# “A CASE OF VULVAL MELANOMA”


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# Initial Presentation: June 2017

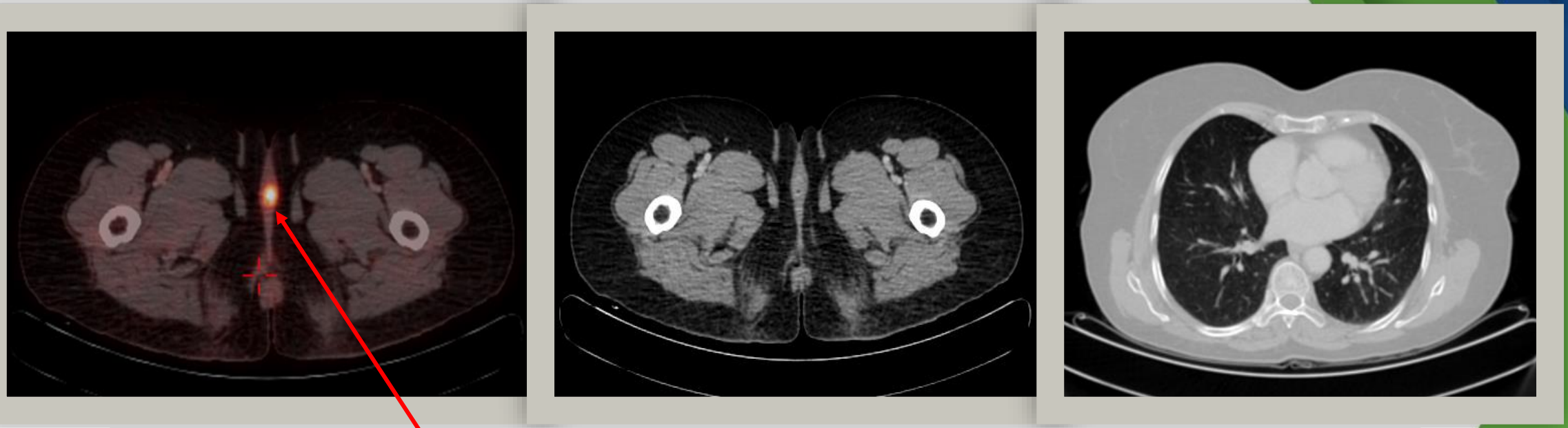
- 60 years lady , G7P7L5 ,without any comorbidities, resident of rural Uttar-pradesh , India
- Presented with the complaints of pruritus in external genitalia

  for ~an year
- Nothing was significant in family , medical and/or or personal history

**On examination :**

- She was, ECOG-PS 1,No lymphadenopathy ,Per abdomen –NAD
- P/S – lesion(black) involving clitoris, adjacent labia majora, involving urethral meatus and vagina

# 2017:PET-CT Scan



Hyper-metabolic vulval lesion(SUV max 15.62 )
No evidence of metastatic disease elsewhere

# Vulva biopsy showing dermal tumour

## FINAL HISTOPATHOLOGY REPORT

30-05-2017

**Microscopic Description**

Vulva punch biopsy (2 stained slides):

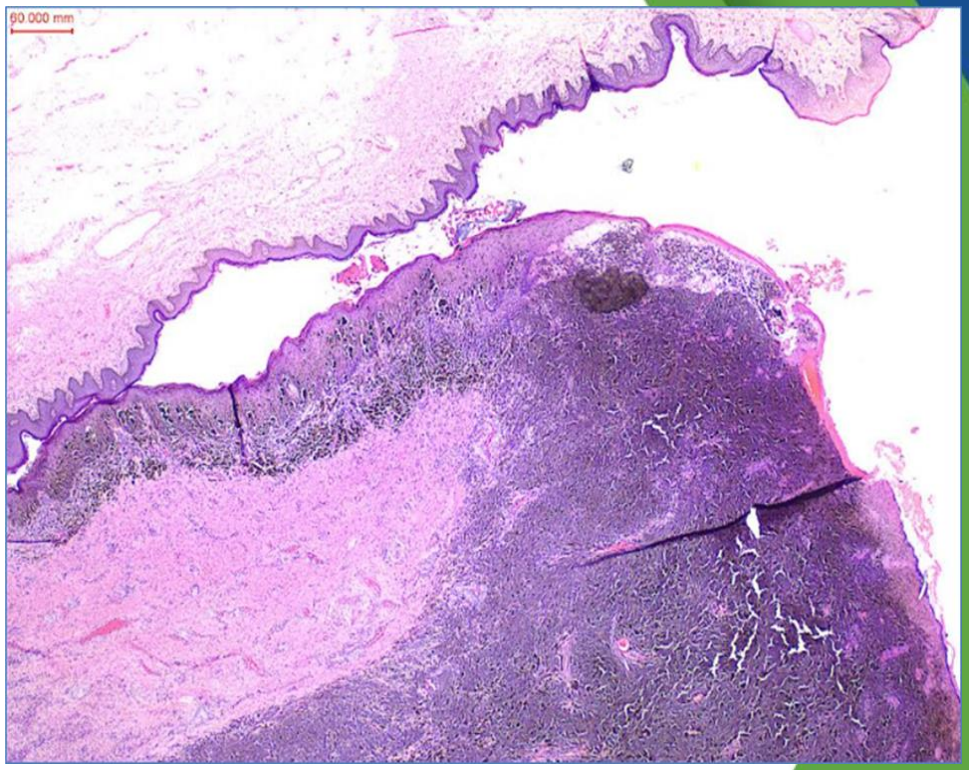
The section reveals a tumor arranged in diffuse pattern. The tumor cells are large plump to spindle with vesicular nuclei and prominent eosinophilic nucleoli.

There is prominent intracellular granular brown pigment seen.

**Impression**

**Vulva punch biopsy (2 stained slides):**

**Melanotic malignant melanoma**




**Pap smear** - bacterial vaginosis. Negative for intraepithelial lesion or malignancy

# Treatment Received

- She underwent Radical Wide Local Excision Of Vulval Lesion With Distal Urethrectomy + Left Sentinel Groin LN Dissection on 8/6/17at TMH

- Post-operative –received Adjuvant ,whole Pelvic RT

(Tumor bed+medial groin nodes+Illiac nodes), using 6 mv photons, 3 d CRT technique, dose- 50Gy/25# **(LD 22/8/17)**

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Nature of Material: 1) Anterior hemivulva with knot at 12 o clock & distal urethra approximated, 2) Left sentinel lymph node

## FINAL HISTOPATHOLOGY REPORT

15-06-2017

**Frozen Section**

FS 1) Sentinel lymph node: Single lymph node bisected, measuring 2.5x1.0x1.0cm. Cut surface fatty.
FS 1) Diagnosis: Single reactive node (0/1).

Dr. Rajiv Kumar.

**Gross Description**

Received a specimen of anterior hemivulva with knot at 12 o Clock position measuring 6x4x2cm.
Blackish tumour is seen measuring 2x1x1cm, involving clitoris and labia majora.
The distances from various cut margins:
Skin cut margin: 1.2cm, Inferior mucosal cut margin: 1.3cm, Right lateral mucocutaneous cut margin: 3cm, Left lateral mucocutaneous cut margin cut margin: 2.5cm, Base: 0.9cm.

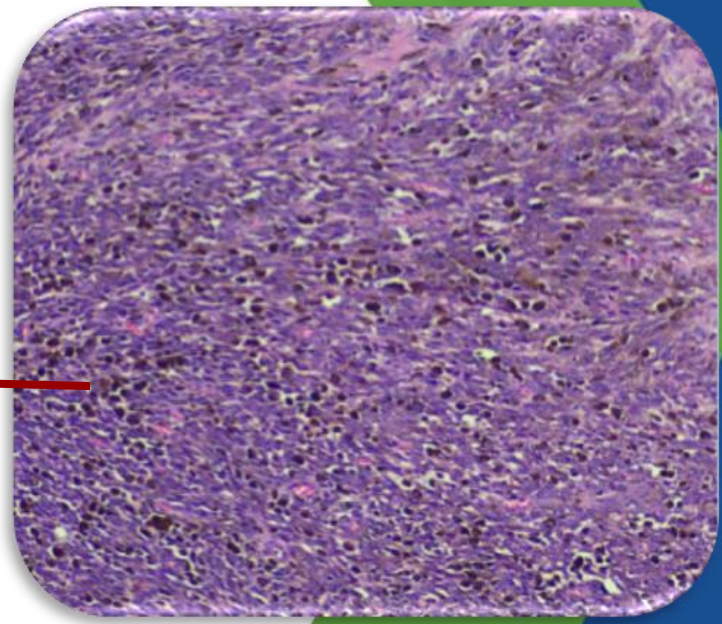
Sentinel lymph node: No lymph node is identified, fibrofatty tissue, submitted entirely.

Sections: 1-4) Tumour, 5) Superior skin cut margin, 6) Inferior mucosal cut margin, 7) Right lateral mucocutaneous cut margin, 8) Left lateral mucocutaneous cut margin, 9) Sentinal lymph node (submitted entirely), 10- 11) FS I.

**Microscopic Description**

Anterior hemivulvectomy:

Multiple sections examined show malignant melanoma involving clitoris and labia majora of vulva.
Prominent melanin pigment is seen.
Maximum depth of invasion of tumour in the stroma is 0.7cm.
Features of lentigo maligna are seen lateral to the main tumour.
Significant inflammatory reaction is not seen.
Lymphovascular emboli are not seen.
Base, skin cut margins, inferior mucosa cut margin, right lateral mucocutaneous cut margin and left lateral mucocutaneous cut margin are free of tumour.



Sentinel lymph node: Single reactive node (0/1).(as sampled in frozen section)

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**Anterior hemivulvectomy:**

**Malignant melanoma of vulva.**

# On Follow-up..

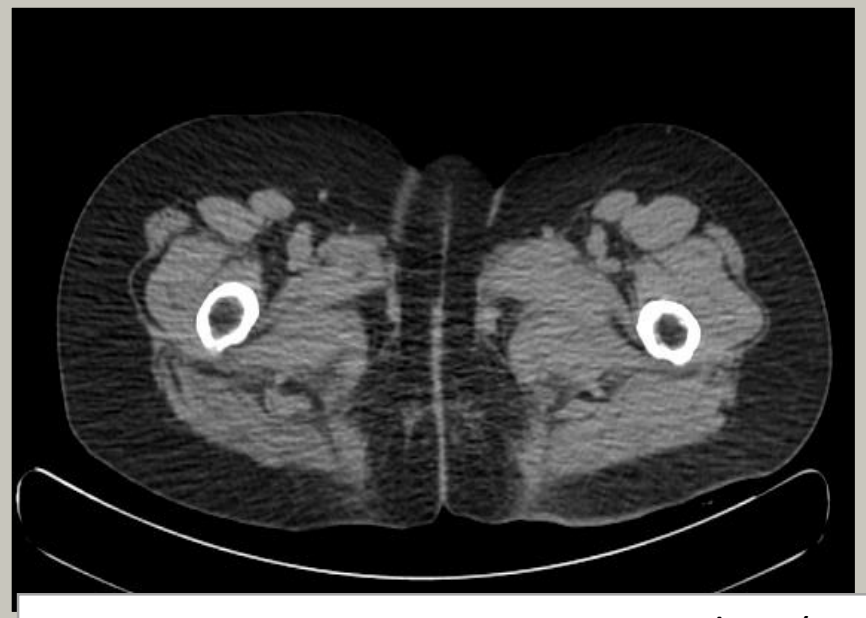
**June 2019(~2 year DFI)** :

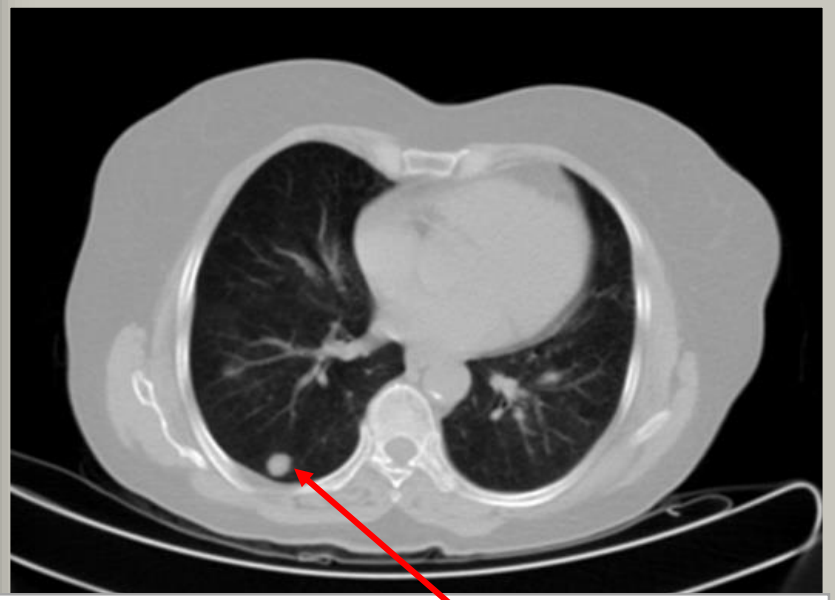
- Presented with complaints of weakness and pain in left lower limb investigate –S/O fracture Right Transcervical Neck of femur , and underwent right TKR

**PET-CT:**

- No metabolically active lesion is seen at the post operative site,
- **Metabolically active lung nodes** are highly suspicious for metastasis ,needs further pathological confirmation.
- Hypermetabolic activity along right femur fracture is suggestive of ongoing active inflammation at the site.

# JUNE 2019





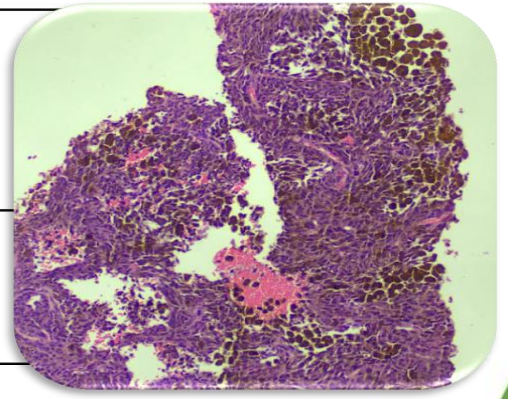
Post surgery and RT (completed in August 2017)-
no evidence of residual disease in the vulva. New onset metastatic lung nodules.

**FINAL HISTOPATHOLOGY REPORT** 03/09/2019

**Nature of Material Received:** 1 Biopsy

**Gross Description:**

Received multiple cores aggregating to 0.5x0.3cm, submitted entirely.



**Impression:**

- **Right Lung-Biopsy :**
  - **Metastatic malignant melanoma,, in a known case**

# Management

- Not affording for standard ICI therapy
- Started on Paclitaxel+carboplatinum
- After 3 cycles –PR

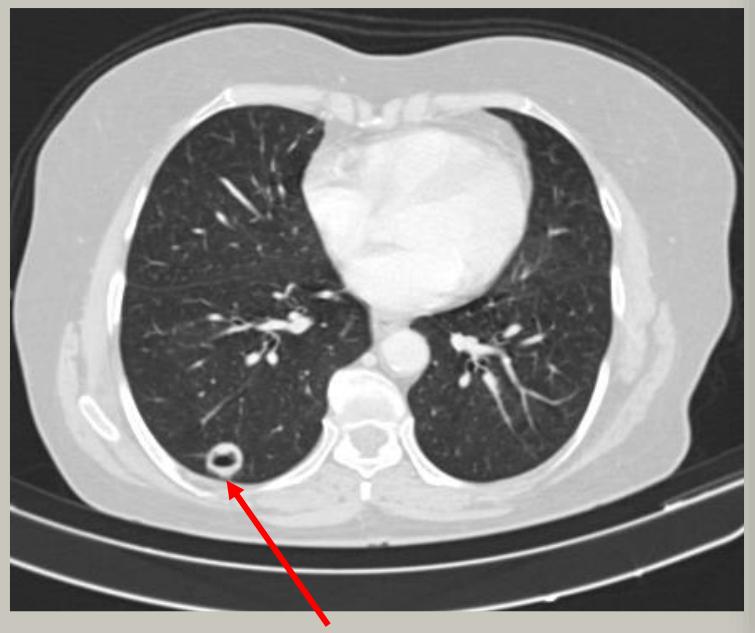
DMG : DMG - GYNEC ONCOLOGY
Service Desc CT Thorax & Abdomen & Pelvis
Reqn Date : 30-10-2019
Provisional Diagnosis 0000000000000000000

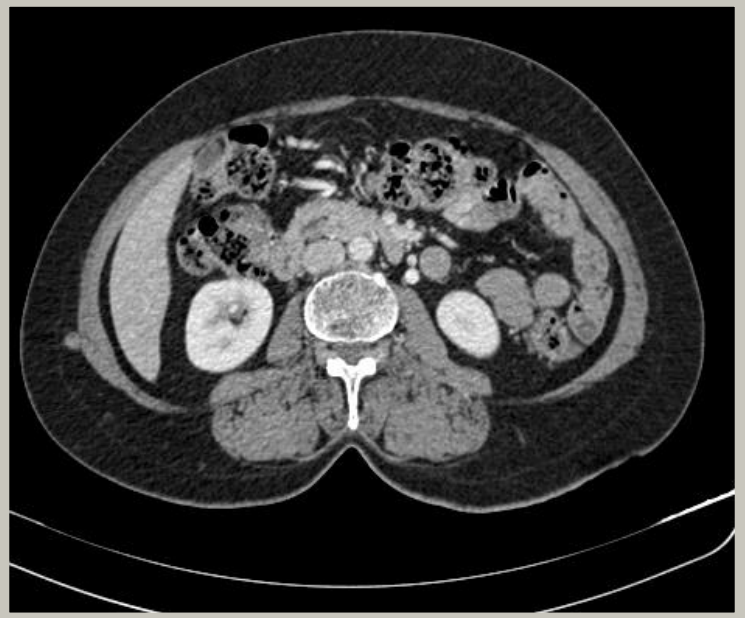
**Final Report** Report Date : 08-11-2019

THORAX:
Few (2) well defined nodules with cavitation are seen in the left lower lobe, largest measuring 16x13mm
The lungs and pleural spaces are clear.
No significantly enlarged mediastinal, hilar or axillary nodes seen.
Trachea and main stem bronchi are normal.
Heart and mediastinal great vessels are unremarkable.

- Los to follow-up for ~ an year
- In b/w-Received 3 more cycles of Paclitaxel+carboplatinum- till Aug 2020
- **Presented in Dec 2020 –Progressive disease**

# 2020





Service Desc CT Thorax & Abdomen & Pelvis

Reqn Date : 03-12-2020

Provisional Diagnosis 0000000000000000000

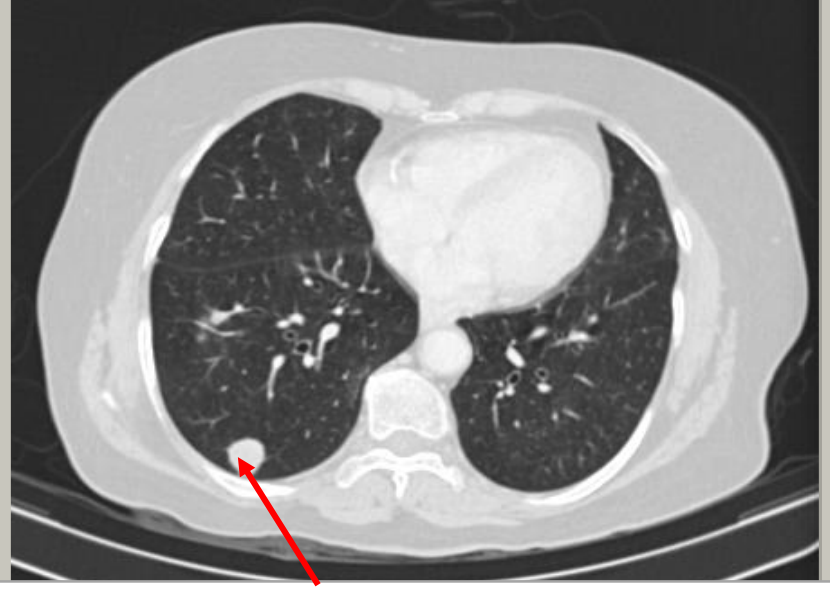
**Final Report**

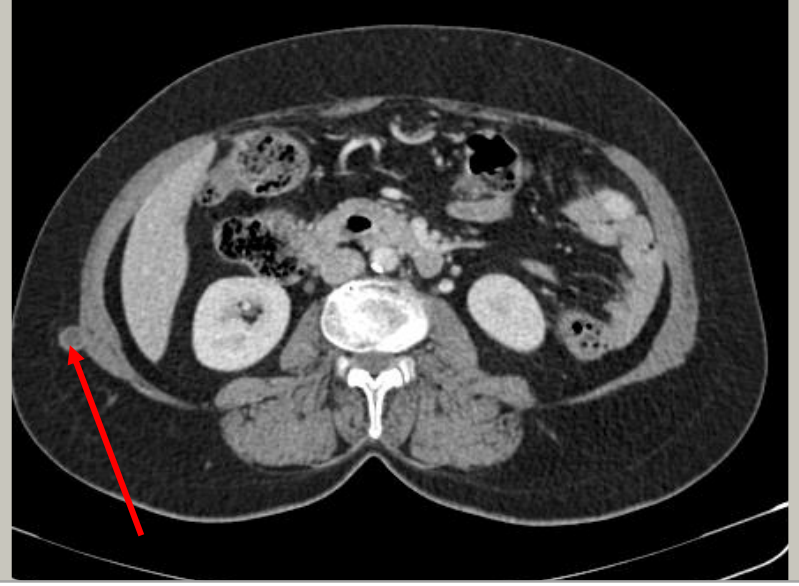
Report Date : 17-12-2020

CT reveals,

- Increase in size with change in morphology of right lower lobe pulmonary lesions with new onset sub-centimeter nodules in the vicinity, likely metastatic.
- New onset subcutaneous enhancing nodules in right lateral thoracic and abdominal wall, suspicious for metastatsis.

**Jan 2021**

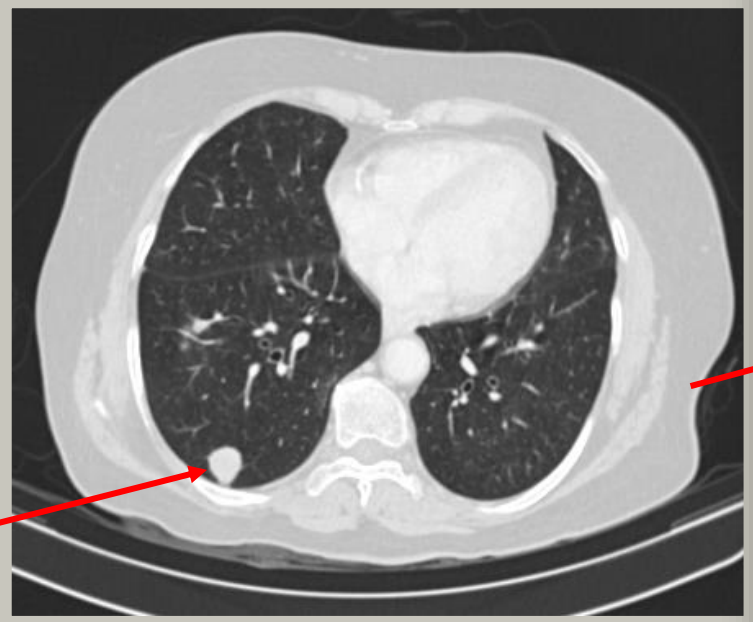


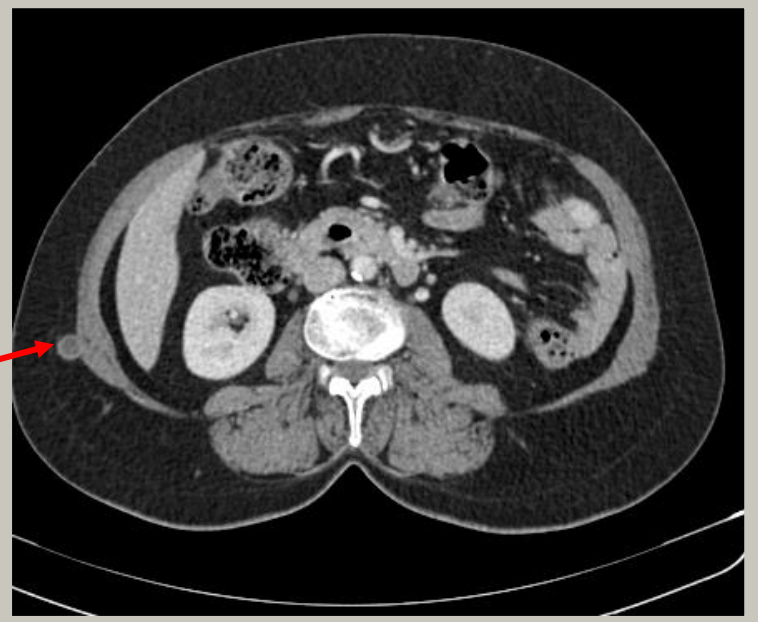


**Started on Pembrolizumab: (Clinical Trial )**

Interval increase in size of abdominal wall deposits.
Solidification with increase in size of metastatic lung nodules.

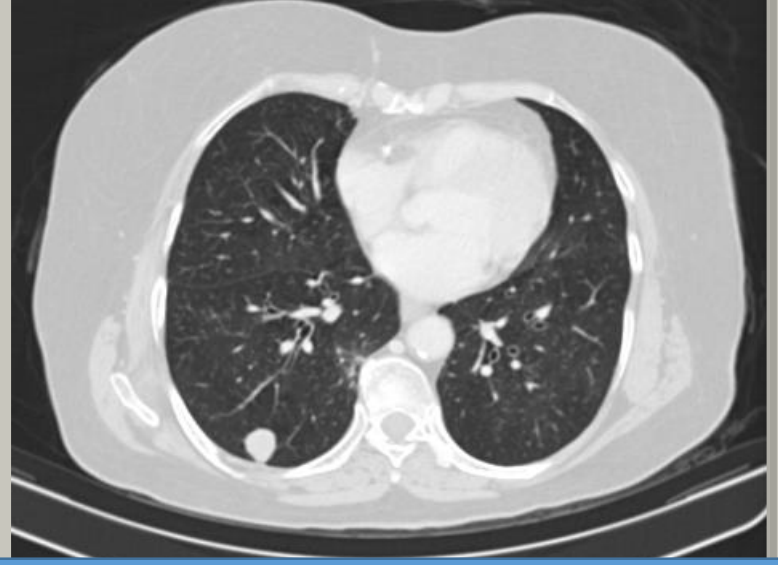
**JULY 2021**

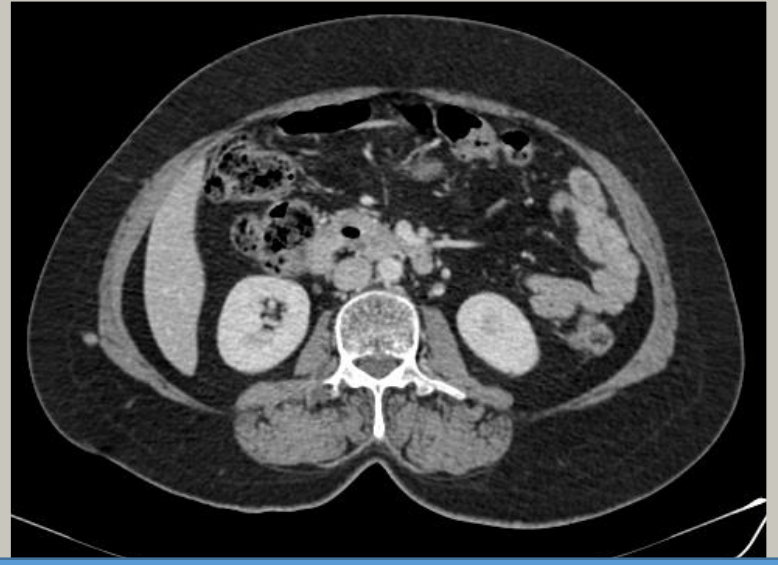




**“Stable disease”**

2022

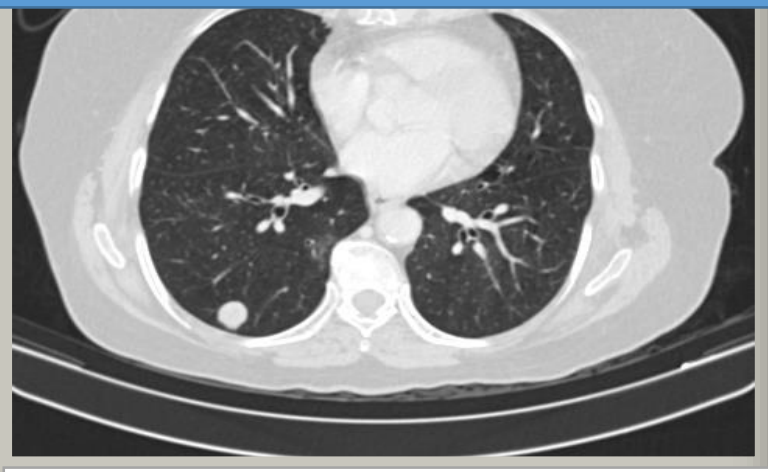


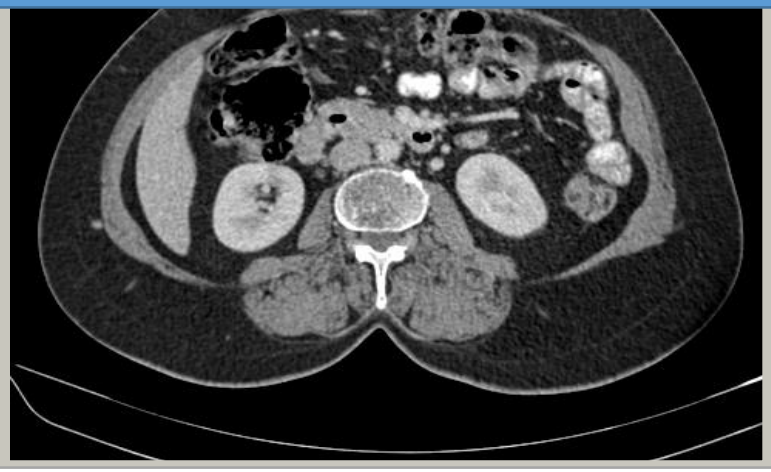


“Stable disease”

- Recurrent , metastatic melanoma , post chemotherapy failure , SD on Pembrolizumab, completed 35 cycles (LD Jan,2023) now on follow up , last sacn in June 23-SD
- Toxicity = Grade I Vitiligo

2023





“Stable disease”

Interval decrease in size of abdominal wall deposits.
Stable metastatic lung nodules.

# Take Home Messages

Journal for ImmunoTherapy of Cancer

# Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of gynecologic cancer

*J Immunother Cancer* 2023;**11**:e006624. doi:10.1136/jitc-2022-006624

Mary L Disis [1], Sarah F Adams,[2] Jyoti Bajpai [3,4], Marcus O Butler,[5] Tyler Curiel [6], Shelley A Dodt,[7] Laura Doherty,[8] Leisha A Emens [9], Claire F Friedman [10,11], Margaret Gatti-Mays [12], Melissa A Geller [13], Amir Jazaeri [14], Veena S John [15], Katherine C Kurnit [16], John B Liao [17], Haider Mahdi,[18] Anne Mills,[19] Emese Zsiros [20], Kunle Odunsi [21]

## Expert Panel recommendations

Considerations of treatment options listed below are based on expert consensus (unless a LE is noted) as there are very few data for these rare tumors.

- For all patients with rare gynecologic malignancies, clinical trial enrollment should be offered, as feasible.
- For all patients with rare gynecologic malignancies, testing for TMB-H and MSI-H by NGS (preferred) and MMR by IHC (as an alternative) is recommended, for potential treatment under tissue-agnostic indications for ICIs (LE:3). For patients with rare gynecologic malignancies, testing for PD-L1 by IHC may be considered (LE:4).

# Vaginal and Vulvar cancers

## Vaginal and vulvar cancers

- For previously treated patients with recurrent or metastatic vulvar or vaginal squamous cell carcinoma, second-line treatment with pembrolizumab (for patients with PD-L1-positive/TMB-H/MSI-H/dMMR tumors) or nivolumab (for patients with HPV-related tumors) should be considered (LE:3).
- For patients with unresectable/metastatic vulvar or vaginal melanoma, treatment can follow the standard of care treatment paradigms for cutaneous melanoma.
- For patients with locally advanced vulvar or vaginal melanoma with high risk of recurrence, adjuvant treatment with an anti-PD-1 ICI with or without an anti-CTLA-4 ICI may be considered.

## Other rare gynecologic cancer variants

- For patients with uterine sarcoma who have exhausted other treatment options, biomarker-driven (ie, dMMR, TMB-H, or MSI-H) treatment with an anti-PD-1 ICI may be considered.
- For patients with previously treated rare epithelial endometrial tumors, second-line treatment with combination pembrolizumab plus lenvatinib should be considered.

## Gestational trophoblastic neoplasia

- For patients with recurrent GTN with prior chemotherapy treatment, treatment with an anti-PD-(L)1 ICI may be considered (LE:3).

# Access of Immunotherapy: Real World Scenario

## Advanced Melanoma –Management

frontiers in Oncology

ORIGINAL RESEARCH
published: 08 September 2021
doi: 10.3389/fonc.2021.710585

# Demographics, Pattern of Care, and Outcome Analysis of Malignant Melanomas - Experience From a Tertiary Cancer Centre in India

*Jyoti Bajpai[1]*, George Abraham[1], Avanish P. Saklani[2], Anshul Agarwal[1], Sashanka Das[1], Ambarish Chatterjee[2], Akhil Kapoor[1], Prathyusha Eaga[1], Pradip Kumar Mondal[1], Arun Chandrasekharan[1], Prabhat Ghanshyam Bhargava[1], Sujay Srinivas[1], Siddharth Turkar[1], Bharat Rekhi[3], Nehal Khanna[4], Amit Kumar Janu[5], Munita Bal[3], Vikas Sureshchand Ostwal[1], Anant Ramaswamy[1], Jitender Rohila[2], Ashwin L. Desouza[2], Amrita Guha[5], Rajiv Kumar[3], Nandini Sharrel Menon[1], Sushmita Rath[1], Vijay Maruti Patil[1], Vanita Maria Noronha[1], Amit Prakashchandra Joshi[1], Siddhartha Laskar[4], Venkatesh Rangarajan[6], Kumar Prabhash[1], Sudeep Gupta[1] and Shripad Banavali[1]*

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**Tata Memorial Centre , Mumbai , India**

**Background:** Treatment of malignant melanoma has undergone a paradigm shift with the advent of immune checkpoint inhibitors (ICI) and targeted therapies. However, access to ICI is limited in low-middle income countries (LMICs).

**Patients and Methods:** Histologically confirmed malignant melanoma cases registered from 2013 to 2019 were analysed for pattern of care, safety, and efficacy of systemic therapies (ST).

**Results:** There were 659 patients with a median age of 53 (range 44–63) years; 58.9% were males; 55.2% were mucosal melanomas. Most common primary sites were extremities (36.6%) and anorectum (31.4%). Nearly 10.8% of the metastatic cohort were BRAF mutated. Among 368 non-metastatic patients (172 prior treated, 185 de novo, and 11 unresectable), with a median follow-up of 26 months (0–83 months), median EFS and OS were 29.5 (95% CI: 22–40) and 33.3 (95% CI: 29.5–41.2) months, respectively. In the metastatic cohort, with a median follow up of 24 (0–85) months, the median EFS for BSC was 3.1 (95% CI 1.9–4.8) months versus 3.98 (95% CI 3.2–4.7) months with any ST (HR: 0.69, 95% CI: 0.52–0.92; P = 0.011). The median OS was 3.9 (95% CI 3.3–6.4) months for BSC alone versus 12.0 (95% CI 10.5–15.1) months in any ST (HR: 0.38, 95% CI: 0.28–0.50; P < 0.001). The disease control rate was 51.55%. Commonest grade 3–4 toxicity was anemia with chemotherapy (9.5%) and ICI (8.8%). In multivariate analysis, any ST received had a better prognostic impact in the metastatic cohort.

**Conclusions:** Large real-world data reflects the treatment patterns adopted in LMIC for melanomas and poor access to expensive, standard of care therapies. Other systemic therapies provide meaningful clinical benefit and are worth exploring especially when the standard therapies are challenging to administer.

~10% of eligible population could afford standard of care therapies i.e. ICI

# Melanoma:Tata Memorial Centre Experience (N=659)

Total Patients during study period (N=659)

Metastatic at diagnosis (N=291)

Non-Metastatic at diagnosis (N=368)

**Overall Metastatic (N=433)**
- 291 – Baseline Metastatic
- 81- Recurrent-Metastatic
- (at presentation to our institute)
- 61 – Non-metastatic at presentation to our institute, at relapse became metastatic

172 (46.7%) had outside Surgery
- 81 - metastatic at presentation to our institute
- 91 - remained Non - metastatic at presentation to our institute

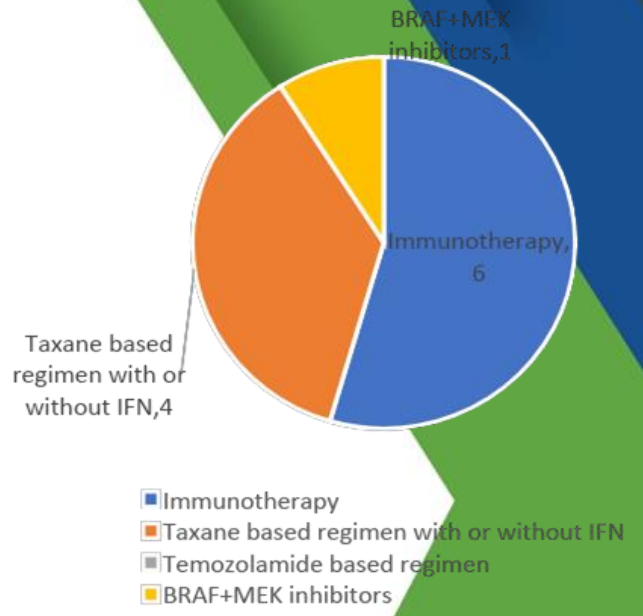
196 denovo non-metastatic
- 142 Surgery at our institute,
- 11 unresectable
- 43 not taken treatment

Non-Metastatic till the end of the study (N=226)

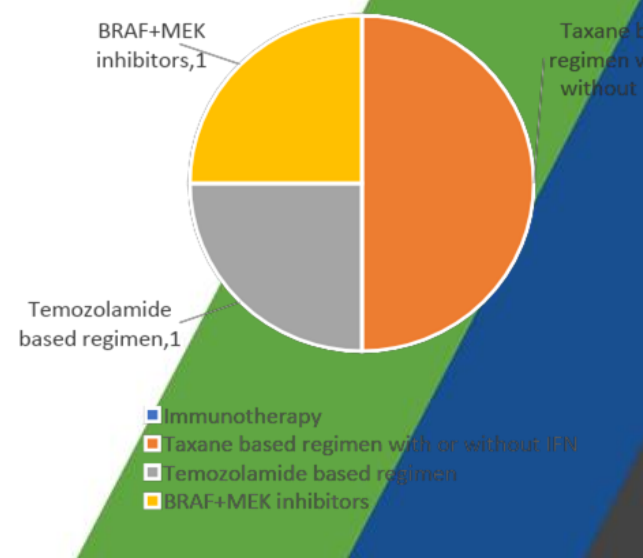
| Treatment categories | Treatment received | n(%) | Median PFS | Disease control rate (SD+PR) |
|---|---|---|---|---|
| Immunotherapy | Immunotherapy | 45 (10.4) | 9 | 30% |
| Taxane based regimens with or without interferons | Paclitaxel +carboplatin | 73 (16.9) | 13.1 | 38.7% |
| | Paclitaxel+Carboplatin +Interferon | 28 (6.5) | 7.9 | 25.8% |
| | Interferon | 27 (6.2) | 4.8 | 25.8% |
| | Paclitaxel alone | 12 (2.8) | 4.3 | 43.7% |
| | Nab paclitaxel+carboplatin | 2 (0.5) | 1.8 | 38.7% |
| | Nab paclitaxel alone | 8 (1.8) | 5.8 | 43.7% |
| | Paclitaxel+thalidomide | 9 (2.1) | 3.1 | 0% |
| Temozolamidebased regimens | Dacarbazine | 8 (1.8) | 3 | 0% |
| | Temozolamide | 18 (4.2) | 4 | 25.8% |
| Oral metronomic therapy | Temozolamide+Thalidomide | 31 (7.2) | 9.4 | 33.3% |
| BRAF +MEK inhibitors | Dabrafenib +trametinib | 3 (0.7) | 14.5 | 33.3% |

**Treatment Received-**
Surgery – 172 (76.1%)
Adjuvant therapy-
Radiation – 53 (30.8%); ICI – 5 (3%);Chemotherapy – 12 (7%)
**54 - not resected (unresectable+ not taken treatment)**
**ST received -**
P+C – 6 (11.1%); P+C+Interferon – 2 (3.7%)
Interferon – 1 (1.9%);ICI – 1 (1.9%),
Oral metronomic therapy– 1 (1.9%),
Temozolamide- 1 (1.9%)
BSC – 10 (18.5%); LFU – 32 (59.3%)

**First line**

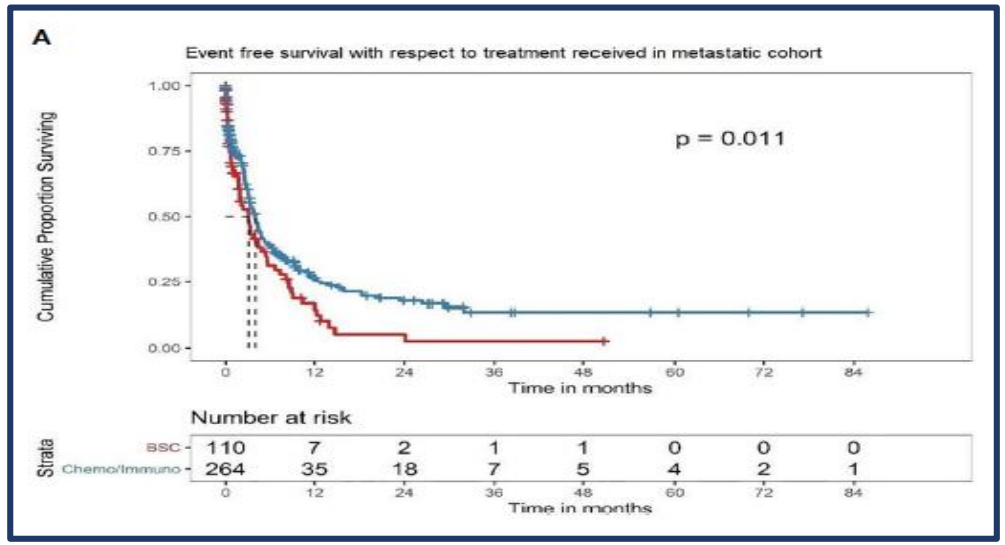


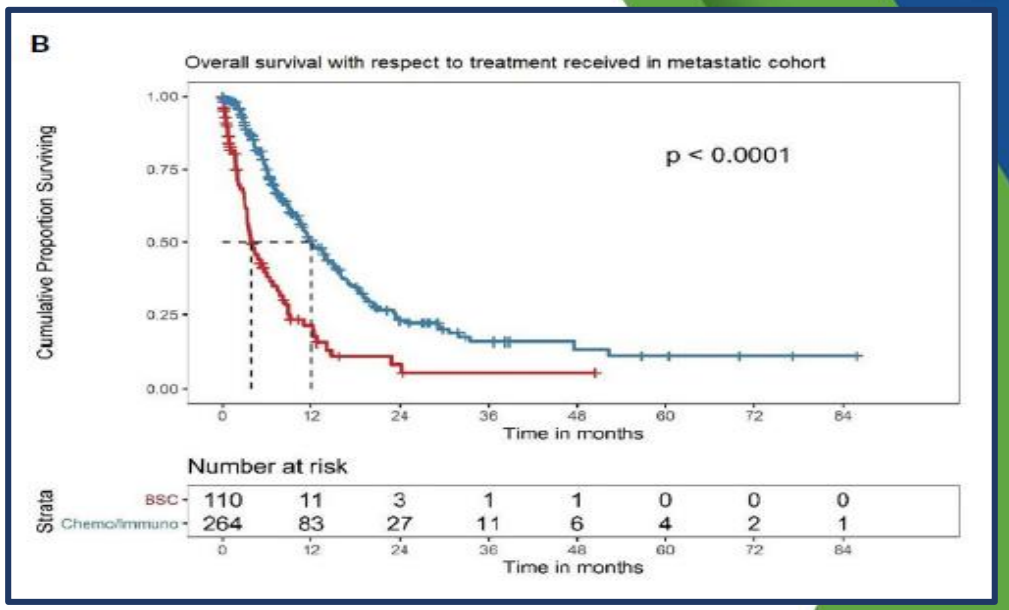

**Second line**




*Bajpai J etal.Front. Oncol., 08 September 2021 | https://doi.org/10.3389/fonc.2021.710585*

# Best Supportive Care Versus Any Systemic Therapy in Overall Metastatic Cohort




**Median EFS:**
BSC - 3.1 (95% CI 1.9–4.8) months
ST - 3.98 (95% CI 3.2–4.7) months
**(HR: 0.69, 95% CI: 0.52–0.92; P = 0.011)**


**Median OS:**
BSC - 3.9 months (95% CI 3.3–6.4)
ST - 12.0 months (95% CI 10.5–15.1)
**(HR: 0.38, 95% CI: 0.28–0.50; P < 0.001)**

~10% could afford standard, other systemic therapies -some benefit (if standard can't be given)

| https://doi.org/10.3389/fonc.2021.710585

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TUMOR IMMUNOLOGY AND MICROENVIRONMENT

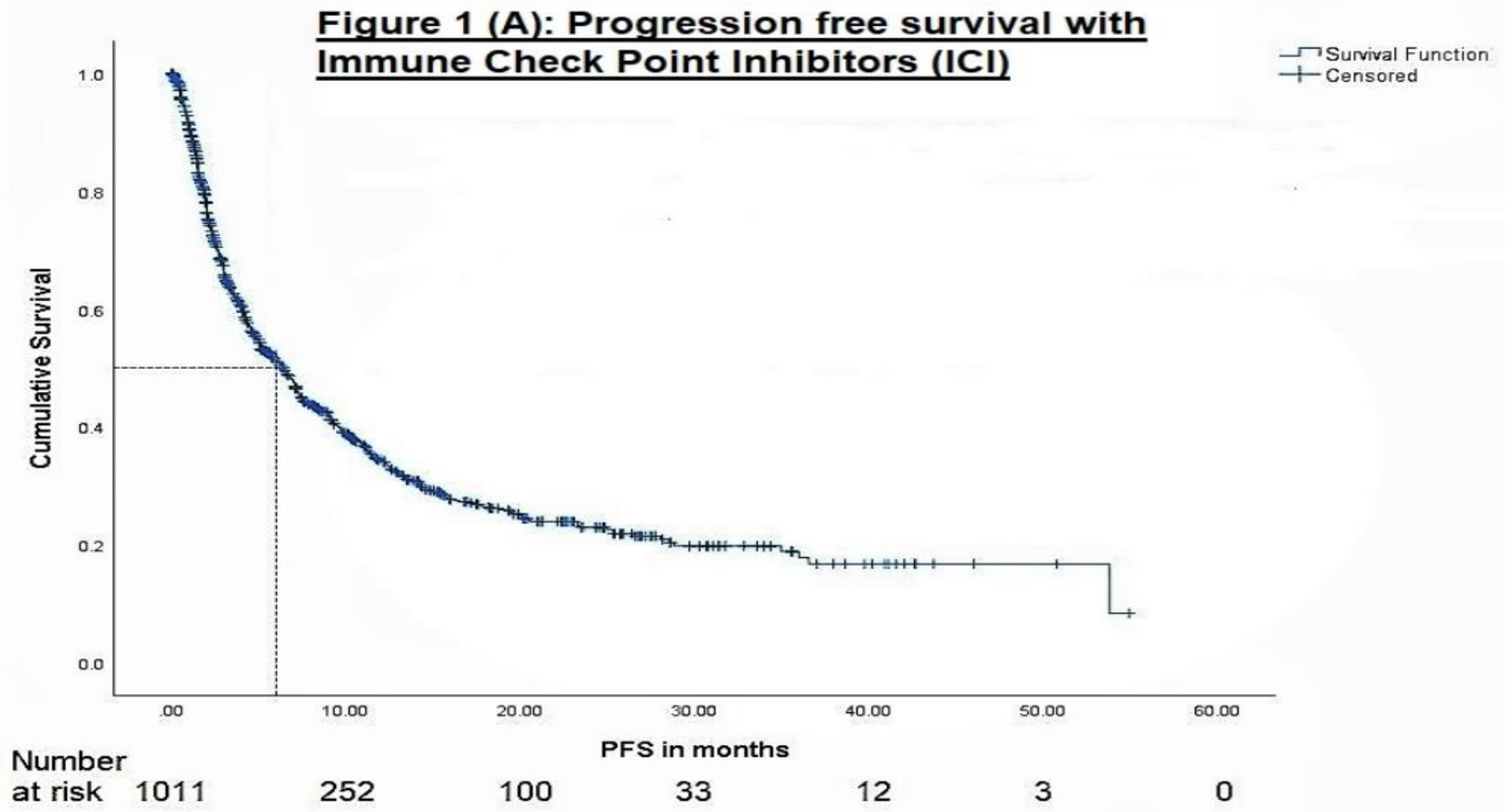
IJC INTERNATIONAL JOURNAL of CANCER

# The clinical utility and safety of short-course immune checkpoint inhibitors in multiple tumours—A real-world multicentric study from India

George Abraham[1] | Vanita Noronha[1] | Senthil Rajappa[2] | Amit Agarwal[3] | Ullas Batra[4] | Naresh Somani[5] | Thirumalairaj Raja[6] | Shekhar Patil[7] | Ashish M. Kaushal[8] | Ashish Joshi[9] | Vivek Radhakrishnan[10] | Navneet Singh[11] | Govind Babu[12] | Rohan Tewani[2] | Saphalta Baghmar[3] | Chandragouda Dodagoudar[3] | Ramya Ananthakrishnan[6] | Shashidhara Haragadde Poppareddy[7] | Vibhor Sharma[13] | Nandini Menon[1] | Vijay M Patil[1] | Amit Joshi[1] | Sudeep Gupta[1] | Kumar Prabhash[1] | Jyoti Bajpai[1]

IMMUNO-ONCOLOGY SOCIETY OF INDIA

**August 2014 to October2020 from 13 centers in India**




Real world data , n=>1000 -short course ICI : comparable to the published data on standard ICI therapy

This merits wide recognition and testing in large randomised cohort for reproducibility &applicability

- With a median follow up of **14.1 (95%CI 12.9-15.3) months, there were 616 events of progression and the median PFS was 6.4 (95%CI 5.5-7.3) months** in the overall cohort.
- The one year and two-year actuarial PFS were **35.8% (95%CI 32.8-41.3%) and 24.0 %** (95% CI 2.4%-30.9%) respectively

# Access and Cost in India

| Molecule | Trade name | Strength | MRP(per month) | PAP |
|---|---|---|---|---|
| **Pembrolizumab** | **Keytruda** | 100mg | 182000 (~$2250) | **1+1** |
| **Nivolumab** | **Opdiva** | 100mg | 186000 (~$2275) | **1+1** |
| **Dabrafenib** | **Rafinlar** | 150mg | 166000 (~$2050) | **Post 9months , free to patient till benefitted** |
| **Trametinib** | **Meqsal** | 2mg | 190000 (~$2350) | |


- Rare gynecological cancers demand **precision care** preferably in reference centers
- Malignant melanoma is **relatively rare in India,** and has a poor prognosis without standard therapy[Immunotherapy and targeted(BRAF positive )]
- SITC guidelines provide management guidance in these challenging scenarios
- Gynecological Melanomas are even rarer and should follow standard management based on cutaneous melanoma
- ~10 %of eligible population could afford standard therapy ,this needs utmost attention and global collaboration (with more trials) are highly warranted
- **Real-world situations,** when standard options are beyond reach**, resource appropriate selection of therapy** is justified after careful MDT discussion involving patient and families

French Toast is not French

# Did you know?

White Chocolate is not chocolate

Danish pastries are not Danish

Guinea pigs are not pigs, nor are they from Guinea

Rare cancers are no so rare (~20% of all cancers)

AND

These forgotton cancers demands –attention and precision care!

Rare Diseases are NOT rare!

#rarediseasechallenge @rarediseasechallenge

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CONCEPTULISATION

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REGISTERTRATION-I-OSI

CONSTITUTION

I-OSI, SITC, Patients & families