(Neo)-Adjuvant Chemotherapy in triple negative early breast cancer

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Division of Experimental Therapeutics
• Neoadjuvant treatment in triple negative early breast cancer

• Picking optimal adjuvant chemotherapy for TN early breast cancer
(Neo)Adjuvant therapy in TN EBC

- Who needs more treatment?
- Addition of carboplatin
- Nab-paclitaxel ready for prime time?
- Tumor infiltrating lymphocytes
- Post-neoadjuvant setting
# Treatment-oriented classification of sub-groups of breast cancer

<table>
<thead>
<tr>
<th>Clinical grouping</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hormone receptor-positive &amp; HER2— a spectrum</strong></td>
<td>ER and/or PgR positive $\geq 1%$¹</td>
</tr>
<tr>
<td>• <strong>high receptor, low proliferation, low burden (“luminal A-like”)</strong></td>
<td>Multi-parameter molecular marker “good” if available. High ER/PgR and clearly low Ki-67. Low or absent nodal involvement (N 0-3), smaller T size (T1 T2)</td>
</tr>
<tr>
<td>• <strong>intermediate</strong></td>
<td>Among multi-parameter molecular markers, only the 21 gene RS reports an intermediate value. Uncertainty persists about degree of risk and responsiveness to endocrine and cytotoxic therapies.</td>
</tr>
<tr>
<td>• <strong>low receptor, high proliferation, high burden (“luminal B-like”)</strong></td>
<td>Multi-parameter molecular marker “bad” if available. Lower ER/PgR with clearly high Ki-67. More extensive nodal involvement, histological grade 3, extensive lymphovascular invasion, larger T size (T3)</td>
</tr>
</tbody>
</table>
ER values between 1% and 9% were considered equivocal. Thus endocrine therapy alone cannot be relied upon for patients with these values.
## News and Progress Neoadjuvant

<table>
<thead>
<tr>
<th>Field or Treatment</th>
<th>Status of research/implications for patient care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoadjuvant systemic therapies</td>
<td>An improved pCR rate was observed with carboplatin for patients with triple negative disease. Such improvement was not observed for HER2-positive disease. An improved pCR was also observed in triple negative breast cancer using nab-paclitaxel instead of solvent-based paclitaxel. pCR rates were higher in patients with lymphocyte predominant breast cancer, either triple negative or HER2-positive, who were treated with carboplatin.</td>
</tr>
</tbody>
</table>
FDA statement on pCR

• The absence of any residual invasive cancer on H&E evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes following completion of neoadjuvant systemic therapy (i.e., ypT0 ypTis ypN0 in the current AJCC staging system).

• This definition resumes the current understanding of major features of the intrinsic biology of early-stage breast cancer.
pCR as surrogate for survival

von Minckwitz G et al, J Clin Oncol 2012
pCR as surrogate for survival

(N=11,955)

Cortazar et al, Lancet 2014
Targeting heterogeneity of TNBC

PIK3CA mutations
AR expression
Apocrine histology
Low path CR chemotherapy

Basal keratin expression

BL1, basal-like 1;
BL2, basal-like 2;
IM, immunomodulatory;
ML, mesenchymal-like;
MSL, mesenchymal stem-like;
LAR, luminal androgen receptor;
AR, androgen receptor;

CCR Focus

Nicholas C. Turner, and Jorge S. Reis-Filho Clin Cancer Res 2013;19:6380-6388
n = 90 treated with non-platinum regimens
 Approximately 85% triple negative

<table>
<thead>
<tr>
<th>Group</th>
<th># path CR/# total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>14/90</td>
<td>16%</td>
</tr>
<tr>
<td>CMF</td>
<td>1/14</td>
<td>7%</td>
</tr>
<tr>
<td>Adria/Docetaxel</td>
<td>2/25</td>
<td>8%</td>
</tr>
<tr>
<td>AC or FAC</td>
<td>11/51</td>
<td>22%</td>
</tr>
</tbody>
</table>

- MD Anderson retrospective series demonstrated path CR of 46% (26/57) in BRCA carriers.

Byrski et al, JCO 2010 and Arun et al JCO 2011
What About Tumors in Patients with Inherited BRCA Mutation?

- 107 patients with *BRCA1* mutations
- Stage I-III disease
- Treatment:
  - Preoperative Cisplatin 75 mg/m² q 3 weeks x 4
  - Mastectomy
- Path CR defined as no invasive tumor in breast/nodes

Pathologic complete response = 61%

Platinum-based neoadjuvant chemotherapy for triple-negative breast cancer

CALGB 40603

GeparSixto

1-sided P=0.0029

P=0.005


INFORM: preop cisplatin vs AC for BRCA 1/2 carriers

Stage II/III BC with BRCA1 or 2 mutation

- Multicenter study
- Designed to show 20% improvement in pCR with cisplatin over AC

N = 170; approximately 60 enrolled

AC x 4
CDDP x 4

Principal Investigators:
Nadine Tung and Judy Garber
TBCRRC and other sites
Do We Have Sufficient Data To Incorporate Platinum in Treatment of BRCA Carriers with TNBC?

- May never have large, definitive trial
- Mounting evidence in neoadjuvant and metastatic settings
- Biology is consistent with clinical observations
- Probably ready or close to it – ideally would like to see results of neoadjuvant INFORM trial
- How do we do it? Add to standard? Substitute for one or more agents?
Is Carboplatin Ready for Primetime in Unselected TNBC in the Adjuvant or Neoadjuvant Setting?

NO

• Need definitive study showing improvement in DFS and/or OS

• If platinum is ultimately used, should it be added to standard therapy or substituted for one or more drugs?

• Are there triple negative subtypes that are particularly sensitive to platinum salts?
Neoadjuvant chemotherapy plus bevacizumab for triple-negative breast cancer

Bear HD, et al. NEJM 2012;366;310-320
Neoadjuvant nabpaclitaxel for triple-negative breast cancer

**Geparsepto**

**N=1200**

Arm A

- Core biopsy
- Paclitaxel 80 mg/ m² weekly
- nab-Paclitaxel 125 mg/ m² weekly
- Epirubicin 90 mg/m²
- Cyclophosphamide 600 mg/m²

Arm B

- Core biopsy
- Paclitaxel 80 mg/ m² weekly
- nab-Paclitaxel 125 mg/ m² weekly
- Epirubicin 90 mg/m²
- Cyclophosphamide 600 mg/m²

**N=60** (HER2 positive)

**6 weeks**

- Core biopsy (after anti-HER2 treatment / before study entry)
- Trastuzumab 8 mg/kg (loading dose) followed by 6 mg/kg Pertuzumab (absolute dose per application) 840 mg (loading dose) followed by 420 mg

**12 weeks**

**Surgery**

*Randomizations carried out simultaneously*
Neoadjuvant nabpaclitaxel for triple-negative breast cancer

Geparsepto


OR 1.53 (95% CI, 1.20 - 1.95), \( P = 0.00085^a \)

- \( nab-P \) remained an independent predictor for pCR after adjustment for baseline and minimization factors (OR 1.66; 95% CI, 1.25 - 2.19; \( P = 0.00043 \))
Neoadjuvant nab-paclitaxel for triple-negative breast cancer

New prognostic factors and new targets

1. Release of cancer cell antigens
   - Chemotherapy
   - Radiation therapy
   - Targeted therapy

2. Cancer antigen presentation
   - Vaccines
   - IFN-α
   - GM-CSF
   - Anti-CD40 (agonist)
   - TLR agonists

3. Priming and activation
   - Anti-CTLA4
   - Anti-CD137 (agonist)
   - Anti-OX40 (agonist)
   - Anti-CD27 (agonist)
   - IL-2
   - IL-12

4. Trafficking of T cells to tumors

5. Infiltration of T cells into tumors
   - Anti-VEGF

6. Recognition of cancer cells by T cells
   - CARs

7. Killing of cancer cells
   - Anti-PD-L1
   - Anti-PD-1
   - IDO inhibitors

Chen & Mellman. Immunity 2013;39:1-10
Prognostic Ability of the Lymphocyte-predominant Breast Cancer (LPBC) Phenotype.

Sherene Loi et al. JCO 2013;31:860-867
TILs in HER2 positive and TN breast cancer

Denkert C et al. J Clin Oncol Dec 2014; epub ahead of print
Neoadjuvant I-O for triple-negative breast cancer

N=272
Primary endpoint: EFS
Secondary endpoint: pCR (ypT0-ypTis ypN0)

- Nab-Paclitaxel 125 mg/m²
- CBDCA AUC2
- +/- ATEZOLIZUMAB 1200 mg

NEOTRIP Trial, PI L. Gianni
Neoadjuvant I-O for triple-negative breast cancer

N=174

Primary endpoint: pCR (ypT0 ypN0)

Nab-Paclitaxel

EC

MEDI 4736/Durvalumab

Placebo

Window of opportunity 2weeks

Nab-P 125 mg/m²

Epirubicin 90 mg/m² + Cyclophosphamide 600 mg/m²

MEDI 4736/Durvalumab 2g total q4w
• pCR increased in TNBC to around 55%
• Adding Carboplatin increased the pCR rate in TNBC
• Do TILs predict Carboplatin benefit in HER2+ patients?
• Should we combine Carboplatin and nab-Paclitaxel to further increase the pCR in TNBC?
• TILs seem to select patients with better response to NAT
Adjuvant CT in TN EBC

Triple-negative Breast Cancer: Is there an optimal adjuvant treatment?
Benefit from CT in TN EBC

- Recurrence:
  - ER neg: 63% [43-76]
  - ER pos: 32% [-7-56]

- Death:
  - ER neg: 59% [34-74]
  - ER pos: 18% [-41-25]

Adjusted for:
- # pos nodes
- Tumor size
- Menopausal status

Berry et al, JAMA 2005
Criteria to define optimal regimens

• Biological
  – Intrinsic heterogeneity within TNBC
  – Lack of targeted therapies

• Clinical
  – Epidemiological links to younger age and heredity
  – Higher risk means lower stage threshold for treatment
  – Chemo question is not “yes/no?” but “which?”
  – Trade-offs still include consideration of short-term and long-term side effects but balanced by tumor risk and treatment needs

• Analytical
  – Few trials specifically for TNBC
  – Subset analyses with familiar limitations, including post hoc analyses and lack of power/events
NSABP B-30. $\text{AC}_4 \rightarrow \text{T}_4$ vs $\text{TAC}_4$ vs $\text{AT}_4$

Overall Survival and Disease-free Survival.

A

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Patients</th>
<th>No. of Events</th>
<th>Hazard Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequential ACT</td>
<td>1753</td>
<td>240</td>
<td>0.86 vs. concurrent ACT</td>
<td>0.09</td>
</tr>
<tr>
<td>Doxorubicin–docetaxel</td>
<td>1753</td>
<td>285</td>
<td>0.83 vs. doxorubicin–docetaxel</td>
<td>0.03</td>
</tr>
<tr>
<td>Concurrent ACT</td>
<td>1758</td>
<td>278</td>
<td>0.96 vs. doxorubicin–docetaxel</td>
<td>0.67</td>
</tr>
</tbody>
</table>

B

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Patients</th>
<th>No. of Events</th>
<th>Hazard Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequential ACT</td>
<td>1753</td>
<td>388</td>
<td>0.83 vs. concurrent ACT</td>
<td>0.01</td>
</tr>
<tr>
<td>Doxorubicin–docetaxel</td>
<td>1753</td>
<td>468</td>
<td>0.80 vs. doxorubicin–docetaxel</td>
<td>0.001</td>
</tr>
<tr>
<td>Concurrent ACT</td>
<td>1758</td>
<td>457</td>
<td>0.96 vs. doxorubicin–docetaxel</td>
<td>0.58</td>
</tr>
</tbody>
</table>

NSABP B-30

<table>
<thead>
<tr>
<th>A. Risk of Death: Sequential ACT vs. Concurrent ACT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subgroup</strong></td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>ER status</td>
</tr>
<tr>
<td>Positive</td>
</tr>
<tr>
<td>Lymph node status</td>
</tr>
<tr>
<td>≥4</td>
</tr>
<tr>
<td>Tumor size</td>
</tr>
<tr>
<td>&gt;2 cm</td>
</tr>
<tr>
<td>Hormone therapy</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Menopausal status</td>
</tr>
<tr>
<td>Postmenopausal</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Risk of Disease Recurrence, a Second Malignant Condition, or Death: Sequential ACT vs. Concurrent ACT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subgroup</strong></td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>ER status</td>
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<tr>
<td>Positive</td>
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<tr>
<td>No</td>
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<tr>
<td>Menopausal status</td>
</tr>
<tr>
<td>Postmenopausal</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>C. Risk of Death: Sequential ACT vs. Doxorubicin–Docetaxel</th>
</tr>
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<tbody>
<tr>
<td><strong>Subgroup</strong></td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>ER status</td>
</tr>
<tr>
<td>Positive</td>
</tr>
<tr>
<td>No. of positive lymph node</td>
</tr>
<tr>
<td>≥4</td>
</tr>
<tr>
<td>Tumor size</td>
</tr>
<tr>
<td>&gt;2 cm</td>
</tr>
<tr>
<td>Hormone therapy</td>
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<tr>
<td>No</td>
</tr>
<tr>
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</tr>
<tr>
<td>Postmenopausal</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>D. Risk of Disease Recurrence, a Second Malignant Condition, or Death: Sequential ACT vs. Doxorubicin–Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subgroup</strong></td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>ER status</td>
</tr>
<tr>
<td>Positive</td>
</tr>
<tr>
<td>No. of positive lymph node</td>
</tr>
<tr>
<td>≥4</td>
</tr>
<tr>
<td>Tumor size</td>
</tr>
<tr>
<td>&gt;2 cm</td>
</tr>
<tr>
<td>Hormone therapy</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Menopausal status</td>
</tr>
<tr>
<td>Postmenopausal</td>
</tr>
</tbody>
</table>

CALGB 9344: AC x 4 ± Paclitaxel x 4

Outcomes for Subtypes

A HER2-Negative, Estrogen-Receptor–Negative

B HER2-Negative, Estrogen-Receptor–Positive

C HER2-Positive, Estrogen-Receptor–Negative

D HER2-Positive, Estrogen-Receptor–Positive

BCIRG 001: TAC vs FAC Outcome for Subtypes

Hugh J et al. JCO 2009;27:1168-1176
GEICAM 9906: FEC vs FEC/P
Outcomes by Subtypes

TRIPLE NEGATIVE

HER2

LUMINAL A

LUMINAL B
Adjuvant therapy in TN EBC

**POSSIBLE REGIMENS**

- AC-paclitaxel (dose dense)
- AC-weekly paclitaxel
- AC-docetaxel (every 3 weeks)
- FEC-docetaxel

NSABP-B30
AC-T x 8 vs AT x 4 vs TAC x 6

Adjuvant therapy in TN EBC

• Standard chemotherapy agents are effective adjuvant therapy, particularly in TNBC
• Enhancements to adjuvant chemotherapy (addition of taxanes, sequential therapy, schedule) are valuable, particularly in TNBC
• While anthracyclines are standard components of modern adjuvant regimens, questions persist about their importance, particularly in TNBC
## Should Stage Affect the Choice of a Treatment Regimen?

<table>
<thead>
<tr>
<th>Year of diagnosis</th>
<th>Percent of adjuvant chemotherapy (±trastuzumab) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR+HER2-</td>
</tr>
<tr>
<td></td>
<td>T1a</td>
</tr>
<tr>
<td>2003</td>
<td>3%</td>
</tr>
<tr>
<td>2005</td>
<td>1%</td>
</tr>
<tr>
<td>2009</td>
<td>2%</td>
</tr>
</tbody>
</table>

IEO Data
Retrospective analysis of MA-5 suggested CMF marginally more effective than CEF in basal-like BC (Cheang et al Clin Can Res 2012)
TC appeared superior to AC in one relatively small trial

Probably at least as good as AC

Would be hesitant about using TC in BRCA mutation carriers

### Options for Stage I Disease

- **Chemotherapy treatment options for low risk disease:**
  - 1) simple regimen (AC, TC, CMF)
  - 2) sequential anthracycline/taxane

<table>
<thead>
<tr>
<th></th>
<th>Enthusiasm for Chemotherapy</th>
<th>Possible Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Microinvasion only</strong></td>
<td>Virtually none</td>
<td>---</td>
</tr>
<tr>
<td><strong>T1a</strong></td>
<td>Low to moderate</td>
<td>Simple</td>
</tr>
<tr>
<td><strong>T1b</strong></td>
<td>Moderate to high</td>
<td>Simple</td>
</tr>
<tr>
<td><strong>T1c</strong></td>
<td>High</td>
<td>Simple or selectively sequential approach</td>
</tr>
</tbody>
</table>
Post-Neoadjuvant setting

C. Liedtke JCO, 26, 8, 2008: pp. 1275-1281
TILs in residual disease: DFS
TILs in residual disease: OS
Post-Neoadjuvant setting

- Preplanned interim analysis of a randomized, open-label phase III study\(^1\)

  *Stratified by ER status, age, neoadjuvant chemotherapy, use of 5-FU, institution, node status*

  Pts 20-74 yrs of age with stage I-IIIB HER2- BC and residual disease (non-pCR, N+) after neoadjuvant chemotherapy* and surgery; ECOG PS 0 or 1; no previous oral fluoropyrimidines (N = 910)\(^\dagger\)

  Primary endpoint: DFS

  Secondary endpoints: OS, time from first day of preoperative chemotherapy to recurrence or death, safety, cost-effectiveness


\(^*\)Anthracycline/taxane, anthracycline containing, or docetaxel/cyclophosphamide.

\(^\dagger\)25 pts were removed from treatment (n = 10) and control (n = 15) arms due to failure to meet eligibility criteria.

\(^\ddagger\)IDMC recommended extension to 8 cycles following interim safety analysis of first 50 pts receiving 6 cycles.\(^2\)
### Post-Neoadjuvant setting

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Capecitabine (n = 440)</th>
<th>No Capecitabine (n = 445)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median yrs (range)</td>
<td>48 (25-74)</td>
<td>48 (25-74)</td>
</tr>
<tr>
<td>Menopausal status, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>59.3</td>
<td>56.0</td>
</tr>
<tr>
<td>Post</td>
<td>40.7</td>
<td>44.0</td>
</tr>
<tr>
<td>Stage, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I, IIA, IB</td>
<td>58.9</td>
<td>62.0</td>
</tr>
<tr>
<td>IIIA, IIIB</td>
<td>40.5</td>
<td>37.5</td>
</tr>
<tr>
<td>Hormonal receptor status, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+ or PgR+</td>
<td>63.9</td>
<td>62.9</td>
</tr>
<tr>
<td>ER- and PgR-</td>
<td>33.4</td>
<td>33.5</td>
</tr>
<tr>
<td>Lymph nodes with metastatic disease, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>39.3</td>
<td>38.7</td>
</tr>
<tr>
<td>1-3</td>
<td>37.5</td>
<td>39.1</td>
</tr>
<tr>
<td>≥ 4</td>
<td>22.7</td>
<td>22.2</td>
</tr>
<tr>
<td>Histologic effect grading by NAC, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0, 1a, 1b</td>
<td>56.4</td>
<td>52.6</td>
</tr>
<tr>
<td>2, 3</td>
<td>41.6</td>
<td>45.4</td>
</tr>
</tbody>
</table>

• Capecitabine achieved significantly higher 5-yr DFS and OS in HER2- BC pts with residual disease

<table>
<thead>
<tr>
<th>Characteristic, %</th>
<th>Capecitabine (n = 440)</th>
<th>No Capecitabine (n = 445)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-yr DFS</td>
<td>74.1</td>
<td>67.7</td>
<td>0.70 (0.53-0.93)</td>
<td>.00524</td>
</tr>
<tr>
<td>5-yr OS</td>
<td>89.2</td>
<td>83.9</td>
<td>0.60 (0.40-0.92)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

Triple negative BRCA mutated

Figure 1. OlympiA study design

- Screening
- Randomization (1:1)
  - Olaparib 300 mg bid (12 months’ duration)
  - Matched placebo (12 months’ duration)
- Invasive disease-free survival assessment (mammogram/breast MRI 6 months from randomization)
- Follow-up for local and distant recurrence and survival status
• Because of the lack of targeted therapy, the intrinsic recurrence risk, and the efficacy of chemotherapy, thresholds for adjuvant chemotherapy treatment for TNBC are low (≈ 0.5 cm, node-negative) despite the familiar side effects of chemotherapy treatment.

• Data suggest “optimal” regimens should include cyclophosphamide, taxanes, and anthracyclines.

• Data are insufficient and/or negative for additional treatments such as:
  – Capecitabine
  – Gemcitabine
  – Platinum-based chemotherapy
  – Bevacizumab
Adjuvant therapy in TN

• **Standard of Care**
  – based on direct comparisons, subset analyses and considerations of toxicity/tolerability
  – *sequential anthracycline, cyclophosphamide and taxane-based therapy*
  – arguably ddAC → paclitaxel

• **Alternative regimens**
  – Preferred regimen without anthracyclines: TC
  – Preferred regimen without taxanes: AC or CMF

• **Neoadjuvant regimens = adjuvant regimens**
Research priorities

– Event rates in TNBC enable familiar adjuvant trial designs
– Design & power studies specifically for TNBC outcomes
– Define role of anthracyclines [NSABP B-49] in modern era
– Molecular / genomic correlatives
– Innovative neoadjuvant FDA accelerated approval pathway exists for potent, novel agents studied through add-on design trials with adequate sample size and planned long-term follow-up for EFS / OS, but the relationship of change in pCR and change in EFS remains unclear
Thank you