual Tumor

Forde PM et al, NEJM 2018
Why we need that? The Cost of Cancer is Soaring

- The average cost of cancer drugs today is 4 times the median household income in US
  - Getting a cancer immunotherapy treatment costs more than a house in many cities in the US, more than putting a few kids through private college.
  - The average cost of cancer drugs has increased from $50,000 per patient in the mid-1990s to $250,000 today.
  - That’s four times the median US household annual income.

*Source: Peter Back, MSKCC, NYC*
Statistical Issues And Challenges With Immunotherapies

Cancer IO Market Analysis By Product

China cancer immunotherapy market by cancer type 2014 - 2025 (USD Billion)

Source: https://www.grandviewresearch.com/industry-analysis/cancer-immunotherapy-market
• Impact of Immunotherapy (IO) in Medical Oncology
• Patients’ Selection and Predictive Factors for IO
• **Treatment End-points for IO**
• Evidences for Real-World beyond Clinical Trials
Challenges to address in IO Clinical Trials

Who to treat
- Patient characteristics
  - Autoimmune disease
  - Viral infection
  - Elderly
  - Brain metastasis
  - BM transplant
  - Limited PS

How to treat
- Predictive biomarkers
- Dosing
  - Frequency
  - Duration
- Combinations
  - Chemotherapy
  - Radiation
  - Immuno-oncology agents

How to evaluate endpoints
- Pseudoprogression
- Hyperprogression
- Toxicity evaluation

Statistical Issues And Challenges With Immunotherapies

Baik CS et al, Clin Cancer Res 2017
Pretreated NSCLC: Immunotherapy is the new Benchmark

Individual Level Estimation (>3,200 pts), FDA-Driven Analysis

- Moderate Association between OS at 12 and 9 months and OS HR
- No correlation between OS and intermediate end-points (PFS and ORR)
- Although 12months-OS has the strongest association it is likely to be not optimal for future trials, which will have:
  - Immunotherapy as control arm
  - Biomarker-enrichment strategies
  - Enrolled patients with longer survival

**Benchmark of Control Arm for Future RCTs:**
- Median OS: 12 months
- 1yr OS: 50%
- PFS and ORR not primary
IO: PFS does not correlate with OS

- No significant correlation between OS and PFS (medians and gains in medians)
- Greater Effects of treatment in OS than PFS.
- Traditional Response Evaluation Criteria in Solid Tumors (ORR and PFS) cannot capture the benefit of PD-1 inhibitors in patients with solid tumors.
- OS should remain the gold standard.

Gyawali B et al, JAMA Network 2019
Statistical Issues And Challenges With Immunotherapies

IO: Which (Best) End-point for Phase II Studies?

Observed vs Predicted 12-Month Overall Survival (OS) Rate

12-mo OS rate predicted by 6-mo PFS rate

12-mo OS rate predicted by ORR

Gyawali B et al, JAMA Network 2019
Expected Survival Modeling according to Drugs’ Features

Typical survival curves (Kaplan-Meier model) observed in clinical trials

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportional Hazard Model</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Delayed Effect</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>Long Term Survival</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
</tr>
</tbody>
</table>

Ferrara R et al, J Thorac Disease 2018
Expected Survival Modeling according to Drugs’ Features

Typical survival curves (Kaplan-Meier model) observed in clinical trials

(x) difference in median survival;
(y) 12-month difference in survival rate.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td></td>
</tr>
</tbody>
</table>
Statistical Issues And Challenges With Immunotherapies

IO: ‘Intercepting’ Lower HR overtime

HR overall

early HR

delayed HR

early HR (HR before separation of the curves) = ~1

delayed HR (HR after the separation of the curves) ≠ 1

Median OS

Cure fraction

Ferrara R et al, J Thorac Disease 2018
Statistical Issues And Challenges With Immunotherapies

Pseudoproggression, Hyperprogression, and Deconvolution of the survival curves IOs

Methodology for the Development of Innovative Cancer Therapies (MDICT) Task Force

Smoragiewicz M et al, Ann Oncol 2018
Statistical Issues And Challenges With Immunotherapies

Crossing survival curves in clinical trials

Keynote 042

Chiampiat S et al, Nat Rev Clin Oncol 2018
Lopes G et al, ASCO 2018
Statistical Issues And Challenges With Immunotherapies

Crossing survival curves in clinical trials

Evaluation using RECIST v1.1

Evaluation Integrating Pre-treatment Tumour Kinetics

Chiampiat S et al, Nat Rev Clin Oncol 2018

[Graph showing statistical issues and challenges with immunotherapies, focusing on crossing survival curves in clinical trials, with evaluations using RECIST v1.1 and evaluation integrating pre-treatment tumour kinetics.]
Biological Hypotheses for IO-related Hyperprogressive disease

Chiampiat S et al, Nat Rev Clin Oncol 2018
### Statistical Issues And Challenges With Immunotherapies

#### Questions & Recommendation of the MDICT task force

<table>
<thead>
<tr>
<th>Question</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>What are the relevant data required to justify a combination immunotherapeyJ trial?</td>
<td>A robust hypothesis, with evidence of efficacy and pharmacodynamic effects in pre-clinical studies Evidence of single agent activity, or compelling pre-clinical data</td>
</tr>
</tbody>
</table>
| What are the optimal end points and designs for combination immunotherapyclinical trials? | Evaluation of pharmacodynamic biomarkers is critical in early phase combination trials and should be incorporated into trial objectives and go/no-go decisions  
Trial designs:  
- Master protocols (basket, umbrella, and platform designs) can significantly enhance efficiencies in evaluating multiple IO combination  
- Sequencing designs based on a pre-emptive strategy could be considered  
Efficacy end points should remain response based, with definitions for response, pseudoprogression, and hyperprogression. iRECIST should be used as secondary or exploratory end point  
Blood based biomarkers should be prospectively evaluated |
| Hyperprogression: a real entity?                                         | Protocols should capture at least one additional tumour measurement before baseline to determine tumour growth kinetics, and consider an early CT scan (at 4 weeks for example) |
| How to optimize efficiency and minimize redundancy?                      | Well-conceived master protocols are strongly encouraged  
Not re-testing a failed combination of in-class agents unless there is a compelling rationale  
Proposals of IO combinations should also have a landscape analysis to prevent duplication |
To establish the concept of minimum *clinically meaningful outcome (mCMO)* of treatment in advanced solid tumors, to establish its threshold and evaluate how many superiority trials of new antineoplastic agents pass this threshold.
Clinical Meaningful Benefit as a Target!

NEJM (‘90s) The ‘Two-Fingers’ Rule: Clinically Data should be considered Meaningful if ‘at least’ two fingers separates curves!

SOLO-1 [Maintenance, BRCA1/2m OC]

ALTA-1L [First-Line, ALK+ NSCLC]

The Biomarker-Based Methodology is leading to the Re-discovery of Clinically Relevant Benefits

Camidge R et al, NEJM 2018

Moore K et al, NEJM 2018
ESMO & ASCO are aiming to add **Quantity** to **Quality**

**MCBS: Magnitude of Clinical Benefit Score**

<table>
<thead>
<tr>
<th>Table 2. Maximal preliminary scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatments with curative intent (form 1)</td>
</tr>
<tr>
<td>&gt;5% improvement of survival at ≥3-year follow-up</td>
</tr>
<tr>
<td>Improvements in DFS alone HR &lt;0.60 (primary end point) in studies without mature survival data</td>
</tr>
<tr>
<td>Treatments with non-curative intent (form 2)</td>
</tr>
<tr>
<td>Primary outcome OS (form 2a)</td>
</tr>
<tr>
<td>Control ≤12 months</td>
</tr>
<tr>
<td>HR ≤0.65 AND gain ≥3 months OR</td>
</tr>
<tr>
<td>Increase in 2-year survival alone ≥10%</td>
</tr>
<tr>
<td>Control &gt;12 months</td>
</tr>
<tr>
<td>HR ≤0.70 AND gain ≥5 months OR</td>
</tr>
<tr>
<td>Increase in 3-year survival alone ≥10%</td>
</tr>
<tr>
<td>Primary outcome PFS (form 2b)</td>
</tr>
<tr>
<td>Control ≤6 months</td>
</tr>
<tr>
<td>HR ≤0.65 AND gain ≥1.5 months</td>
</tr>
<tr>
<td>Control &gt;6 months</td>
</tr>
<tr>
<td>HR ≤0.65 AND gain ≥3 months</td>
</tr>
</tbody>
</table>

**NHB: Net Health Benefit (NHB)**

![Diagram showing NHB calculation](image_url)

**Schnipper LE, et al, JCO 2016**
Statistical Issues And Challenges With Immunotherapies

Presentation Outline

• Impact of Immunotherapy (IO) in Medical Oncology
• Patients’ Selection and Predictive Factors for IO
• Treatment End-points for IO

• Evidences for Real-World beyond Clinical Trials
What do we assess in clinical trials?

**Activity:**
- ability of the treatment to induce modifications of the disease thanks to which it is assumed that the patient may have a benefit [Phase II]

**Efficacy:**
- ability of the treatment to induce a clinical benefit in patients who are administered *in an experimental context* [Phase III]

**Effectiveness:**
- ability of a treatment to be effective in a *non-experimental, concrete and coincident with the clinical practice* [are Phase IV, ‘Real World’ Data]
Statistical Issues And Challenges With Immunotherapies

Targeted Therapy Performance in the ‘Real World’

**Trials’ Ineligible Pts vs. Eligible**
(all receiving targeted agents)

Median OS 12.5 vs. 28.4 months \( p<0.0001 \)

**Addition of Bevacizumab to FOLFOX, ‘Registry’ Context**

\[ P = .62 \]

---

Deng DY et al, Ann Oncol 2014

Meyerhardt T et al, JCO 2012
Take Home message(s)

[Nivolumab]: Overall Survival [EAP vs. CM 017]

Real World Data ITA-EAP [Nivolumab]

<table>
<thead>
<tr>
<th>Aged &lt;65 years (n = 126)</th>
<th>Aged 65–75 years (n = 175)</th>
<th>Aged ≥75 years (n = 70)</th>
<th>Overall population (N = 371)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo (95% CI)</td>
<td>8.0 (6.2, 11.0)</td>
<td>8.0 (6.6, 10.4)</td>
<td>7.5 (6.2, 8.6)</td>
</tr>
</tbody>
</table>

1-yr OS = 42%
1-yr OS = 39%
1-yr OS = 38%
1-yr OS = 35%

Grossi F et al, Eur J Cancer 2018
Statistical Issues And Challenges With Immunotherapies

RWD: NON-Sq. ITA & FRA-EAP [Nivolumab]

<table>
<thead>
<tr>
<th></th>
<th>KRASm (n = 206)</th>
<th>EGFRm (n = 102)</th>
<th>Never smokers (N = 305)</th>
<th>Never smokers EGFRm (N = 51)</th>
<th>All patients (N = 1588)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (%)</td>
<td>20</td>
<td>9</td>
<td>9</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>DCR (%)</td>
<td>47</td>
<td>30</td>
<td>42</td>
<td>22</td>
<td>44</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>11.2 (9.3, 13.1)</td>
<td>8.1 (2.1, 14.1)</td>
<td>10.4 (8.6, 12.2)</td>
<td>5.6 (3.3, 7.9)</td>
<td>11.3 (10.2, 12.4)</td>
</tr>
</tbody>
</table>

Ardizzoni A et al, WCLC 2017; Grossi F et al, WCLC 2017; Garassino M et al, WCLC 2017

Girard N et al, WCLC 2017
Statistical Issues And Challenges With Immunotherapies

FDA Analysis: IO as a new Standard for Elderly NSCLC Pts

Marur S et al, Semin Oncol 2018
CONCLUSIONS - 1

- Immunotherapy has significantly revolutioned treatment opportunity (particularly) for (the majority) of (non-oncogene addicted) lung cancer patients
  - Head-to-head comparisons have ‘displaced’ 2\textsuperscript{nd} line chemo
  - Head-to-head comparisons have ‘displaced’ 1\textsuperscript{st} line chemo (in pts with PD-L1>50%)
  - Almost all pts (regardless of PD-L1) will receive the combination of chemotherapy and Immunotherapy

- Nevertheless, long-term survival is expected for few patients, thus the maximization of the benefit is pursued by investigating new potential biomarkers for clinical practice
  - Tumor Mutational Burden has conflicting results, prospective predictive validation is ongoing
CONCLUSIONS - 2

• Traditional end-points are becoming useless (ex. ORR for Phase IIs, or PFS for Phase IIIs), and new models (for potential surrogates and intermediate end-points) are currently under investigation for improving the best way to intercept the benefit of IO

• Deriving the benefit of IO in clinical trials to clinical practice in the ‘Real World’ represents a challenge to date, although expanded-access data with IO do not significantly appear to differ from RCTs data

• In order to rapidly continue to impact upon patients’ prognosis:
  – Innovative Trials for Precision Medicine are needed
  – Partnership between Pharma/Acamedia/Government is CRUCIAL!