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SCLC and locally advanced NSCLC

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Disclosure

- Nothing to declare

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Small Cell Lung Cancer

- 12-15% of all lung cancers
- Chemotherapy cornerstone of treatment
- Poor outcomes following progression on FL
- Less than 5% alive at 1 year after PD

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Second line

- The quality and duration of response to frontline strongly predict the survival outcomes
- Patients previously treated with PE can be empirically divided in :
  - **Refractory**: no objective response
  - **Resistant**: very early recurrence < 3 months
  - **Sensitive**: free interval of ≥ 3 months

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Rechallenge as an option for second line treatment

- Widely accepted for selected patients
- Even recommended for several guidelines in sensitive relapse
- However
  - It is not based on RCT
  - The induction CT regimens were not platinum based

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Rechallenge chemotherapy

- Giaccone et al *(Eur J Cancer Clin Oncol 1987)*
  - Retrospective analysis (1980-1984)
  - **19 pts** reinduced (1VAC, 4 VAC-PE, 8 CDE)
  - Treatment free interval (TFI) median 30 wks
  - **ORR 50%** (CR 16.7%, PR 33%)
- Postmus et al *(Eur J Cancer Clin Oncol 1987)*
  - **37 pts** treated and retreated with CDE
  - TFI median 34 wks
  - **ORR 62%**
    - 19 first response > 34 wks: 15/19 responded
    - 18 first response < 34 wks: 8/18 responded

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Rechallenge chemotherapy

- Giaccone et al[1]
  - Retrospective analysis (1980-1984)
  - 19 pts reinduced (1VAC, 4 PE, 8 CDE)
  - T
  - O
- Postm
  - 3
  - T
  - O
    - 18 first response < 34 wks: 8/18 responded
- Vincent et al[3]
  - 15 patients, different induction regimens (CbE 10)
  - PR 67% (10/15)
  - First response longer than 8 months related to second response

It is unclear whether rechallenge with the current standard is effective

1 EJCCO 1987, 2 EJCCO 1987, 3 CCP 1988

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Small cell lung cancer

- Outcomes of platinum-sensitive SCLC patients treated with platinum-based chemotherapy rechallenge: a multi-institutional retrospective analysis

  G. Genestreti, G. Metro, H. Kenmotsu, F. Carloni, M.A. Burgio, C. Casanova, M. Tiseo, E. Scarpi,T. Korkmaz, R. Califano.

- Cabazitaxel vs topotecan in patients with SCLC with progressive disease during/after first-line treatment with platinum-based chemotherapy

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Outcomes Of Platinum-Sensitive SCLC Patients Treated With Platinum-based Chemotherapy Rechallenge: A Multi-institutional Retrospective Analysis

- 2000 p. analyzed (2007 - 2011). LD 44%
- 112 sensitive SCLC rechallenged PE (5.6%).
- Median time to relapse from completion FL 240 days
- 36% received further CT: PE (6%)
- Efficacy of rechallenge:
  - CR 3%, PR 42%, SD 19%, PD 27%, NE 9%
  - Median PFS 5.5 months
  - Median OS from diagnosis 21.4 mo and from rechallenge 7.9 months
- **Platinum sensitive disease may be rechallenged**

Califano et al. ELCC 2014

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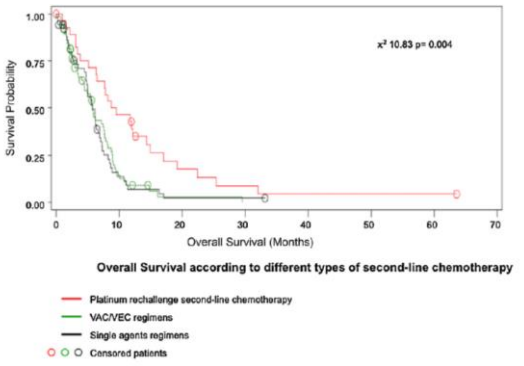
Outcomes of small-cell lung cancer patients treated with second-line chemotherapy: A multi-institutional retrospective analysis

Marina Chiara Garassino[a,1], Valter Torri[b,1], Giovanni Michetti[c,1], Monica Lo Dico[d,1], Nicla La Verde[a,1], Stefania Aglione[e,1], Andrea Mancuso[f,1], Elisa Gallerani[g,1], Domenico Galetta[h,1], Olga Martelli[i,1], Elena Collovà[j,1], Sonia Fatigoni[k,1], Antonio Ghidini[l,1], Chiara Saggia[m,1], Claudia Bareggi[n,1], Antonio Rossi[o,1], Gabriella Farina[a,1], Nicholas Thatcher[p,1], Fiona Blackhall[p,1], Paul Lorigan[p,1], Raffaele Califano[p,*,1]

- Retrospective analysis 161 SCLC (1999-2008), Sensitive (75.2%)
- Rechallenge 18% (30 p.), VAC 44.8%, Topo 22%
- Rechallenge showed **non-statistically significant trend** toward higher RR (34.5% vs 17.5%, p : 0.06) and OS when compared to non platinum-based regimen
- The highest benefit: TTP 12 months
- Prognostic factors
  - **PE containing regimen** HR 0.46, p: 0.030
  - **PS at second line** HR 1.9, p: 0.004
  - **Response to FL** HR 0.39, p: 0.022



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Efficacy of Rechallenge Chemotherapy in Patients With Sensitive Relapsed Small Cell Lung Cancer

Kazushige Wakuda, MD, Hirotsugu Kenmotsu, MD,* Tateaki Naito, MD, PhD,* Hiroaki Akamatsu, MD,* Akira Ono, MD,* Takehito Shukuya, MD,* Yukiko Nakamura, MD,* Asuka Tsuya, MD PhD,* Haruyasu Murakami, MD, PhD,* Toshiaki Takahashi, MD, PhD,* Masahiro Endo, MD, PhD,† Takashi Nakajima, MD, PhD,‡ and Nobuyuki Yamamoto, MD, PhD**

- 65 pts (19 rechallenge / 46 other drugs, 21 of them amrubicin)
- No significant difference in OS between the 2 groups
- MST rechallenge, 14.4 mo and other group 13.1 mo; p = 0.51.
  - Amrubicin MST 12.6 mo

Rechallenge chemotherapy did not prove superior *to other chemotherapies, suggesting that monotherapy, such as amrubicin, might be reasonable as second-line chemotherapy for sensitive-relapse SCLC patients*

Wakuda K et al. Am J Clin Oncol 2013

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A Systematic Analysis of Efficacy of Second-Line Chemotherapy in Sensitive and Refractory Small-Cell Lung Cancer

Taofeek K. Owonikoko, MD,# Madhusmita Behera, MS,* Zhengjia Chen, PhD,† Chandar Bhimani, MD,* Walter J. Curran, MD,‡ Fadlo R. Khuri, MD,* and Suresh S. Ramalingam, MD**

- 1692 patients enrolled (912 sensitive and 780 refractory).
- ORR: 17.9%
  - Sensitive 27.7% (range, 0%–77%)
  - Refractory 14.8% (range, 0%–70%); p=0.0001.
- Median OS following second line 6.7 months
  - Sensitive 7.7 months
  - Refractory 5.4 months; p = 0.0035.
- **Conclusions:**

  Sensitive cases are more likely to respond than refractory cases

  Refractory SCLC patients derive modest clinical benefit from second-line chemotherapy.

Owonikoko T and cols. J Thorac Oncol. 2012

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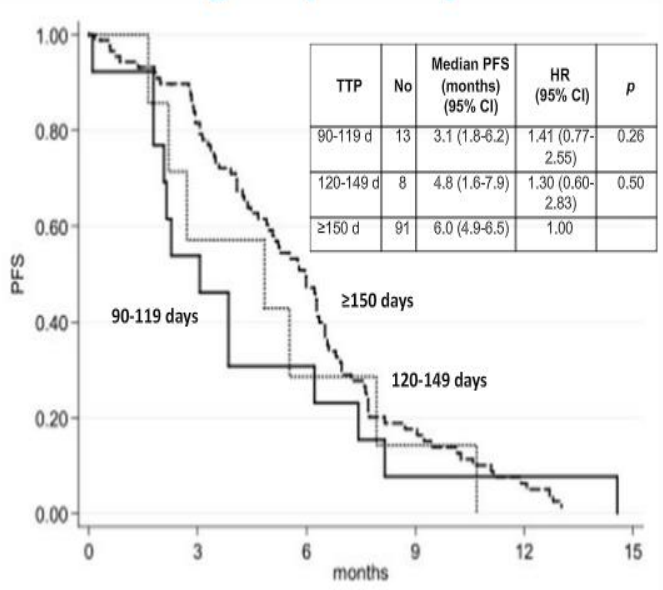
Outcomes Of Platinum-Sensitive SCLC Patients Treated With Platinum-based Chemotherapy Rechallenge: A Multi-institutional Retrospective Analysis

Median PFS 5.5 months

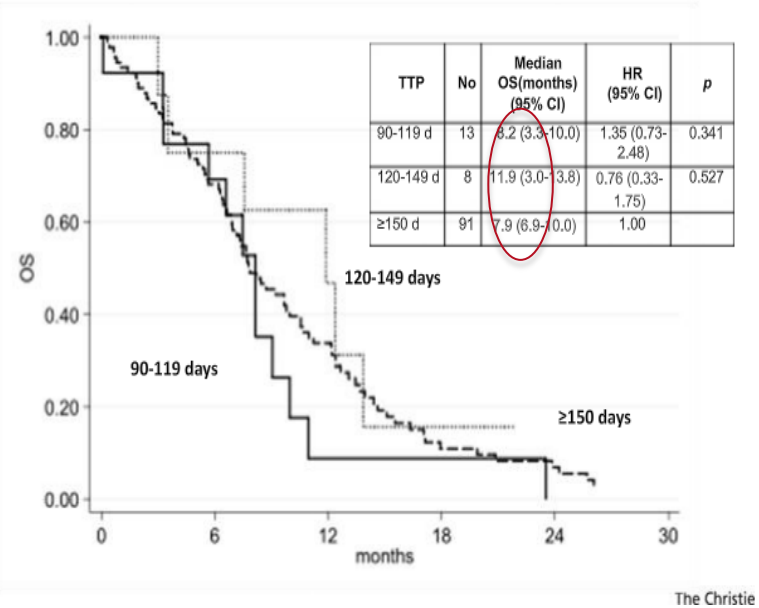
MST from diagnosis 21.4 mo and from rechallenge 7.9 mo

PFS from Rechallenge Subgroup Analysis



TTP	No	Median PFS (months) (95% CI)	HR (95% CI)	p
90-119 d	13	3.1 (1.8-6.2)	1.41 (0.77-2.55)	0.26
120-149 d	8	4.8 (1.6-7.9)	1.30 (0.60-2.83)	0.50
≥150 d	91	6.0 (4.9-6.5)	1.00	

OS from Rechallenge Subgroup Analysis



TTP	No	Median OS(months) (95% CI)	HR (95% CI)	p
90-119 d	13	8.2 (3.3-10.0)	1.35 (0.73-2.48)	0.341
120-149 d	8	11.9 (3.0-13.8)	0.76 (0.33-1.75)	0.527
≥150 d	91	7.9 (6.9-10.0)	1.00	

The Christie

Time to progression *from completion* of FL:

Median 240 days, range 90-1200

Califano et al. ELCC 2014

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Outcomes Of Platinum-Sensitive SCLC Patients Treated With Platinum-based Chemotherapy Rechallenge: A Multi-institutional Retrospective Analysis

- Strengths
  - Number of patients (112 sensitive relapse rechallenged)
  - Multi-institutional (8 institutions)
  - Recent era (2007-2011)
- “Weaknesses”
  - Retrospective analysis
  - Highly selected population (112/2000) difficult to extrapolate conclusions
  - No pathological review (MST 21.4 mo)
  - Missed data: site and number of metastases, correlation between response to FL and SL, PCI, toxicities…

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Outcomes Of Platinum-Sensitive SCLC Patients Treated With Platinum-based Chemotherapy Rechallenge: A Multi-institutional Retrospective Analysis

- Platinum sensitive disease ***may be*** rechallenged

- Results of the ongoing Japanese randomized phase II trial of amrubicin versus platinum rechangelle in sensitive relapse (NJLCG0702) will help us to clarify the role of the retreatment.

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Cabazitaxel vs Topotecan in patients with SCLC with progressive disease during/after first-line treatment with platinum-based CT

- N: 179 (Cbz 90; Tpt 89). ≈50% each arm ctx-refractory.
- Primary endpoint not met:
  - Median PFS 1.4 mo Cbz and 3.0 mo Tpt; p< 0.0001.
  - Similar results in sensitive (1.5 vs 3. 8 mo; p 0,0045) and refractory p (1.4 vs 2.7 mo; p< 0.0001).
- MST 5.2 mo Cbz vs. 6.8 mo Tpt; p=0.0125
- Topotecan more toxic:
  - All-grade AEs Tpt (94.3%) vs. Cbz (88.8%),
  - Grade 3–4 AEs (Tpt 71.6%, Cbz 58.4%).
- Similar: Febrile neutropenia (Tpt 15.9%, Cbz 11.2%), neutropenic infection (Tpt 6.8%, Cbz 4.5%) and neutropenic sepsis (Tpt 1.1%, Cbz 3.4%)
- 7 patients died as a result of AEs possibly related to treatment

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Topotecan

- Only drug approved for second line SCLC treatment, independently of the type of relapse
- Randomized trials:
  - Oral Topotecan + BSC vs. BSC (*O´Brien M et al. JCO 2006)*:
    - Oral Topo is associated with prolongation of survival and QoL benefit
    - MST 25.9 wk vs. 13.9 wk (HR, 0.64; p: 0.0104)
  - IV Topotecan vs. CAV *(Von Pawel et al. JCO 1999)*
    - Topotecan is at least as effective as CAV and results in improved symptoms control
  - Oral Topotecan vs. IV Topotecan (Von Pawel et al JCO 2001, Eckardt JCO 2007)
    - No differences in ORR and MST

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Topotecan Profile

- Efficacy of Topotecan:
  - Sensitive patients: ORR 24%, MST 6 mo
  - Refractory disease: ORR 4% to 12%, MST 3.4 - 5.8 mo
- Grade 3 - 4 Toxicities:
  - Neutropenia, 86–89%,
  - Thrombocytopenia, 43–57%
  - Anemia 31–40%,
  - Diarrhea 6–8%,
  - Fatigue 5–8%.

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Cabazitaxel

- Evaluation of novel agents is urgently needed in relapsed SCLC.
- Cabazitaxel has demonstrated efficacy in several tumors.
- No clear signal in SCLC based on phase I studies.[1-3]
- Toxicity profile: diarrhea, fatigue and neutropenia.

[1]Diéras et al. Eur J Cancer 2013;
[2]Mita et al, Clin Cancer Res 2009;
[3]Fumoleau P et al, BMC Cancer 2013

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Cabazitaxel vs. Topotecan in patients with SCLC with progressive disease during/after first-line treatment with platinum-based CT

- 25% Brain mets.
- ≈ 45% > ULN LDH level
- 50% > 4 organs involved
- 50% “refractory” disease
  - Median time from initial diagnosis to study treatment : ≈ 7 mo in refractory vs. ≈10 mo in sensitive

Evans T et al. ELCC 2014

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Cabazitaxel vs. Topotecan in patients with SCLC with progressive disease during/after first-line treatment with platinum-based CT

	Cabazitaxel N: 90 S 45 / R 45	Topotecan N: 89 S 46 / R 43
RR (%)	0	10
Sensitive	0	11.9
Refractory	0	8.11
PFS (mo)	1.4	3
Sensitive	1.5	3.8
Refractory	1.4	2.7
MST (mo)	5.2	6.8
Sensitive	6.4	7.2
Refractory	3.4	5.7
G≥ 3 Neut. (%)	56.8	78.4

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Randomized phase III trial of amrubicin versus topotecan as second-line treatment for SCLC

- 637 patients included
- Randomization 2:1 (424 amrubicin versus 213 Topotecan)
- Refractory 47% versus 45%
- Amrubicin 40 mg/m^2 d 1-3 /21 d versus Topotecan 1.5 mg/m^2 d 1-5/ 21 d
- Prophylactic G-CSF in last 1/3 of trial.

Jotte R et al. J Clin Oncol 29: 2011 (suppl; abstr 7000)

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	Cabazitaxel	Topotecan	Topotecan*	Amrubicin*
RR (%)	0	10	17	31
PFS (mo)	1.4	3	4	4.1
MST (mo)	5.2	6.8	7.8	7.5
G ≥ 3 N. (%)	56.8	78.4	53	41

* Jotte R, et al. J Clin Oncol, 2011 ASCO Annual Meeting Abstracts. Vol 29, No 15_suppl (May 20 Supplement), 2011: 7000

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Conclusions

- There is a clear need for active agents with better toxicity profile in patients with recurrent SCLC because of the poor prognosis and the importance of symptom palliation.
- SCLC is a genetically complex cancer but we should focus on identifying the underlying mechanism for rapid development of resistance to find more effective treatments.

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