

# Adrenocortical Carcinoma

**Alfredo Berruti**  
**Università degli Studi**  
**di Brescia**  
**ASST-Spedali Civili**  
**Brescia**



Sistema Socio Sanitario



Regione  
Lombardia

ASST Spedali Civili



## Disclosures

I received research funds for ACC from  
Janssen Cilag  
Sanofi  
Novartis  
Pharmamar

# ACC: epidemiology

- Annual incidence: (adult) 0.7-2.0 cases per million people per year  
Spain: 33 - 94 new cases every year
- Ratio Male/Female: 1 : 1.5
- Bimodal age distribution:
  - First peak < 10 years
  - Second peak 4°-5° decade (mean age 45)

# ACC: genomics and pathophysiology

## 9 Driver genes

**CTNNB1,**  
**ZNRF3**  
**TP53,**  
**RB1**  
**CDKN2A,**  
**MEN1**  
**DAXX,**  
**TERT**  
**MED12**

## 3 major pathways

**Wnt/beta catenin pathway**

(activating mutations in >30%)

**Insulin-like Growth Factor-2 (IGF-2)**

pathway (overexpressed in 90%)

**p53 pathway**

(inactivating mutations in >30%; allelic losses (LOH) in >85% )

## Journal Pre-proof

Adrenocortical carcinomas and malignant pheochromocytomas: ESMO-EURACAN  
Clinical Practice Guidelines for diagnosis, treatment and follow-up<sup>†</sup>

M. Fassnacht, G. Assie, E. Baudin, G. Eisenhofer, C. de la Fouchardiere, H.R. Haak,  
R. de Krijger, F. Porpiglia, M. Terzolo, A. Berruti, on behalf of the ESMO Guidelines  
Committee



## European guidelines

Ann Oncol. 2020 Aug 27  
Online ahead of print.

### Clinical Practice Guideline

M Fassnacht and others

Management of adrenocortical  
carcinoma in adults

179:4

G1-G46

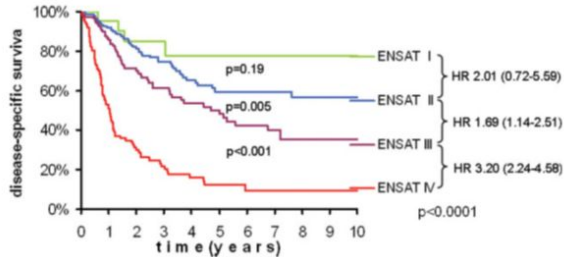
## European Society of Endocrinology Clinical Practice Guidelines on the management of adrenocortical carcinoma in adults, in collaboration with the European Network for the Study of Adrenal Tumors

Martin Fassnacht<sup>1,2</sup>, Olaf M Dekkers<sup>3,4,5</sup>, Tobias Else<sup>6</sup>, Eric Baudin<sup>7,8</sup>, Alfredo Berruti<sup>9</sup>,  
Ronald R de Krijger<sup>10,11,12,13</sup>, Harm R Haak<sup>14,15,16</sup>, Radu Mihai<sup>17</sup>, Guillaume Assie<sup>18,19</sup> and Massimo Terzolo<sup>20</sup>

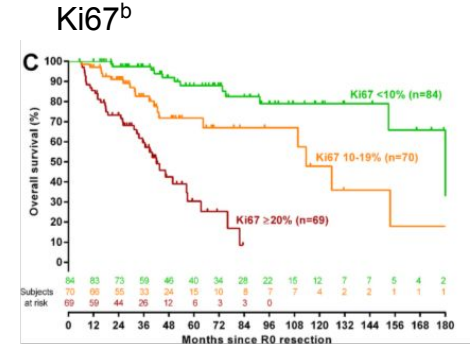
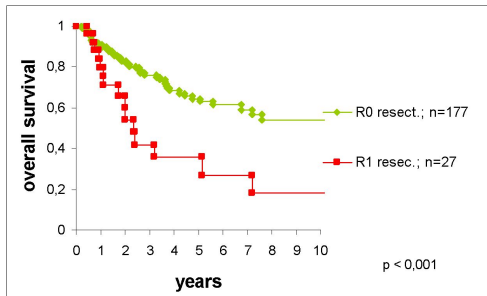
Eur J Endocrinol. 2018 Oct 1;179(4):G1-G46

# ACC Prognostic Parameters

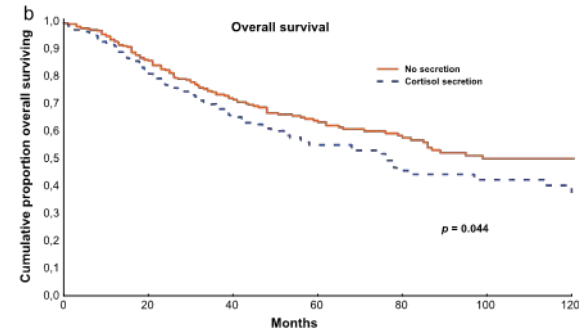
Disease Stage<sup>a</sup>



Radical Surgery<sup>c,d,e</sup>



Cortisol hypersecretion<sup>f</sup>



<sup>a</sup>Fassnacht M et al Cancer. 115(2):243-50; 2009; <sup>b</sup>Beuschlein F et al J Clin Endocrinol Metab. 100(3):841-9; 2015 <sup>c</sup>ACC German Registry, <sup>d</sup>Crucitti F et al Surgery 119(2):161-70; 1996 <sup>e</sup>Icard P et al Surgery. 112(6):972-9; 1992, <sup>f</sup>Berruti A et al. Eur Urol 65(4):832-8; 2014

# The GRAS\* prognostic score

\*Grade, Resection, Age, Symptoms

## AGE

< 50 Yrs: 0 points  
≥ 50 Yrs: 1 point

## Surgical Resection

R0: 0 points  
RX: 1 point  
R1: 2 points  
R2: 3 points

## ENSAT Stage

I – II: 0 points  
III: 1 point  
IV: 2 points

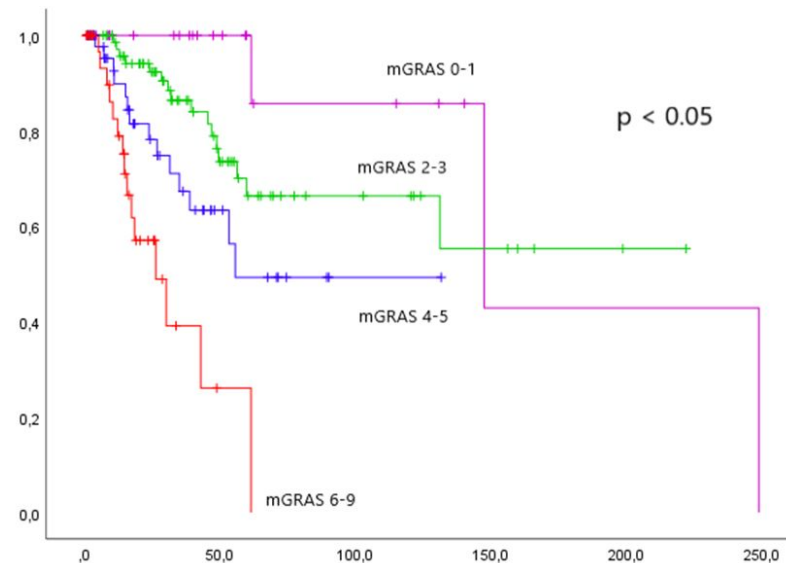
## KI67

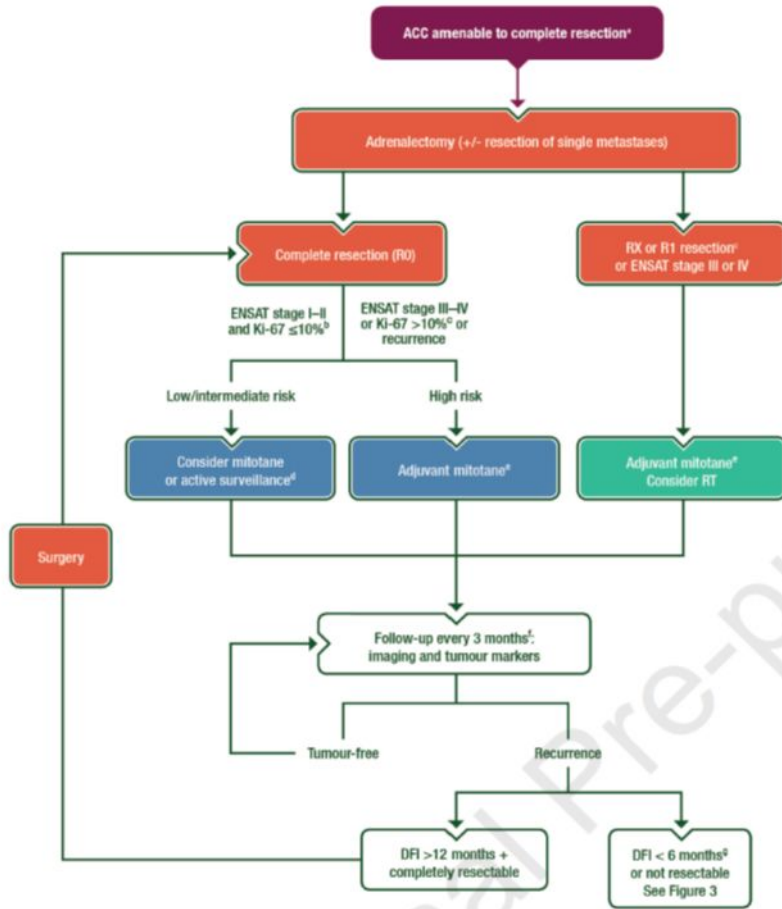
0 – 9%: 0 points  
10 – 19%: 1 point  
≥ 20%: 2 points

## SYMPTOMS

Absent: 0 points  
Present: 1 point

## The Brescia experience: 219 patients





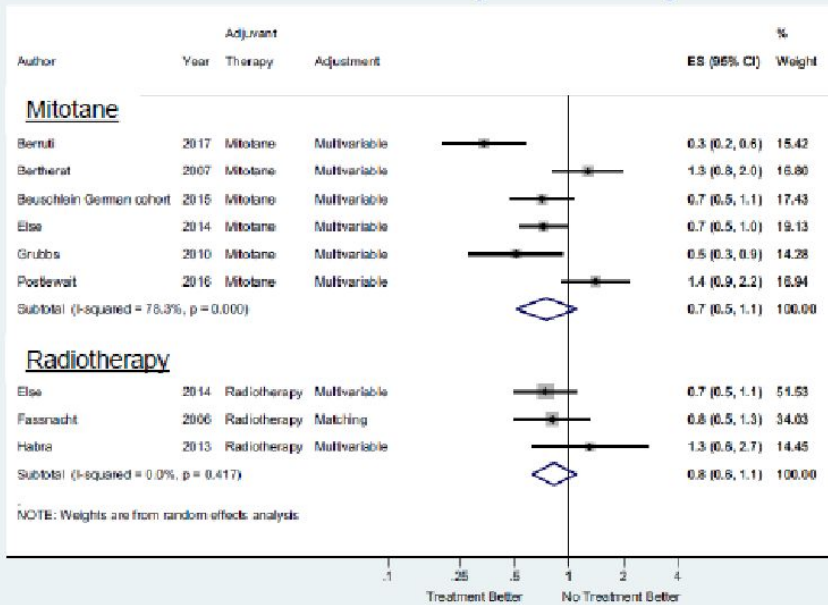
**Surgery is the mainstay of therapy**

**Adjuvant mitotane is recommended in patients with high/moderate risk of disease relapse and death**

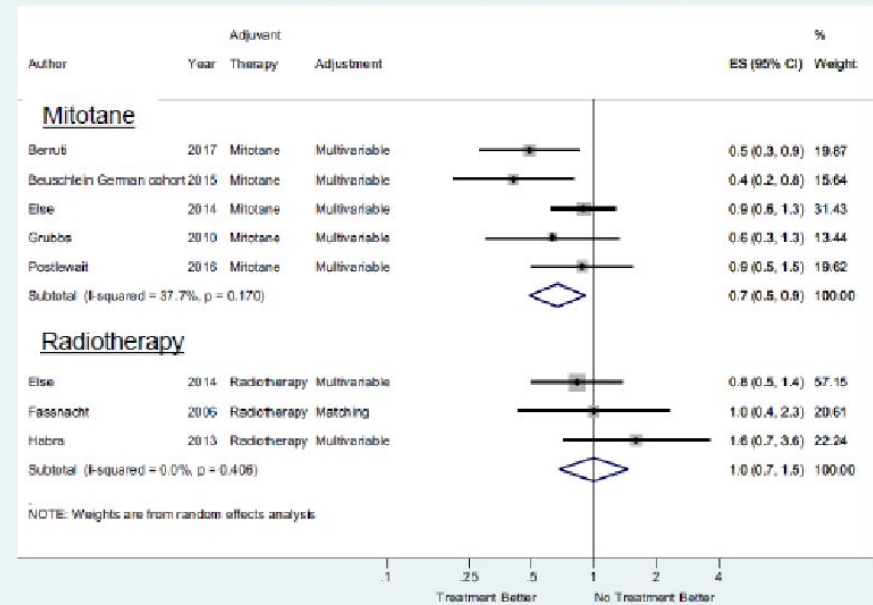
**Adjuvant radiation therapy an option in R1 disease**

# ACC: Adjuvant studies

**A** Recurrence in the adjuvant setting



**B** Mortality in the adjuvant setting



# Randomized Prospective Clinical Trials

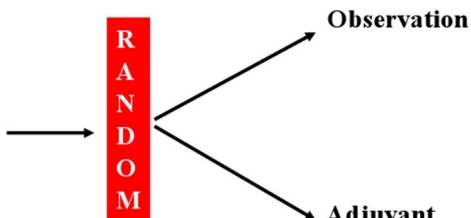
Low risk disease

**ADIUVO STUDY**  
[www.adiuvo-trial.org](http://www.adiuvo-trial.org)

Low-intermediate  
risk patients

- ✓ Stage I-III
- ✓ R0 resection
- ✓ Ki67  $\leq 10\%$

# patients 200

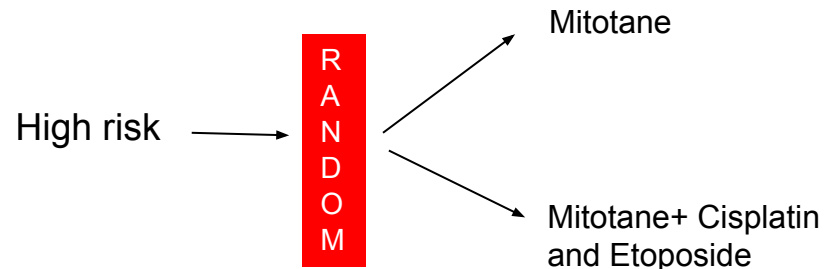


Primary endpoint: Recurrence Free Survival

Accrual closed, data expected soon

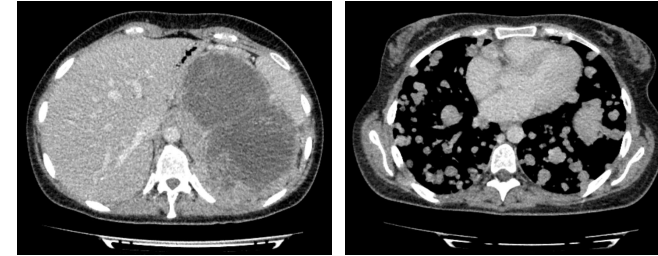
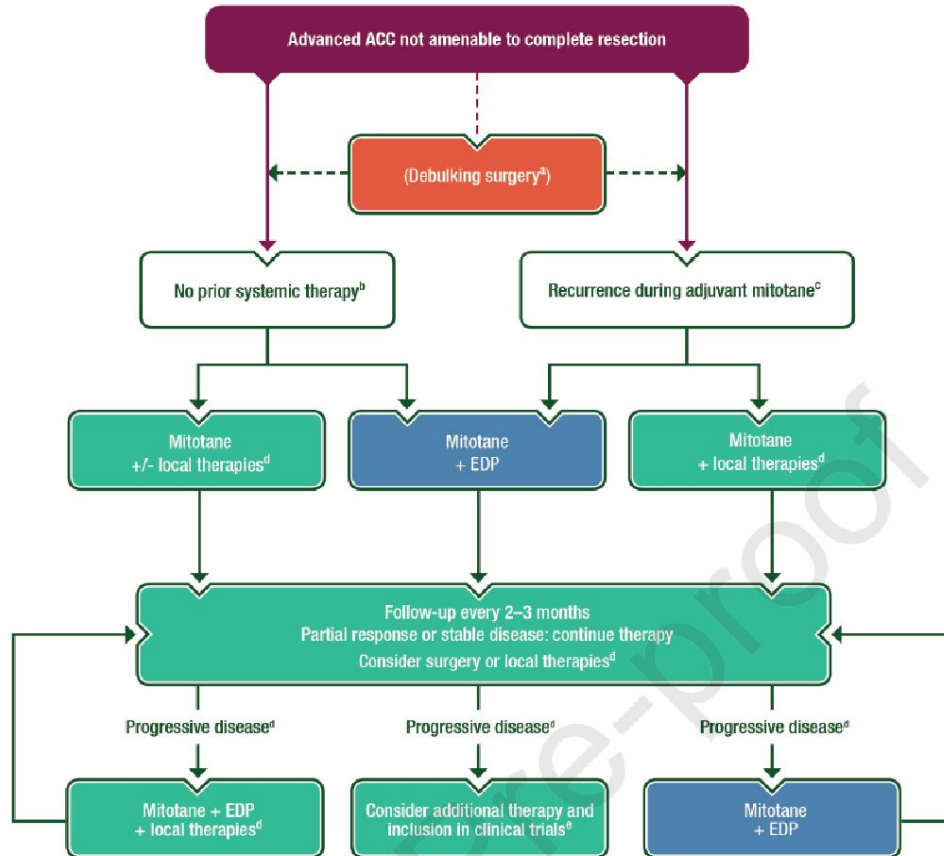
High risk disease

**ADIUVO 2**  
NCT03583710  
**ACACIA**  
NCT03723941



Recruiting

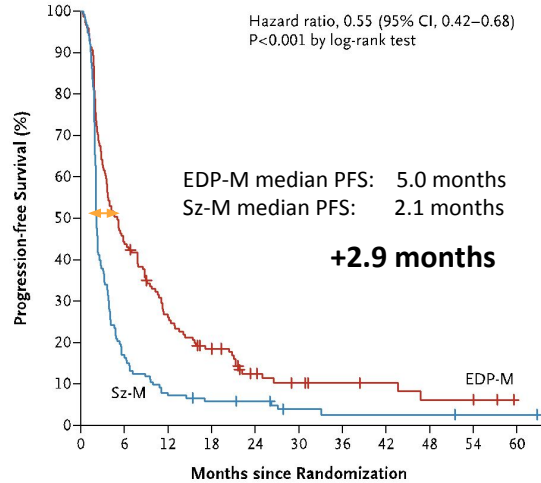
## Advanced/Metastatic disease



**Mitotane**  
or  
**Etoposide, Doxorubicin and Cisplatin**  
+ Mitotane (EDP-M)

# The FIRM-ACT trial: results

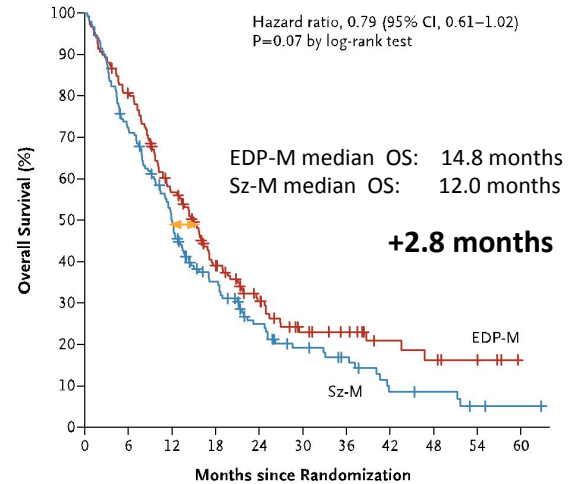
**A Progression-free Survival**



No. at Risk

|       |     |    |    |    |    |   |   |   |   |   |   |
|-------|-----|----|----|----|----|---|---|---|---|---|---|
| EDP-M | 151 | 66 | 38 | 25 | 12 | 8 | 6 | 5 | 3 | 2 | 0 |
| Sz-M  | 153 | 26 | 11 | 8  | 7  | 3 | 2 | 2 | 2 | 1 | 1 |

**B Overall Survival**



No. at Risk

|       |     |     |    |    |    |    |    |   |   |   |   |
|-------|-----|-----|----|----|----|----|----|---|---|---|---|
| EDP-M | 151 | 120 | 81 | 51 | 32 | 19 | 15 | 9 | 7 | 3 | 0 |
| Sz-M  | 153 | 109 | 72 | 44 | 27 | 18 | 13 | 6 | 5 | 2 | 1 |

# Molecular Target therapies in ACC

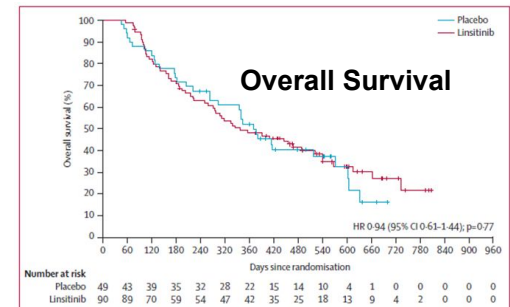
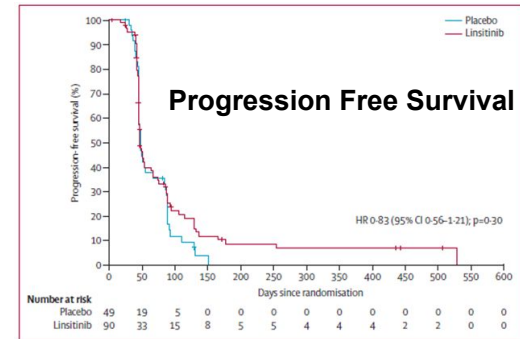
| Target        | Drug                        | Setting                 | Phase | No patients | Results                     |
|---------------|-----------------------------|-------------------------|-------|-------------|-----------------------------|
| EGFR          | Gefitinib                   | Advanced ACC pretreated | II    | 19          | No disease response         |
| EGFR          | Erlotinib + Gemcitabine     | Advanced ACC pretreated | II    | 10          | 1 minor response            |
| Angiogenesis  | bevacizumab capecitabine    | Advanced ACC            | II    | 10          | No disease response         |
| Angiogenesis  | sunitinib                   | Advanced ACC pretreated | II    | 36          | SD>4 months in 5 pts        |
| Angiogenesis  | Sorafenib Weekly paclitaxel | Advanced ACC pretreated | II    | 10          | PD in all pts               |
| Angiogenesis  | Axitinib                    | Advanced ACC pretreated | II    | 13          | No disease response         |
| IGF-1R        | Figitumumab                 | Advanced ACC pretreated | I/II  | 14          | SD $\geq$ 3 months in 6 pts |
| IGF-1R + mTOR | Cixutumumab temsirolimus    | Advanced tumours        | I/II  | 10 ACC      | SD $\geq$ 8 months in 4 pts |
| IGF-1R + mTOR | Cixutumumab temsirolimus    | Advanced ACC pretreated | II    | 26          | SD>6 months in 11 pts       |



**Linsitinib (OSI-906) versus placebo for patients with locally advanced or metastatic adrenocortical carcinoma: a double-blind, randomised, phase 3 study**

Martin Fasanacht, Alfredo Bernini, Eric Baudin, Michael J Demeure, Jill Gilbert, Harm Haak, Matthias Kroiss, David Quinn, Elizabeth Hesselting, Cristina L Ronchi, Massimo Terzola, Tonik Chouvet, Srinivasa Poondra, Tanya Flegge, Ramona Rorig, Jibong Chen, Andrew W Stephens, Francis Worden, Gary D Hammer

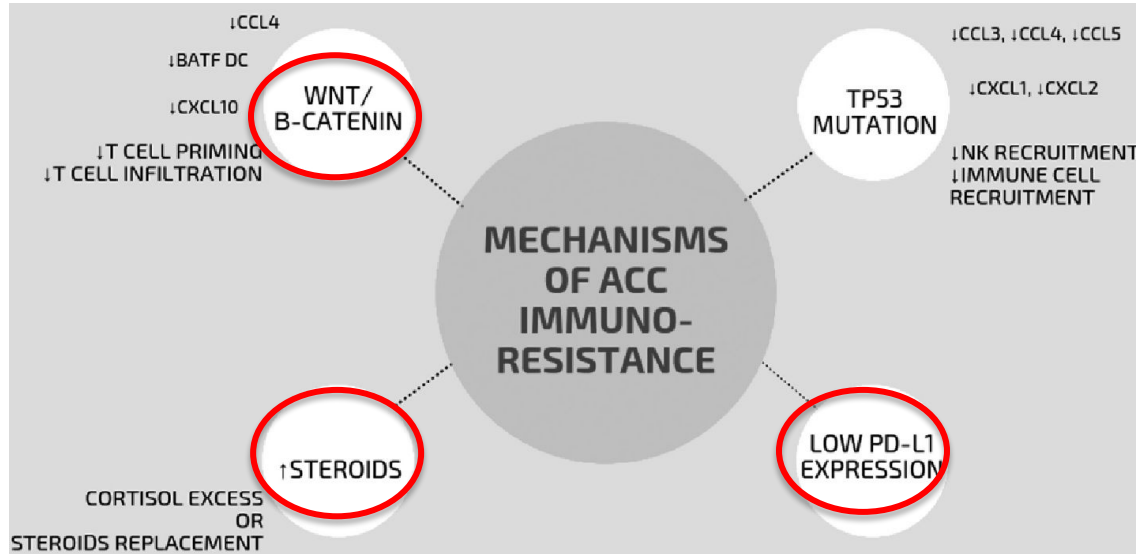
**Lancet Oncol 2015; 16: 426–35**



## Immunotherapy in ACC

| Author/y          | N. pts     | MSI-H %   | PD-L1 (score≥1%) (%) | TIL (score≥1) (%) | m-Pr ev. Lines | Agent | Concomit Mitot | ORR (%)         | SD (%)          | m-PFS (mo)  | m-OS (mo)              |
|-------------------|------------|-----------|----------------------|-------------------|----------------|-------|----------------|-----------------|-----------------|-------------|------------------------|
| LeTourn eau/ 2018 | 50         | NR        | 15/42 (30)^          | NR                | 2              | Avelu | 25/50 (50%)    | 3 (6)           | 21 (42)         | 2.6         | 10.6                   |
| Raj/ 2019         | 39         | 6/38 (16) | 7/34 (21)^           | 39/39 (100)       | 1              | Pembr | No             | 9 (23)          | 7 (18)          | 2.1         | 24.9 (4.2-Not reached) |
| Habra/ 2019       | 14         | 0/12 (0)  | 0/14 (0)             | 13/14 (93)        | 2              | Pembr | No             | 2 (14)          | 7 (50)          | NR          | NR                     |
| Carneiro /2019    | 10         | 0/5 (0)   | 6/10 (60)            | 6/6 (100)         | 1              | Nivo  | Yes            | 1 (10)          | 2 (20)          | 1.8         | 21.2                   |
| <b>Total</b>      | <b>113</b> |           |                      |                   |                |       |                | <b>15 (13%)</b> | <b>37 (33%)</b> | <b>2.35</b> | <b>18.7</b>            |

## Mechanisms of primary resistance of ACC to immunotherapy



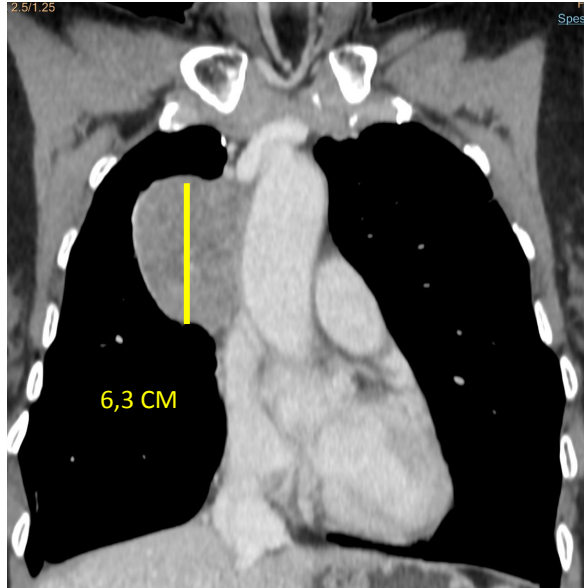
## How can we best use the EDP-M regimen

If possible, do not reduce the doses

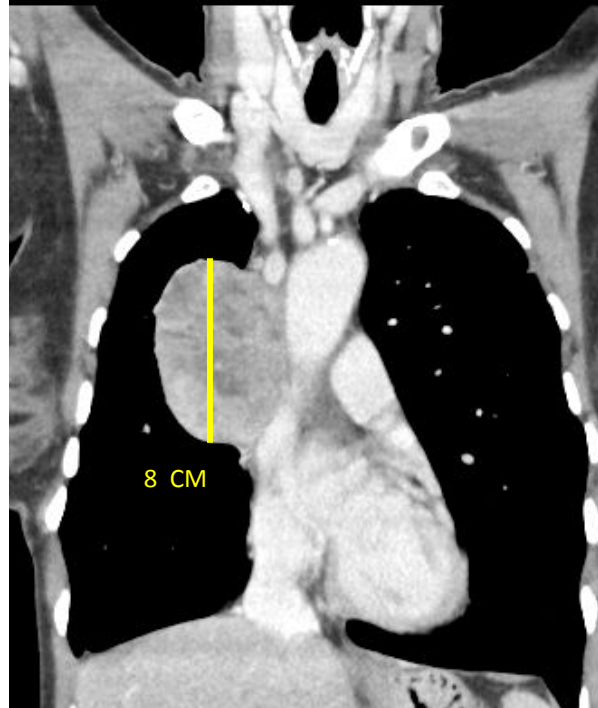
Disease progression after 2-3 months does not necessarily mean failure

Use both RECIST and CHOI criteria in the definition of response

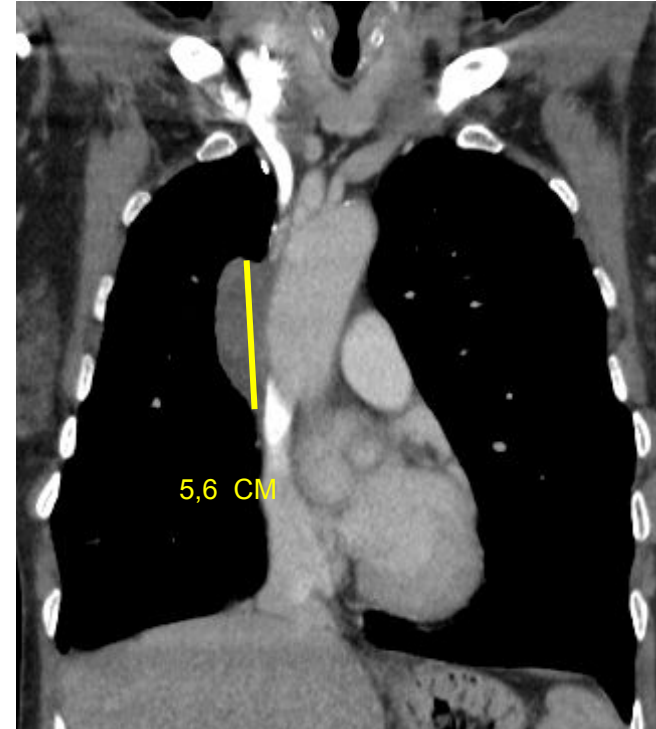
Consider debulking surgery, if residual disease after surgery  $\leq 10\%$



NOVEMBER 21 2018



FEBRUARY 13 2019 AFTER 3 EDP-M CYCLES

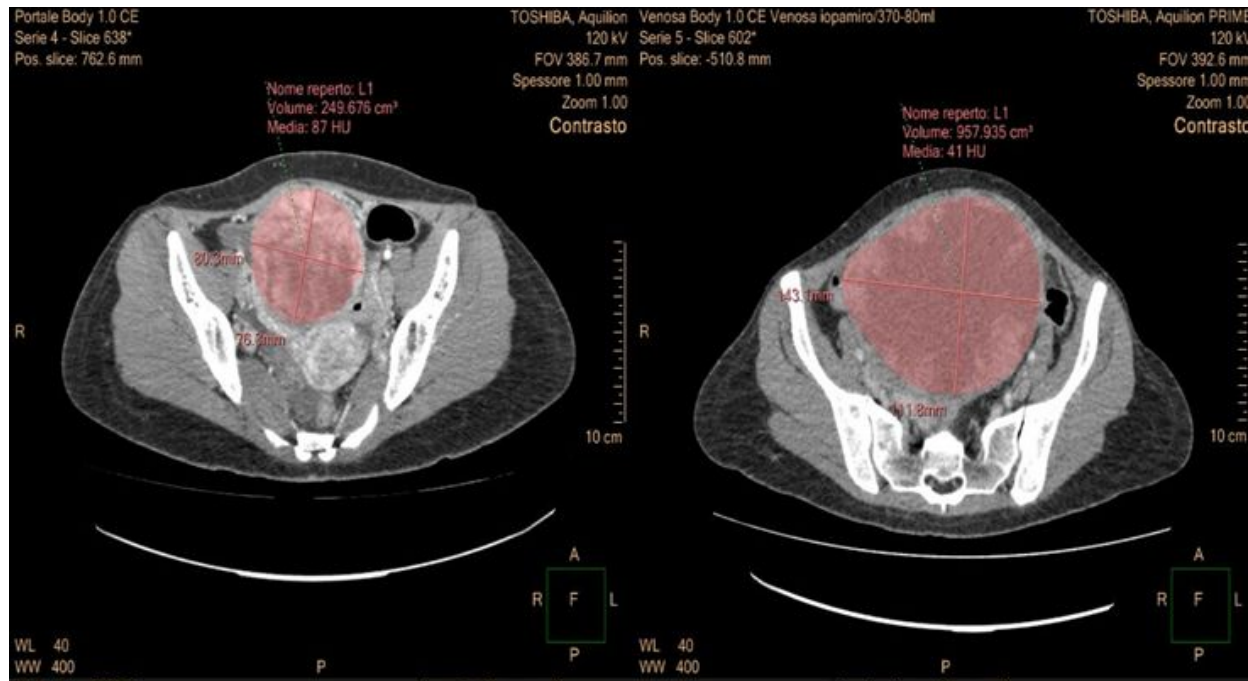


June 29 2019 after 6 EDP-M cycles

Surgery of residual disease:  
Pathological Complete  
Response



## ACC response to EDP-M: consider also CHOI criteria



# Conclusions

The management of patients with adrenal cortical carcinoma is challenging and requires an experienced multidisciplinary group

We should not be pessimistic and fight together with our patients



# THANK-YOU



[alfredo.berruti@unibs.it](mailto:alfredo.berruti@unibs.it)

SPEDALI CIVILI DI BRESCIA  
AZIENDA OSPEDALIERA



Sistema sanitario Regione Lombardia



## Brescia Adrenal FANS



**Wellcome to Brescia next year (hopefully)**

