What's new in the systemic treatment of SCLC?

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Disclosures

- Conflict of interests: none

Seminar

Small-cell lung cancer

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SCLC: no progress for many years

- app 15% of all lung cancers
- associated with heavy smoking
- Eto-Cis standard of care in first-line therapy (ORR 65-70%, OS 10 months)
- Topotecan standard of care in second-line therapy (PFS app 3 months!)
- No new approval in past 10 years (except oral topotecan)

Testing of novel agents in SCLC

Target	Agent	Type of Study	Status
MMP	Marimastat	Phase III	Negative
	Tanomastat	Phase III	Negative
c-kit	Imatinib	Phase II (multiple)	Negative
EGFR	Gefitinib	Phase II	Negative
mTOR	Temsirolimus	Randomized Phase II	Negative
Ganglioside	BEC-2	Phase III	Negative
Immunologic, angiogenesis	Thalidomide	Phase III (multiple)	Negative
Antifolate	Pemetrexed	Phase III	Negative
Bcl-2	AT-101	Phase II	Negative
	Navitoclax	Phase II	Negative
	Obatoclax	Phase II	Negative

Slide courtesy of Cathy Pietanza, MSKCC

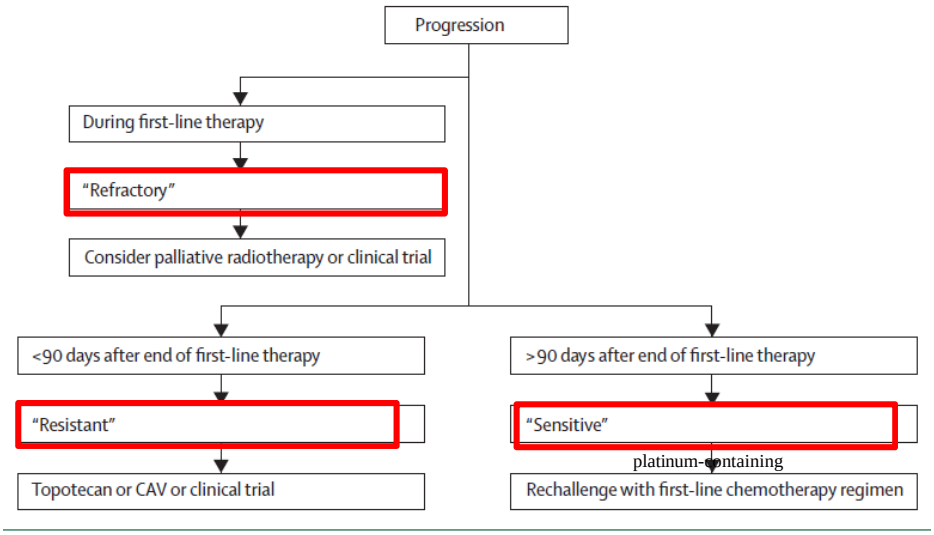


Figure 5: **Simplified algorithm for the management of relapsing SCLC**
SCLC=small-cell lung cancer. CAV= cyclophosphamide, doxorubicin, and vincristine.

What's new?

- Weekly topotecan
- Not so new agents
  - **Temozolomide**
- New agents
  - **Amrubicin**
  - **Picoplatin**
- Not so targeted agents
- Genomics of SCLC and its implications
- Conclusions

Weekly topotecan

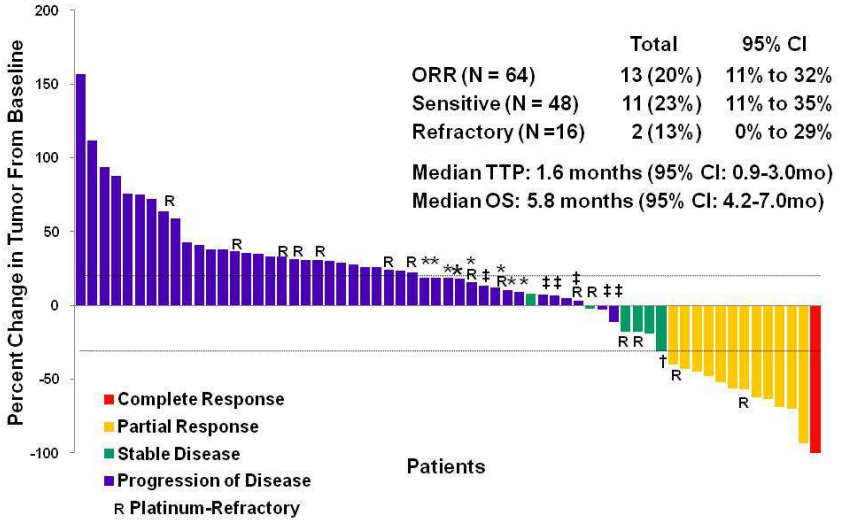
- Topotecan only approved agent for second line
  - Equal to CAV but superior palliation of symptoms
  - Oral administration equivalent to iv
  - T d1-5 q3w schedule comes with significant hematol toxicity
- TOWER trial (*Sehouli, JCO 2011; 29:242-8*)
  - Platinum resistant ovarian cancer
  - T weekly (4 mg/m(2)/wk administered on days 1, 8, and 15) q4w vs. T conventionally (1.25 mg/m(2)/d on days 1 to 5) q 3w
  - Comparable OS
  - Tw significantly lower risks of
    - anemia (RR, 0.35; 95% CI, 0.16 to 0.79),
    - neutropenia (RR, 0.38; 95% CI, 0.23 to 0.65)
    - thrombocytopenia (RR, 0.23; 95% CI, 0.09 to 0.57)
- Weekly topotecan new SOC?

Not so (new) agents

- Thalidomide
- Statines
- Nitroglycerine
- Metformin
- Chloroquine
- Azithromycine
- Beta blockers
- ACE inhibitors
- Antidepressants
- …
- *EORTC randomized trial of PE +/- repurposing drug*

- **Temozolomide**
  - Alkylating agent
  - Oral precursor drug of 5FU, crosses BBB
  - SOC in GBM and astrocytoma
  - Mild toxicity profile
    - 6% gr 3-4 hematol tox.
  - Expression of MGMT prognostic and predictive of efficacy

Phase II Study: Temozolomide in SCLC
Response in 21-day Schedule



Pietanza MC, et al. *Clin Cancer Res* 2012;18:1138.

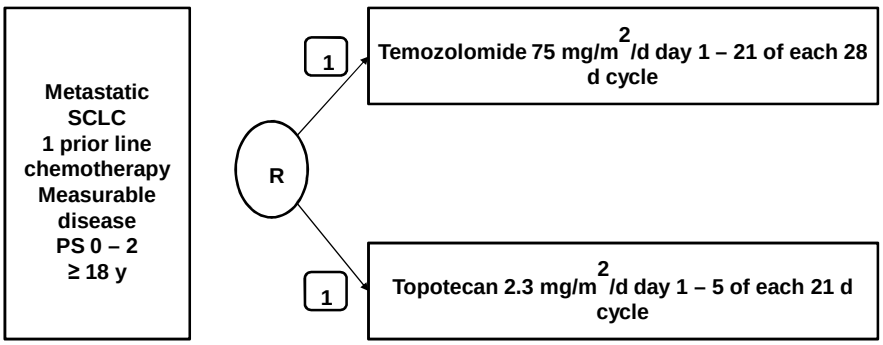
Presented By Roman Thomas at 2014 ASCO Annual Meeting

A multicentre randomized phase 2 study of temozolomide versus topotecan in patients with relapsed or refractory SCLC (*PI B Hiddinga*)

- Inclusion criteria
  1. Patients with metastatic SCLC
  2. Relapsing after or refractory to first line platinum-based treatment
  3. Measurable disease according to RECIST 1.1
  4. Performance status WHO 0, 1 or 2
  5. Informed consent

- Endpoints
  1. progression free survival (PFS) at 12 weeks
  2. overall survival (OS)
  3. correlation of MGMT expression and promoter methylation in blood & tissue with activity and outcome

Trial schema



Amrubicin

- Synthetic anthracycline
- Doxorubicin-like
  - Also camptothecine activity: stabilises topoisomerase II
- Amrubicinol accumulates in tumour cell
  - Less (cardio-)toxicity?
  - NADPH oxidase critical enzyme in metabolism
    - polymorphism in Asian influences pharmacogenomic profile
- Promising phase 2 trials in 1st and 2nd line in Japan
- Randomized trials in 1st line, combined with cisplatin (PA)
  - Vs. cisplatin etoposide (PE) EORTC 08062
  - Vs. cisplatin irinotecan (PI) JCOG 0509
- Phase 3 trials in 2nd line ACT-1
  - vs. Topotecan (T)

Amrubicin (conclusion)

- Outcome in Caucasian population
  - 1st line: equal to etoposide and inferior to irinotecan
  - 2nd line: equal to topotecan, superior in refractory pts
- Toxicity
  - Higher rate of (febrile) neutropenia
- No valid alternative for current SOC's in Caucasian pts

Picoplatin

- Platinum analogue not avid for thiol groups (e.g.G-SH) responsible for platinum resistance
- Promising single agents phase 2 studies in *sensitive* en *refractory* pts
- SPEAR: picoplatin vs BSC in relapsed SCLC
  - N= 401
  - No difference in outcome but for PFS in subgroup of refractory pts
  - Imbalance in 3th line treatment

Not-so targeted agents

- SCLC highly angiogenic tumour
  - High microvessel density and levels of VEGF
- Bevacizumab: Mab against VEGF
  - IFCT-0802 trial (*Pujol, ASCO 2014*)
    - Randomized phase 2 in 147 ES SCLC; no biomarker selection
    - Chemo x 6 +/- bevacizumab: no difference in outcome
- Aflibercept: VEGF trap
  - SWOG S0802 (*Allen, JCO 2014*)
    - Randomized phase 2 in 189 pretreated SCLC: no biomarker selection
    - Topotecan weekly +/ - afibercept
    - Improved PFS @ 3m; similarOS; increased rate of gr 3-5 toxicities
- Sunitinib: oral tyrosine kinase inhibitor of VEGFR-2/3
  - CALGB 30504 (ALLIANCE) – (*Ready, ASCO 2014)*
    - Randomized phase 2 in 144 ES SCLC: no biomarker selection
    - Maintenance treatment with sunitinib or placebo until progression
    - improved PFS; trend to improved OS

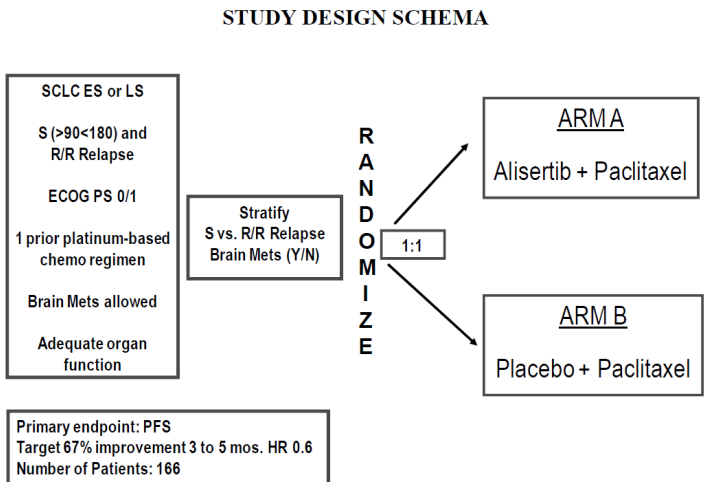
Not-so targeted agents (2)

- Vandetanib: oral TKI of VEGFR-2/3, EGFR and RET
  - Hoosier Oncology LUN06-113 (*Sanborn, ASCO 2014*)
    - Randomized phase 2 in 74 ES SCLC: no biomarker selection
    - Carbo etoposide +/- vandetanib
    - No difference in outcome, higher incidence of grade 3/4 toxicities
- Insuline growth factor (IGF-R) frequently overexpressed
  - Vismodegib and cixutumumab inhibit IGF-R
    - ECOG 1508 (*Belani ASCO, 2012*)
      - Cisplatin/etoposide +/- either V or C
      - No difference in outcome
- Check point inhibition: blocking antibodies of CTLA4
  - Chemotherapy +/- ipilimumab (*Reck, Ann Oncol 2013*)
    - Trend for improved >OS at long follow up

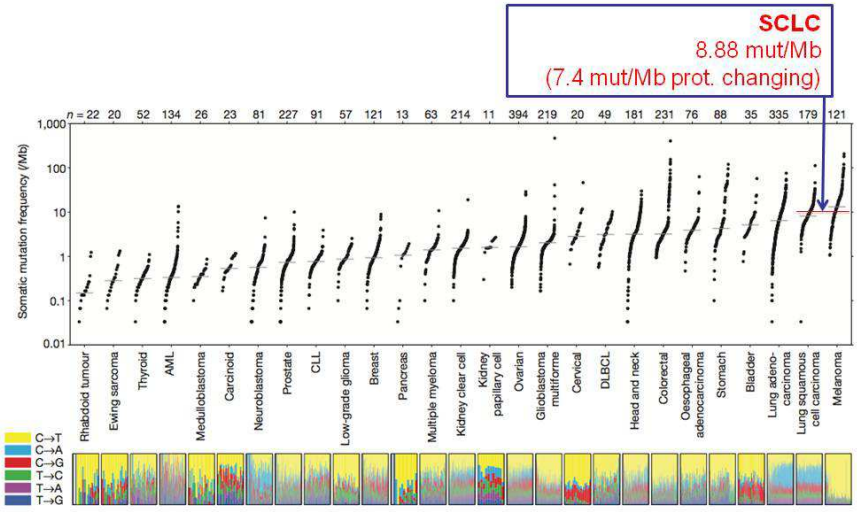
Aurora A kinase inhibition

- Serine/threonine kinases with critical function during mitosis
  - Overexpression associated with increased cell proliferation via aneuploidy, supernumerary centrosomes, defective mitotic spindles, and resistance to apoptosis.
  - Not yet a proper biomarker
- Given the obligatory role of mitosis in tumor proliferation, an Aurora A kinase inhibitor would have potential applications across a broad range of human solid tumors
  - Alisertib: selective small-molecule inhibitor of Aurora A kinase
    - additive or synergistic antitumor activity in vivo when combining with tubulin inhibitors paclitaxel or docetaxel in SCLC xenograft models
    - predominant toxicities reflect the mechanism of action in proliferating tissues (bone marrow, GI epithelium, and hair follicles)

Alisertib



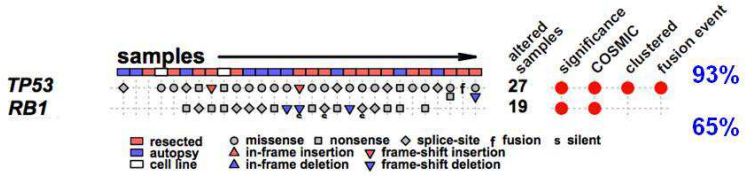
Somatic mutation frequency in lung cancer



Lawrence et al. *Nature* (2013)
Peifer et al., Nat Genet (2012)

From exomes to 100 genomes…

- Pilot study: Whole exome sequencing on 29 T/N pairs



- WGS on 77 T/N pairs

	TP53	RB1
Mutations	**95 %** (73/77)	**82 %** (63/77)
CN Changes - Deletions	**61 %** (47/77)	**69 %** (53/77)
Genomic Rearrangements (translocations, inversions, larger deletions within the gene or gene region)	**6.5 %** (5/77)	**12 %** (9/77)

Julie George

Fundamental Issue in SCLC biology

No "driver" mutation!

Many interesting genes, but…

- No smoking gun mutation
- No link yet with characteristic phenotypes
  - Universal sensitivity to chemo
  - Rapid development of resistance
  - Highly metastatic disease
  - Small cells
  - Neuroendocrine features
- Are there infrequent actionable alterations?

SCLC and DNA damage

- Paradoxical and unique sensitivity to chemo (RR first line >60 %) despite…
- …universal biallelic loss of p53!
- Therapeutically amenable DNA damage dependency?
- High expression of PARP in SCLC (Byers et al., Cancer Discov 2012)
- Trials testing PARP inhibitors in SCLC are ongoing (10% RR with BMN673, abstract 7522)

Conclusions

- Weekly topotecan acceptable alternative in second line treatment
- No real progress in cytotoxic or targeted agents
- Despite many TSG mutations, no obvious ‘smoking gun’
- Need to explore multi-mutational, complex biology in detail to identify novel therapies
- Several interesting phase 2 trials ongoing
  - Repurposed drugs
  - Immune checkpoint inhibition
  - Aurora kinase A inhibitors

Programme

11th Thoracic Oncology Winter Symposium
Saturday 17 January 2015

09:00 **Registration**
09:30 Welcome
Jan van Meerbeeck, UZ Antwerpen, Belgium

09:35 **Research lecture**
Chair: Jan van Meerbeeck, UZ Antwerpen, Belgium
Volatomics in (lung) cancer diagnosis
Kevin Lamote, UZ Gent, Belgium

09:55 – 11.00 Session 1: Can local therapy benefit a systemic disease?
Chairs: Yolande Lievens, UZ Gent & Birgitta Hiddinga, UZ Antwerpen, Belgium
09:55 Consolidation thoracic radiotherapy in ES SCLC
Ben Slotman, VUmc, Amsterdam, the Netherlands
10:20 Prophylactic cranial irradiation in ES SCLC
Takashi Seto, National Kyushu Cancer Center, Fukuoka, Japan
10:45 Interactive Q & A with voting
Thomas Malfait, UZ Gent, Belgium

11:00 Break

11:30 – 13.00 Session 2: The winding road to cure in metastatic NSCLC
Chairs: Egbert Smit, NKI-AvL, Amsterdam, the Netherlands & Veerle Surmont, UZ Gent, Belgium
11:30 Targeting rank ligand for survival or for bone recovery?
Solange Peters, CHU Lausanne, Switzerland
11:50 2nd generation ALK-inhibitors: luxury or necessity?
Christian Rolfo, UZ Antwerpen, Belgium
12:05 2nd generation EGFR-TKI: progress or redundancy?
James Yang, Taipeh, Taiwan
12:25 3rd generation EGFR-TKI's: drowning the fish?
Benjamin Besse, IGR, Paris, France
12:45 Will we ever cure mNSCLC?
Egbert Smit, NKI-AvL, Amsterdam, the Netherlands

13:00 Adjourn
Veerle Surmont, UZ Gent, Belgium