




## Shining a Light on Rare Forms of Bladder Cancer

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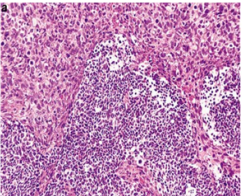

### Rare Forms of Bladder Cancer: Small Cell Carcinoma

**Dr. Apolo:** These occur in about 1% of bladder cancers in pure form, but generally these are mixed. These are mixed with urothelial carcinoma. But if there's any small cell component within that specimen, we treat it as a small cell carcinoma because it behaves more aggressively. And the treatment for small cell that we use for other tumor types, like lung cancer, seem to work better than the treatments that we give for regular urothelial carcinoma of the bladder. These tumors are associated with smoking. Again, these are aggressive tumors. 94% of

these present as muscle-invasive disease and 67 of them have systemic metastases. And these can include the lymph node, the lung, the liver, the bone, and the brain. The patients, after their treatment, they can develop metastases in the brain, especially in patients with high, bulky tumors.

#### Small Cell Carcinoma of the Bladder

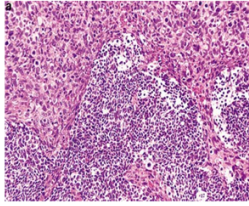
- Associated with smoking
- <1% of bladder cancer in pure form (>50% of cases are mixed)
- Aggressive biology even with small focus of small cell carcinoma
- 94% with muscle-invasive disease
- 67% with systemic metastases
  - Lymph node, lung and liver, and also bone and brain
- Brain relapses may occur in patients with bulky, high-stage tumors

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## Small Cell Carcinoma of the Bladder

- Systemic at presentation with early microscopic metastasis, rapid progression and poor outcome
- Neoadjuvant chemotherapy with cisplatin and etoposide based regimens followed by cystectomy for both muscle-invasive and non-muscle-invasive disease
- Chemoradiation for those unable to undergo cystectomy
- Brain imaging given high risk for metastases
  - Clinical trial with prophylactic cranial radiation



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So again, these tumors, we think of these as systemic tumors that grow very rapidly. But because they grow very fast, they also respond really well to chemotherapy. So, they actually shrink with standard chemotherapy. And the chemotherapy that we use, we borrow from the lung cancer literature. So, there was a study done at MD Anderson where they gave neoadjuvant chemotherapy with a small cell lung cancer regimen of cisplatin and etoposide. And they found that if the patients received chemotherapy before having the surgery,

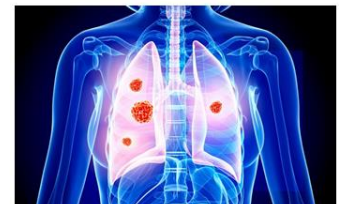
the radical cystectomy, those patients did a lot better than waiting until afterwards or not getting it at all. If the patient cannot have a cystectomy, cannot have surgery after they receive the chemotherapy and their disease is localized, it's a localized disease, chemoradiation is an option for definitive therapy for localized disease. But it's important then when these patients are managed, even in the localized muscle-invasive setting, they still have brain imaging because there is a chance for a spread into the brain and brain metastases.

For lung cancer, sometimes a prophylactic cranial radiation is given. So that means even though there's no brain metastases, radiation is given anyway to the brain to prevent, or if there's any micro metastases that are there, they're eradicated before they form into something substantial. That is not the case for bladder cancer. We just don't have any evidence that doing that makes a difference. That is not a practice done for small cell bladder cancer.

So, I'm going to tell you a little bit about some recent data in lung small cell carcinoma. And the reason this is important is because we borrow from lung small cell carcinoma for small cell carcinoma of the bladder. So there was a study called CheckMate 032 in lung cancer patients, where they were treated with two immunotherapies. One, a newer generation, and one older generation of nivolumab plus ipilimumab. And there were different dosages that were given. This is 216 patients.

Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicenter, open-label, phase 1/2 trial

- 216 patients:
  - N=98 Nivo3 mg/kg      ORR=10%
  - N=3 Nivo1/Ipi1      ORR=33%
  - N= 61 Nivo1/Ipi3      ORR=23%
  - N= 54 Nivo3/Ipi1      ORR=19%



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98 patients were treated just with the nivolumab by itself at a dose of three mgs per kilogram. Three patients were treated with nivolumab one milligram. Ipi means ipilimumab, and they received one milligram of ipilimumab. 61 patients were treated with nivolumab one milligram, and ipilimumab three

milligrams per kilo. These were just different dosages to see which ones had the higher activity. And 54 patients were treated with nivolumab three mgs per kilogram, and ipilimumab one mg per kilogram. And really the point of this trial is to show the activity, and this was after they had received chemotherapy. And what this study showed is that immunotherapy, which is now a new pillar for treatment of patients with multiple different cancers, was also active in small cell lung cancer. So, that was an important trial in small cell lung cancer.

And kind of building on this work, there was a large trial of 400 patients, in small cell lung cancer, that tried to move it up a little bit earlier and include it with the chemotherapy. So basically in this trial, called IMpower133, patients with small cell lung cancer were randomized to receive immunotherapy, this is atezolizumab with chemotherapy or chemotherapy with placebo, to see how these patients did. And based on the results of this trial, checkpoint inhibitor, which is an immunotherapy atezolizumab, is now approved in combination with chemotherapy for small cell lung cancer. Next slide.

And these are the results. The median survival for the patients that got the immunotherapy plus the chemotherapy was 12.3 months. For the patients that only got the chemotherapy with the placebo, it was 10.3 months. So there was a two month improvement in overall survival. And in terms of how quickly the cancer came back in the patients that received the immunotherapy, the atezolizumab plus the chemo, the patients were cancer-free for 5.2 months. And the patients that only got the chemo were cancer-free for about 4.3 months. So, not as significant as the survival benefit, but there was a little bit of an improvement in the time that the cancer came back. And in terms of the response rate, there was really no difference. This is the measurement of the tumor shrinking. The tumor shrank in both arms; 60% in the immunotherapy arm, and 64% in the chemotherapy arm. So, adding the immunotherapy to the chemotherapy did not improve the response rate, but did improve the survival.


### Adopting from Small Cell Lung Carcinoma



- March 18, 2019, FDA **atezolizumab in combination with carboplatin and etoposide**, for the first-line treatment of patients with extensive-stage small cell lung cancer (ES-SCLC).
- IMpower133 (NCT02763579), a randomized (1:1), multicenter, double-blind, placebo-controlled trial in 403 patients with ES-SCLC who received no prior chemotherapy
  - atezolizumab + carboplatin/etoposide every 21-day for 4 cycles, then atezolizumab every 3 weeks
  - placebo + carboplatin/etoposide every 21-day for 4 cycles, then placebo every 3 weeks

N Engl J Med 2018

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## Adopting from Small Cell Lung Carcinoma



- Median overall survival was
  - **12.3 months** for patients receiving atezolizumab+ chemotherapy vs **10.3 months** for those receiving placebo +chemotherapy
- Median Progression Free Survival was
  - **5.2 months** compared with **4.3 months**
- ORR same 60 vs 64%

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And this led to FDA approval of combination immunotherapy plus chemotherapy for the first-line treatment of small cell lung cancer. And I think that until we have more data in bladder cancer, it is reasonable to apply this to small cell lung cancer in terms of the primary treatment. And there are ongoing trials right now. There's one with pembrolizumab given with carboplatin, cisplatin, and etoposide in patients with small cell bladder cancer to see the effects. But of course, this is a phase one, smaller

study because doing these large 400-patient trial studies, is almost impossible in such a rare form of bladder cancer with only less than 1% of all bladder tumors being small cell, it's really hard to do such a large randomized perspective trial as was done here for lung cancer.

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