ASCO 2014: Induction and Adjuvant Treatment in Locally Advanced Head and Neck Cancer-New Insights, Old Challenges

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September 6, 2014
Treatment Goals

- **Induction chemotherapy (ICT)**
  - Initial tumor shrinkage may allow for improved locoregional control, decrease radiation dose, reduce radiation field
  - Reduce risk of relapse leading to improved survival
  - Select for biologically favorable tumor

- **Adjuvant chemotherapy**
  - Reduce risk of tumor relapse (locoregionally or distantly) leading to improved survival
Challenges with Induction or Adjuvant Treatment

- **Induction**
  - Delay definitely local therapy
  - Up to 10-15% patients may not receive local treatment
  - May result in accelerated tumor repopulation, reducing efficacy of radiotherapy –RT duration > 8 w was an independent prognostic factor for survival in Tax 324 (Sher IJROBP 2011)

- **Adjuvant**
  - Poor compliance

- **Both**
  - Prolonged course of treatment
  - Increased cost
  - May lead to more acute & late toxicity
ICT vs. CRT

PARADIGM (N=145)  DeCIDE (N=285)

- Are these studies underpowered to detect an advantage for ICT?
- Which patient population would benefit the most from ICT?
PHASE III PART: 2 X 2 FACTORIAL DESIGN

- Oral cavity, hypo, Oropharynx, SCC
- ECOG PS 0-1
- Stage III-IVM0
- Stratification: T stage, N stage, Primary tumor site
- Q 3 weeks x 3 cycles
- Randomize
- PF

Primary endpoints:
1) 3y OS Induction vs no induction: A1 + A2 vs B1 + B2
2) G3-4 in field toxicity: A1 + B1 vs A2 + B2
Survival Results

**Progression-Free Survival**

- Median PFS mo: 29.7 vs 18.5
- HR: 0.73; 95% CI: 0.57-0.94, p=0.0155

**Overall Survival**

- Median OS mo: 53.7 vs 30.3
- HR: 0.72; 95% CI 0.55-0.96; p=0.025

Presented by: MG Ghi

Presented By Quynh-Thu Le at 2014 ASCO Annual Meeting
Oropharynx cancer: PFS and OS (unplanned)

Progression-Free Survival

Overall Survival

*HPV status analysis in progress

Presented by: MG Ghi
Non OPC: PFS and OS (unplanned)

Progression-Free Survival  Overall Survival

Median OS mo: 23.5 vs 11.7
HR: 0.66; 95% CI 0.45-0.96

Median OS mo: 33.6 vs 18.7
HR: 0.65; 95% CI 0.43-0.97
## OS Subgroup Analysis (Unplanned) Cox Model

<table>
<thead>
<tr>
<th>Study Arms</th>
<th>patients</th>
<th>events</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPF → CRT</td>
<td>129</td>
<td>69</td>
<td>0.80</td>
<td>0.56 – 1.15</td>
</tr>
<tr>
<td>CRT</td>
<td>129</td>
<td>62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPF → cet/RT</td>
<td>79</td>
<td>27</td>
<td>0.57</td>
<td>0.34 – 0.93</td>
</tr>
<tr>
<td>cet/RT</td>
<td>78</td>
<td>43</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 415 patients
- 4 arms
- 6 possible comparison
- unplanned
- hypothesis generator
- random effect?

Presented by: MG Ghi
Questions Pertained to the Italian Study

- Is the benefit for ICT seen primarily in HPV(-) tumor? Need analysis
- Is the benefit for ICT the same for each concomitant regimen? May be not
- Why are the PFS & OS results of this study lower than other published studies? Is it HPV? Is it smoking? Is it something else?
What can we conclude about ICT?

- Its benefit in non-OPC need to be validated in a larger study using one single concomitant regimen.
- RT quality assurance needs to be addressed, especially in the era of high complexity IMRT.
- Additional analysis on pattern of failure is important to determine the contribution ICT.
- This trial has revived interest in ICT but has not definitely proven its role in HNC.
Rationale for using Induction Chemotherapy to Decrease RT Dose

- Induction chemotherapy with Paclitaxel & Carboplatin in E2399 resulted in high RR (82%) & 2y OS (95%) in HPV+ OPC
- Cetuximab added to a platinum/taxane regimen has been associated with higher CR rate
- Induction chemotherapy allowed for successful RT dose reduction in HD & NHL
- Can triple drug induction chemotherapy be used to decrease RT dose in HPV+ OPC

Presented by Quynh-Thu Le at 2014 ASCO Annual Meeting
ECOG 1308: Phase II Schema

**Eligibility**
- OPSCC
- resectable
- HPV ISH + and/or p16+
- Stage III, IVA

**Induction Chemotherapy**
- Cisplatin 75mg/m² d1
- Paclitaxel 90mg/m² d1, 8, 15
- Cetuximab 250mg/m² d1, 8, 15
- Q 21 days for 3 cycles

**Concurrent Chemoradiation**
- **CLINICAL CR**
  - Low dose IMRT 54Gy/27fx* + Cetuximab qWeek
- **CLINICAL PR/SD**
  - Full dose IMRT 69.3Gy/33fx* + Cetuximab qWeek

**Evaluation**

**IMRT margins for primary:** 1.0 to 1.5cm around gross dz
**Nodal margin:** 1cm margin minimum
### Endpoint: 2yr PFS and OS

<table>
<thead>
<tr>
<th>Cohort (n)</th>
<th>2 year PFS (90% CI)</th>
<th>2 year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>All low dose pts (62)</td>
<td>0.80 (0.70, 0.88)</td>
<td>0.93 (0.85, 0.97)</td>
</tr>
<tr>
<td>T4a (7)</td>
<td>0.54 (0.19, 0.79)</td>
<td>0.86 (0.45, 0.97)</td>
</tr>
<tr>
<td>Non-T4a (55)</td>
<td>0.84 (0.73, 0.91)</td>
<td>0.94 (0.86, 0.98)</td>
</tr>
<tr>
<td>N2c (19)</td>
<td>0.77 (0.56, 0.89)</td>
<td>0.95 (0.76, 0.99)</td>
</tr>
<tr>
<td>Non-N2c (43)</td>
<td>0.82 (0.69, 0.90)</td>
<td>0.93 (0.82, 0.97)</td>
</tr>
<tr>
<td>Smoker &gt;10pk-yrs (22)</td>
<td>0.57 (0.35, 0.73)</td>
<td>0.86 (0.67, 0.94)</td>
</tr>
<tr>
<td>Smoker ≤10pk-yrs (40)</td>
<td>0.92 (0.81, 0.97)</td>
<td>0.97 (0.87, 0.995)</td>
</tr>
<tr>
<td>Smoker ≤10k-yrs, ≤T4, N2c (27)</td>
<td>0.96 (0.82, 0.99)</td>
<td>0.96 (0.82, 0.99)</td>
</tr>
<tr>
<td>All high-dose pts (15)*</td>
<td>0.65 (0.41, 0.82)</td>
<td>0.87 (0.63, 0.96)</td>
</tr>
</tbody>
</table>

* 3 high-dose pts did not go on to receive RT
Good risk HPV+ Tumors may do Well with RT Alone

Table 4. Pattern of Failure in HPV-Positive Low-Risk Category

<table>
<thead>
<tr>
<th>Cohort</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>N0-N2a</th>
<th>N2b</th>
<th>N2c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distant control rate at 3 years, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT alone</td>
<td>95</td>
<td>92</td>
<td>85</td>
<td>97</td>
<td>89</td>
<td>73</td>
</tr>
<tr>
<td>95% CI</td>
<td>82 to 99</td>
<td>81 to 96</td>
<td>68 to 93</td>
<td>89 to 99</td>
<td>75 to 95</td>
<td>47 to 88</td>
</tr>
<tr>
<td>CRT</td>
<td>88</td>
<td>97</td>
<td>94</td>
<td>88</td>
<td>98</td>
<td>92</td>
</tr>
<tr>
<td>95% CI</td>
<td>68 to 96</td>
<td>87 to 99</td>
<td>79 to 98</td>
<td>66 to 96</td>
<td>90 to 99</td>
<td>77 to 97</td>
</tr>
<tr>
<td><em>P</em></td>
<td>.29</td>
<td>.09</td>
<td>.28</td>
<td>.07</td>
<td>.03</td>
<td>.02</td>
</tr>
</tbody>
</table>


Presented By Quynh-Thu Le at 2014 ASCO Annual Meeting
Questions to address in good risk HPV+ patients

• What is the best strategy to decrease treatment while minimizing late toxicity in these patients (induction chemo -> reduced RT dose, surgery -> reduced RT dose, RT alone, low dose CRT)?

• What is the best way to measure long-term function and late toxicity in these patients?

• What is the best way to address the cost of treatment and toxicity in these patients?
EGFR Tumor Expression & Outcomes

Overall Survival

Locoregional Relapse

Ang et al., Cancer Research 62: 7350, 2002
Study Design

Randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of lapatinib combined with chemoradiotherapy, before administration as a maintenance monotherapy for 1 year, in patients with resected SCCHN

**SURGERY/SCREENING**
- Eligibility criteria:
  - SCCHN
  - Stage II/III/IVa
  - High-risk (R1, R2 and/or ECS)

**RANDOMIZATION**
- Stratification:
  - Tumour site
  - Nodal status
  - EGFR expression
  - Geographical region

**TREATMENT**
- Lapatinib (1500 mg/d)
  - 3–7 days
- Cisplatin/RT* + Lapatinib (1500 mg/d)
  - 6–7 weeks
- Lapatinib (1500 mg/d)
  - 12 months

**MAINTENANCE/FOLLOW-UP**
- Placebo
- Cisplatin/RT* + Placebo
- Placebo

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* Cisplatin 100 mg/m² on Days 1, 22 and 43; RT 2Gy/day, 5 days/week
† Patients were followed up every 4 months for 2 years and then every 6 months until withdrawal from the study, or death, whichever occurred first.

ECS, extracapsular spread; F/U, follow-up; RT, radiotherapy; RTQA, Radiotherapy Quality Assurance; SCCHN, squamous cell carcinoma of the head and neck

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Primary endpoint: IRC-assessed DFS (ITT population)

HR = 1.10
(95% CI 0.85, 1.43; p=0.4502)

- Median DFS (95% CI): Placebo arm, NR (54.6, NR); lapatinib arm, 53.6 (45.8, NR)
- Investigator-assessed DFS: HR = 1.03 (95% CI 0.81, 1.30; p=0.8208)

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Discussion

- Results consistent with prior studies showing EGFR TKI has less activity than cetuximab in unselected HNSCC
- Will Lapatinib be more active when combined with CRT in definitive setting?
- Will adjuvant TKI targeting the HER pathway be more active in selected high risk population?
ASCO 2014: Another option for refractory thyroid cancer

Fadlo Raja Khuri, MD
Professor and Chair
Department of Hematology & Medical Oncology, Deputy Director
Winship Cancer Institute of Emory University
Roberto C. Goizueta Chair in Cancer Research

September 6, 2014
A phase 3, multicenter, randomized, double-blind, placebo-controlled trial of lenvatinib (E7080) in patients with $^{131}$I-refractory differentiated thyroid cancer (SELECT)

Martin Schlumberger, 1 Makoto Tahara, 2 Lori J. Wirth, 3 Bruce Robinson, 4 Marcia S. Brose, 5 Rossella Elisei, 6 Corina E. Dutcus, 7 Begoña de las Heras, 8 Junming Zhu, 7 Mouhammed Amir Habra, 9 Kate Newbold, 10 Manisha H. Shah, 11 Ana O. Hoff, 12 Andrew G. Gianoukakis, 13 Naomi Kiyota, 14 Matthew H. Taylor, 15 Sung-Bae Kim, 16 Monika K. Krzyzanowska, 17 Steven I. Sherman 9

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Study 303: Study Schema

Global, randomized, double-blind, phase 3 trial

Patients with DTC (N = 392)
- IRR evidence of progression within previous 13 months
- $^{131}$I-refractory disease
- Measurable disease
- Up to 1 prior VEGF or VEGFR-targeted therapy

Randomization 2:1

Stratification
- Geographic region (Europe, N. America, Other)
- Prior VEGF/VEGFR-targeted therapy (0,1)
- Age ($\leq 65$ years, $> 65$ years)

Lenvatinib (n = 261)
24 mg daily PO

Treatment until disease progression confirmed by IRR (RECIST v1.1)

Placebo (n = 131)
24 mg daily PO

Primary endpoint
- PFS

Secondary endpoints
- ORR
- OS
- Safety

Lenvatinib (Optional, open-label)

DTC, differentiated thyroid cancer; $^{131}$I, radiodine; IRR, independent radiologic review; ORR, objective response rate; OS, overall survival; PO, by mouth; RECIST, response evaluation criteria in solid tumors.
Primary Endpoint: Kaplan-Meier Estimate of PFS

Median PFS, months (95% CI)
- Lenvatinib: 18.3 (15.1–NR)
- Placebo: 3.6 (2.2–3.7)

HR (99% CI): 0.21 (0.14–0.31)
Log-rank test: P < 0.0001

Progression events, 41%
Progression events, 86%

Number of subjects at risk:
- Lenvatinib: 261 225 198 176 159 148 136 92 66 44 24 11 3 0
- Placebo: 131 71 43 29 19 13 11 5 4 2 2 2 0 0

CI, confidence interval; HR, hazard ratio; NR, not reached.
PFS by Previous VEGF-Targeted Therapy

No Previous VEGF-Targeted Therapy (n = 299)

- Lenvatinib: 18.7 (16.4–NR)
- Placebo: 3.5 (2.1–5.3)
- HR (95% CI): 0.20 (0.14–0.27)
- Log-rank Test: P < 0.0001

Previous VEGF-Targeted Therapy: 1 line (n = 93)

- Lenvatinib: 15.1 (8.8–NR)
- Placebo: 3.6 (1.9–3.7)
- HR (95% CI): 0.22 (0.12–0.41)
- Log-rank Test: P < 0.0001

Presented by: Martin Schlumberger, MD

Presented By Martin Schlumberger at 2014 ASCO Annual Meeting
Best Tumor Response

Treatment group: Lenvatinib

Median tumor shrinkage for responders (range): -52% (-100%, -30%)

Best Overall Response (n = 245)
- CR (n = 4)
- PR (n = 165)
- SD (n = 60)
- PD (n = 16)

Treatment group: Placebo

Median tumor shrinkage for all patients (range): +2% (-53%, +54%)

Best Overall Response (n = 126)
- PR (n = 2)
- SD (n = 71)
- PD (n = 61)
- NE (n = 2)

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

Presented by: Martin Schlumberger, MD

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Overall Survival, ITT population

Median OS, months (95% CI)
- Lenvatinib: NR (22.0–NR)
- Placebo: NR (20.3–NR)

HR (95% CI): 0.73 (0.50–1.07)
Log-rank test: P = 0.1032

No significant difference was observed in the RPSFT-adjusted OS (secondary endpoint: P = 0.051), which was used to correct for a potential cross-over effect in the placebo arm.

Number of subjects at risk:
- Lenvatinib: 261 248 239 230 219 211 203 169 114 78 55 22 10 3 0
- Placebo: 131 126 126 118 108 103 96 78 53 39 23 8 2 1 0

ITT, intent-to-treat; RPSFT, rank-preserving structural failure time.

Presented by: Martin Schlumberger, MD

Presented By Martin Schlumberger at 2014 ASCO Annual Meeting
# TEAEs of Special Interest

Presented By Martin Schlumberger at 2014 ASCO Annual Meeting

<table>
<thead>
<tr>
<th>Adverse Event, %</th>
<th>Lenvatinib (n = 261)</th>
<th>Placebo (n = 131)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade ≥ 3</td>
</tr>
<tr>
<td>Hypertension *</td>
<td>73</td>
<td>44</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>32</td>
<td>10</td>
</tr>
<tr>
<td>Venous TEs</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Arterial TEs</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Renal failure b</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>PRES</td>
<td>0.4</td>
<td>0</td>
</tr>
</tbody>
</table>

* Includes ‘hypertension’ and ‘blood pressure increased’.

b Includes ‘renal failure’ and ‘renal failure acute’.

PRES, posterior reversible encephalopathy syndrome; TE, thromboembolic event; TEAEs, treatment-emergent adverse events.
Conclusions

- In patients with RR-DTC, lenvatinib significantly prolonged median PFS by 14.7 months compared with placebo:
  - Lenvatinib median PFS: 18.3 months (95% CI 15.1–NR)
  - Placebo median PFS: 3.6 months (95% CI 2.2–3.7)
    • HR 0.21 (99% CI, 0.14–0.31)

- Response rates for lenvatinib and placebo, respectively, were:
  - ORR: 65% vs 2% (with CR: 2% vs 0%)
  - The median time to objective response for lenvatinib was 2.0 months (95% CI, 1.9–3.5 months)
  - The median duration of response for lenvatinib has not been reached
    • 75% of responders had an objective response >9.4 months

- Toxicities of therapy, although considerable, were managed with dose modification and medication